

**COMPARATIVE STUDIES OF THE ANAESTHETIC EFFICACY OF 4%  
ARTICAINE USED AS MANDIBULAR INFILTRATION VERSUS 2%  
LIDOCAINE USED AS INFERIOR DENTAL NERVE BLOCK IN  
EXTRACTION AND PULPOTOMY OF MANDIBULAR PRIMARY MOLARS**

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**Submitted in accordance with the requirements for the  
Integrated degree of Doctor of Philosophy and Master Science (Oral Science)**

**The University of Leeds  
School of Dentistry / Paediatric Department**

**July 2015**

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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## Dedication

*To the memory of my grandmother, will remember her words and*

*standing by my side at the beginning of my life*

*To my parents, for starting me on this journey of life.*

*To my children Khalid, Sattam and Reem, I love you forever.*

*To my wonderful husband, Abdullah, for joining me along the way.*

*I could not have done it without you*

## Acknowledgements

It would have not been possible to write this doctorate thesis without the help and support of the kind people around me, who contributed to the completion of this doctoral thesis, each on their own way, and to only some of them it is possible to give particular mention here.

Foremost, I would like to express my sincere gratitude to my supervisor, Professor Monty S. Duggal who was abundantly helpful and offered invaluable assistance, support and guidance I am grateful for the way he has challenged me. He managed to keep a precise balance between readily offering his advice yet prompting me to think critically and independently.

I would like to extend my warmest thanks to my supervisor Dr Jinous F. Tahmassebi, her inspirational ideas formed the basis of this thesis; her outstanding help and encouragement brought it to light. Ms Theresa Munyombwe who offered invaluable support and guidance throughout the statistical part of this project.

My thanks are due to my sponsor 'ministry of defence' in the Kingdom of Saudi Arabia for giving me this opportunity to complete my postgraduate study.

I would like to acknowledge the help of all the dental team in the Leeds Dental hospital, children department. In particular, Professor Jack Toumba for his support and help with this study. I would like to thank all the dental nurses who worked with me in the clinical trial. I would like to thank the children and parents who volunteered to take part in this study. This study would not be possible without them.

I very much appreciated the help of Mary Godfrey for her support and guidance in the qualitative part of this thesis.

A very special thanks to my friends and classmates throughout my study period for loving support and treasured memories we have had in the last five years.

My deepest and most grateful thank you goes to my husband Abdullah for the unconditional love and support you have given me. You have been my rock throughout this whole process and I would not have got through this without you. I also thank my children; Khalid, Sattam and Reem, for the smile that they always brought to my face during hard times of this project and ever.

## Summary

This thesis is presented in a chapter format. Chapter one was divided into two parts, the first part is a general literature review about the local anaesthetics which includes: classification and properties of local anaesthetic agents, their pharmacodynamics, the types and lastly about the reversal of local anaesthetics. The second part, deals with the efficacy and safety of the local anaesthetics, specifically with regards to the articaine hydrochloride, local anaesthetic's injection methods in terms of differences and how it can impact the efficacy and safety of the local anaesthetics. This part also includes a brief discussion regarding the use of articaine when treating irreversible pulpitis, extraction of third molars and when used as supplemental injection. In addition, the use of articaine in children has been discussed particularly with regard to the mandibular infiltration technique.

Chapter two presents a systematic review of anaesthetic efficacy of articaine versus lidocaine in children's dentistry. The concept of a systematic review, and why this approach was used is presented. The key steps in the systematic review process has been discussed, in relation to the research question. In addition, the quality assessment process of the included studies has been discussed in details. Results and conclusion of this part of the thesis formed the basic background for the randomised control clinical trial.

In chapters three, four and five, the randomised clinical trial comparing 4% articaine hydrochloride with 2% lidocaine hydrochloride have been discussed in terms of rational, aim and objectives, trial design, material and methods, results and discussion. The study conclusion and the study limitations are elaborated in chapter five.

Chapter six, was designed as mixed method approach (qualitative and quantitative). The aim of this sub-study was to investigate children's/parents' acceptance of the dental treatment provided under local anaesthetics, and explore the differences between the two types of the local anaesthetics in more depth. The integration of this sub study within the main study was to enhance and enrich the meaning of a singular perspective (i.e. the quantitative findings) and to develop a more complete understanding of a dental treatment under local anaesthetic.

The concluding chapter seven provides a conclusion of the research undertaken followed by the applicability of the research findings in the clinical field. The main contributions of the research were noted together with the limitations of the work and future directions in which this research will be taken.

## Global abstract

The research presented in this thesis is in several parts. Firstly, the aim of systematic review was to systematically review available evidence on the efficacy of two local anaesthetic solutions lidocaine and articaine used for dental treatment in children. The findings from this review served as a basis for the next phase of the project, which was to address the deficiencies identified from the systematic review. This took the form of a Randomised Controlled Trial, the aim of which was to carry out an equivalence parallel prospective, randomised, controlled study, in order to evaluate and compare the anaesthetic efficacy of mandibular infiltration using 4% articaine (1:100,000 epinephrine) with mandibular nerve block using 2% lidocaine (1:80,000 epinephrine) in the extraction and restoration of mandibular primary molars. The translational intention was to be able to recommend the most effective and acceptable method of achieving anaesthesia for dental treatment of mandibular primary molars in children.

In addition, a mixed method research strategy was implemented, in order to assess and explore the child's experience associated with dental injection, and compare the two different techniques that were used (buccal infiltration and inferior dental nerve block). This comparison was in terms of children acceptance as well as parent satisfaction of their child's dental treatment under local anaesthesia and their perception of the impact of this treatment on their child.

### **Methods**

**Systematic review:** A systematic search was conducted on Cochrane CENTRAL Register of Controlled Trials, MEDLINE (OVID; 1950 to June 2013), Cumulative

Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost; 1982 to June 2013), EMBASE (OVID; 1980 to June 2013), SCI-EXPANDED (ISI Web of Knowledge; 1900 to June 2013), key journals, and previous review bibliographies through June 2013. No restrictions were placed on years, language or publication status. Original research studies that compared articaine with lidocaine in children dental treatment were included and methodological quality assessment including assessment of risk of bias was carried out for each of the included studies.

**RCT:** In total 98 children aged 5–9 years old were randomly assigned into two groups: one group (treatment group) received mandibular infiltration with 4% articaine with 1:100,000 epinephrine; the other group (control group) received an inferior alveolar nerve block with 2% lidocaine with 1:80,000 epinephrine. All local anaesthetic injections were given by a single operator, who had the role of assessing the presence/absence of pain as well as the child's behaviour during the injection and treatment procedures (using W-BFRS, VAS and Frankl Behaviour Scale). Each child received one treatment for one tooth only.

**Qualitative sub-study:** Concurrent mixed method data collection strategies were used. The qualitative and quantitative data were collected from the same participants as well as in the same timeframe. Thematic analysis was performed on the semi-structured interviews.

## **Results**

**Systematic review:** Electronic searching identified 520 publications. After the primary and secondary assessment process, only three studies were included in the final analysis. The RCTs included in this review investigated the efficacy of local anaesthetic solutions when given as a combination of both techniques, local

infiltration as well as block anaesthesia. The data analyses showed superiority of articaine over that of lidocaine in terms of achieving anaesthetic success, although these results were not statistically significant.

**RCT:** During the injection phase the absolute differences between the two anaesthetic techniques using W-BFRS VAS and behaviour scales was zero (no difference), 0.060 (95% CI -0.110 to 0.230) and -0.080 (95% CI -0.190 to 0.030) respectively. During the treatment phase, the absolute difference were -0.020 (95% CI -0.180 to 0.140), -0.040 (95% CI -0.220 to 0.150) and zero (no difference). The equivalence margin was set at  $\pm 0.2$  and all comparisons showed equivalence of the two treatments except for the comparison of VAS during injection and W-BFRS during treatment with the 95% confidence intervals exceeding the equivalence margin.

**Qualitative sub-study:** A total of 42 (56%) participants in the qualitative part of the study, were in articaine group while 31 (41%) were in lidocaine group. Only two of the participants (3%) had received both local anaesthetics. Parent's responses to the questionnaire reflected their opinion based on their observation of the dental treatment. Majority of the parents were happy about the treatment in general. The children's responses were very positive as well.

The questionnaire/interviews with the children, parents, along with the dentist's comments, allowed the development of three major themes addressing the aims and purposes of the study. The three major themes emerged were: Firstly, "Experience of the anaesthetic procedures". Second major theme "Ease vs difficulty of the dental treatment" and the third major theme was "Perception of the dentist approach during the treatment".

## **Conclusion**

The quality of the included RCTs in the systematic review was generally inadequate. All the included studies had several limitations in reporting which indicated a need for a randomised clinical trial with standardised methodology to address these limitations.

The findings of the systematic review indicated that, articaine and lidocaine presented similar efficacy when used as infiltration and blocks respectively for routine dental treatments. The effect of numbness of soft tissues was longer using articaine than lidocaine, and few adverse events were reported following the use of both solutions. The results from this review indicate that articaine injections can cause slightly more post injection pain in the area injected than lignocaine, the difference was not statistically significant.

Overall, the results of the present RCT pointed out that it would be acceptable to carry out invasive dental treatment for mandibular molars with the administration of infiltration with buccal intrapapillary infiltration using 4% articaine instead of the traditional method of inferior dental block using lidocaine, which many children find difficult to cope with.

Considering the findings from the survey, along with the results from the questionnaire/interview, it was established that, the reactions of the patients with both of the local anaesthetics were very similar. The interview findings added meaning and depth to the survey findings, in terms of explaining and clarifying the children's responses and answers. Parents/children reported a high degree of satisfaction with the treatment outcomes. The satisfaction expressed by parents/children can have a positive impact on the children's future dental treatment.

**Registration**

**SR Registration:** PROSPERO registration: CRD42013004620.

**Trial registration:** EudraCT number: 2011-004711-23

## Abbreviation

<b>AE</b>	Adverse Events
<b>BI</b>	Buccal Infiltration
<b>BMS</b>	Behaviour Management Strategies
<b>CI</b>	Confidence Interval
<b>CMF</b>	Clinical Master File
<b>CNS</b>	Central Nervous System
<b>CONSORT</b>	Consolidated Standards of Reporting Trials
<b>CRD</b>	Centre for Reviews and Dissemination
<b>CRF</b>	Case Report Form
<b>EPT</b>	Electric Pulp Tester
<b>EudraCT</b>	European Clinical Trials Database
<b>GCP</b>	Good Clinical Practice
<b>IA</b>	Interim Analysis
<b>ICH</b>	International Conference on Harmonisation
<b>IDNB</b>	Inferior Dental Nerve Block
<b>IRAS</b>	Integrated Research Application System
<b>ITT</b>	Intention to Treat Analysis
<b>LA</b>	Local Anaesthetic
<b>MeSH database</b>	Medical Subject Heading terms
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>NHS</b>	National Health Services
<b>NRES</b>	National Research Ethics Service
<b>NS</b>	Narrative Synthesis
<b>OR</b>	Odd Ratio
<b>PI</b>	Principle Investigator
<b>PICO</b>	Patient /Population, Intervention, Comparison, and Outcomes
<b>PIS</b>	Patient's Information Sheet
<b>R&amp;D</b>	Research and Development
<b>RCTs</b>	Randomised Controlled Trials
<b>REC</b>	Research Ethics Committee
<b>SD</b>	Standard Deviation

<b>SOP</b>	Standard Operating Procedure
<b>SSC restorations</b>	Stainless Steel Crown
<b>SSI</b>	Site-Specific Information
<b>TGA</b>	Therapeutic Goods Administration, in Australia
<b>VAS</b>	Visual Analogue Scale
<b>W-B FRS</b>	Wong- Baker Faces Pain Rating Scale

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## **Chapter 1**

### **LITERATURE REVIEW**

#### **1.1 INTRODUCTION**

This part of the thesis consist of general literature review and basic knowledge about the local anaesthetics, anaesthetic efficacy and safety with particular attention to use of articaine in children's dentistry.

#### **1.2 PROPERTIES OF LOCAL ANAESTHESIA**

At present, there are a variety of anaesthetic solutions which are extremely safe and fulfil most of the characteristics of an ideal local anaesthetic (LA). Variations in the clinical characteristics of the LA agents can be attributed to differences in chemical properties of their molecular structures (Moore and Hersh, 2010).

It is clear that lipid solubility, ionisation, and protein binding properties contribute to the clinical characteristics of local anaesthetics. However, factors such as the site of injection, drug and vasoconstrictor concentration, volume of injection, and inherent vasodilating properties of the anaesthetic, also influence the clinical performance of an LA (Moore and Hersh, 2010).

Local anaesthesia are composed of a lipophilic/hydrophobic group (an aromatic ring) connected by an amide or ester intermediate chain to a hydrophilic or ionisable group (a secondary or tertiary amine). The Lipophilic aromatic group enhances the ability of the local anaesthetic molecule to penetrate various anatomical structures between the site of injection and the target site—the sodium channel in the nerve axon; while the hydrophilic amino group imparts water solubility to the molecule, ensuring that on injection into the tissue, the local anaesthetic will not precipitate.

The intermediate chain or link determines the classification of the local anaesthetic either amide or ester, therefore, it determines the biotransformation and metabolism of the local anaesthetic (Catterall and Mackie, 2006; Malamed, 2013).

Local anaesthetics are prepared as a water-soluble hydrochloride salt, they generally have a pH of 5-6 and exist in ionised and non-ionised forms, the proportions of which vary with the pH of the environment. The non-ionised portion is the form that is capable of diffusing across nerve membranes and blocking sodium channels. Anaesthetics with the presence of greater non-ionised portions have a faster onset of action. Local anaesthetics differ in respect to the pH at which the ionised and non-ionised forms are present at equilibrium, but this pH is generally in the range of 7.6-8.9. The more closely the equilibrium pH for a given anaesthetic approximates the physiologic pH of tissues (i.e. 7.35-7.45), the more rapid the onset of action. A decrease in pH shifts equilibrium towards the ionised form, delaying onset of action. This explains why local anaesthetics are slower in onset of action and less effective in the presence of inflammation, which creates a more acidic environment with a lower pH (Catterall and Mackie, 2006; Malamed, 2013).

When the LA contains epinephrine, the pH of the solution will be in the range of 3-4, which represents a stable environment. However, the solution will have less freebase, slowing the onset of action. The addition of sodium bicarbonate is used clinically to increase the pH of LA solutions, thereby enhancing onset of action. However, increasing the volume of sodium bicarbonate added to the local anaesthetic preparation might lead to precipitation of the LA molecules (Catterall and Mackie, 2006; Malamed, 2013).

Local anaesthetics are prepared in the cartridges as slightly acidic hydrochloride water-soluble salts. When injected into normal tissue there is rapid equilibration of

the pH, allowing the un-protonated compound to diffuse across the cell membrane. The cationic form of the LA binds with the sodium pore: ionisation must occur after passage through the membrane in order for the LA to take effect. The charged form of the LA will not diffuse through the membrane; therefore, anything that alters the pH of the local milieu will affect the LA's ability to get through the cell membrane. That explains why the effect of LA is reduced when injected into inflamed tissue, the environment is acidic, the LA is charged, and it cannot pass through the cell membrane to exert its effect (Catterall and Mackie, 2006).

### 1.2.1 Classification

The local anaesthetic can be classified into two groups based on the intermediate chain or link (-CO- ester or -HN-CO- amide) that joins both the aromatic ring and the secondary or tertiary amine. These are considered weak bases, tertiary amines with three structures in common as shown in Figure 1-1.

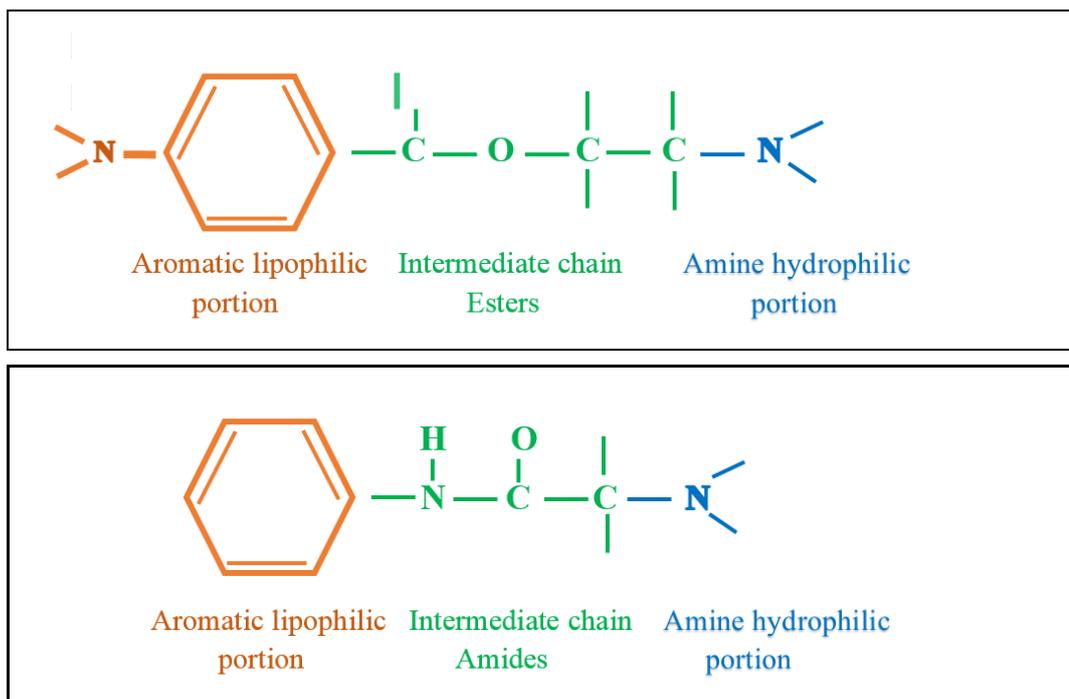


Figure 1-1: Local anaesthetic chemical structure

Aromatic group: confers lipid solubility and allows nerve membrane penetration.

Intermediate chain: differentiates anaesthetic as ester or amide.

Amino group: contributes water solubility, which prevents precipitation of anaesthetic.

#### **1.2.1.1 Esters**

Esters are formed from an aromatic acid and an amino alcohol and include; Procaine, Chlorprocaine, Tetracaine, Cocaine and Benzocaine.

#### **1.2.1.2 Amides**

Amides are formed from an aromatic amine and an amino acid and include; Articaine, Lidocaine, Mepivacaine, Bupivacaine, Prilocaine, Etidocaine and Ropivacaine.

### **1.2.2 Local anaesthetics' mechanism of action**

The local anaesthetics exert their pharmacological actions at the nerve membrane, and many theories have been published over the years to explain their mechanism of action. Four current theories for the mechanism of action of local anaesthetics are:

- Local anaesthetics interfere with a chemical, such as acetylcholine, which is involved in nervous conduction;
- Local anaesthetics alter the density of fixed charges on the surface of the membrane;
- Local anaesthetics cause an expansion of a volume of membrane that is critical for conduction; and
- Local anaesthetics react with a specific receptor in the nerve membrane.

- **Acetylcholine interference**

This first theory fails due to the fact that there is a lack of evidence to substantiate that acetylcholine is involved physiologically in conduction (Ritchie, 1975; Malamed, 2013).

- **Membrane expansion**

Local anaesthetics are highly lipid soluble and therefore easily penetrate the lipid portion of the cell membrane. This causes the nerve membrane to expand, resulting in a decrease in the diameter of the sodium channels, thereby inhibiting the influx of sodium and nerve impulse generation.

- **Specific receptor theory**

Specific receptor theory explains the mechanism of action of almost all LAs. Local anaesthetic agents block nerve conduction by inhibiting the voltage-gated sodium channels of the neuronal membrane. However, the membrane expansion theory explains the action of benzocaine, a local anaesthetic that does not have an amino acid terminus, and therefore, cannot be protonated (i.e. cannot bind electrostatically to the negatively charged group in the sodium channel).

LAs are agents that reversibly block action potentials at the level of the sodium channels. Blocking the entry of sodium ions into their channels, interrupts axonal conduction, thus preventing the transient increase in the permeability of the nerve membrane to sodium, which is required for an action potential. Local anaesthetics' actions are nonspecific: they work on any nerve with a functioning sodium channel (Malamed, 2013).

The sodium pore channel is a complex entity. There is a hydrophobic entity in the sodium channel pore that has a binding affinity for the lipophilic/hydrophobic group of the LA. Binding can only occur with the sodium gate or pore in an open or

stimulated position; LAs need access to get to their binding site. Once there, the LA stabilises the channel in its inactive state and the nerve cannot repolarise. Only a critical length of nerve need be affected to stop conduction. The channel eventually recovers but at a speed 10 to 10,000 times slower than normal. The stronger the bond between the hydrophobic groups, the longer the effect. The strength and duration of this bond affect the therapeutic window, making it smaller, and hence influencing toxicity. Amide linkages are less prone to hydrolysis than ester linkages and therefore influence the duration of effect (Catterall and Mackie, 2006).

Nerve fibres have differing susceptibilities to the effects of LAs. These differences are most likely due to differences in fibre diameter and myelination. The small-diameter unmyelinated fibres, such as type C pain fibres, are the most sensitive to LA blocking effects. Heavily myelinated, thicker fibres such as type A motor fibres, are less sensitive to the blocking effects of LAs. Any fibre that requires an action potential to function, however, can potentially be blocked by the effects of LAs (Malamed, 2013).

### **1.2.3 Pharmacokinetics**

Local anaesthetics are distributed throughout the body via blood circulation to all the organs. The concentration of the local anaesthetic will be greater in the highly perfused organs such as the brain and kidney, as well as in the skeletal muscles, which represent the largest mass of tissue in the body, and therefore will contain a high percentage of the local anaesthetic solution (Malamed, 2013).

The distribution of local anaesthetic in the body occurs in two phases, the rapid disappearance phase which is related to uptake by rapidly equilibrating tissue (highly perfuse organs) and the slow phase of disappearance, which is the function

of the individual local anaesthetic's distribution, biotransformation, and excretion (Catterall and Mackie, 2006).

Metabolism of LAs relates to their duration of effect and their toxicity. The more free LA there is in plasma, the more toxic it is. Ester-linked LAs are generally much shorter acting as they are rapidly inactivated by plasma cholinesterase. Ester local anaesthetics undergo extensive hydrolysis in the plasma by pseudo-cholinesterase enzymes (plasma cholinesterase or butyrylcholinesterase). Ester hydrolysis is rapid, resulting in water soluble metabolites which are excreted in the urine.

An amide local anaesthetic metabolism varies and it occurs primarily by microsomal P-450 enzymes in the liver and, to a lesser extent, in other tissues. The excretion of amide and ester local anaesthetics occurs in the kidneys. Less than 5% of the unchanged medication is excreted by the kidneys (Catterall and Mackie, 2006; Malamed, 2013). Articaine undergoes metabolism in both blood and liver as it contains both ester and amide components (Malamed, 2013).

#### **1.2.4 Potency**

Potency is directly related to lipid solubility, because 90% of the nerve cell membrane is composed of lipid. Increased lipid solubility leads to faster nerve penetration and blockade of sodium channels. Protein binding is related to the duration of action. The more firmly the local anaesthetic binds to the protein of the sodium channel, the slower the anaesthetic is released from the receptor sites in the sodium channels, therefore the longer the duration of action (Covino, 1976). Differences in protein binding also result in differing durations of unwanted side effects, and this is one of the reasons that bupivacaine is considered more toxic than lignocaine. The duration of action of the drug is also related to its structure,

primarily to the length of the intermediate chain joining the aromatic and amine groups (Malamed, 2013). In general, LAs that are highly tissue bound are absorbed at a slower rate. In addition, absorption is dependent on the individual local anaesthetic's intrinsic ability to cause vasodilatation (Covino, 1976).

#### **1.2.5 Maximum dosage of local anaesthesia**

According to Rosenberg (2004), the recommendations regarding maximum doses of local anaesthetics as presented in physicians' pharmaceutical reference books or in anaesthesiology text books, are not evidence based. Manufacturers have issued dosing guidelines for LAs that are more empirically based rather than evidence based. The reason for this may be the companies attempting to ensure a very generous margin of safety for these widely used medications, with these margins possibly being applied as a result of liability concerns. Moreover, the recommendation of a maximum dose is expressed as the total amount of the local anaesthetic, and other important factors like, the site of administration, size and age of the patient, concomitant diseases and medications are not taken into account.

Local anaesthetics are potentially toxic agents and should be handled with care. In a normal clinical setting, the appropriate dose for each clinical procedure must be known, and this dose should be adjusted based on drug-related factors as well as the patient-related factors, as these will both influence the absorption, distribution, metabolism and elimination of the local anaesthetics. In another words, the magnitude of the reduction should be related to the expected influence of the pharmacodynamic or pharmacokinetic change.

#### **1.2.5.1 Calculation of the maximum recommended dose**

Dosing calculations used to avoid systemic reactions to LAs are dependent on the agent administered and the patient's body weight. Frequently the dentist administers a combination of local anaesthetic formulations, and it must be appreciated that systemic effects of these combinations follow principles of summation. When adhering to maximum dosage guidelines, systemic effects of various agents should be regarded as additive. For example, if you have administered half the maximum dose for lidocaine and wish to add bupivacaine, reduce its maximum dose by half (Finder and Moore, 2002; Becker, 2011).

#### **1.2.5.2 Calculation of the maximum recommended dose in children**

Pharmacodynamics of local anaesthetics in children is comparable to those in adults. Pharmacokinetics, on the other hand, differs significantly. Special caution should be observed when using amide local anaesthetics because a lower intrinsic clearance or decreased serum protein binding can easily lead to an increased risk of toxic reactions in younger patients (Malamed, 2013).

Toxicity reactions in children may occur more frequently because of a child's lower body weight. True dose-dependent toxicity reactions to LAs are most frequently reported in paediatric patients. Children may be at greater risk of toxicity reactions because their lower body weight does not represent a proportionate decrease in orofacial anatomy. The consequence of this disparity is that local anaesthetic toxicity reactions occur more frequently in children. Additionally, systemic drug interactions involving local anaesthetics and other CNS depressant drugs are more likely to occur in children (Finder and Moore, 2002).

### **1.2.6 Adverse reactions**

Allergic and hypersensitivity reactions to local anaesthetics and sulfites may occasionally occur. Most of these reactions are to some degree predictable based on the pharmacodynamic properties of the drug; however, reactions are very rare. Signs and symptoms of the various adverse reactions associated with local anaesthetics, such as Methemoglobinemia, are quite distinctive, permitting rapid diagnosis and treatment. Serious reactions are extremely infrequent and when treated properly, they are unlikely to result in significant morbidity or mortality (Haas, 2002; Moore and Hersh, 2010).

Other adverse reactions associated with the most commonly used local anaesthetics may include, psychogenic reactions i.e. anxiety induced events and alteration in heart rate, toxicity, allergic reaction, Methemoglobinemia and paraesthesia (Haas, 2002). In addition, ophthalmologic complications following dental anaesthesia are one of the complications that are seldom reported in the literature (Arx et al., 2014).

In a recent review by Sambrook and colleagues (2011), the database for the Office of Product Review of the Therapeutic Goods Administration in Australia, was searched retrospectively from 1973 to 2008, to identify serious adverse reactions to dental LAs. This study reported that severe adverse reactions to dental LA are rare and multifactorial in origin. The most common type of adverse reaction was syncope. The second major adverse effects were central nervous system (CNS) responses with persistent depression, agitation or tremor. Other common manifestation on the autonomic nervous system include changes in heart rate and blood pressure, hyperventilation, nausea, and vomiting (Becker and Reed, 2012).

### **1.2.6.1 Toxicity**

High levels of LA in the circulation system are responsible for drug toxicity and this could be due to repeated injections or as a result of a single accidental intravascular administration (Haas, 2002). These reactions are preventable with proper patient assessment and dosage calculations. The addition of epinephrine to local anaesthetic formulations can significantly reduce the absorption of the anaesthetics; Therefore minimising the risks from toxicity (Haas, 2002; Moore and Hersh, 2010).

Moreover, the risk of systemic toxicity is proportional to the concentration of LA within the body. Different factors determine the plasma concentration of LAs, including the dose of the drug administered, the rate of absorption of the drug, the site of injection, vasoactivity of the drug, use of vasoconstrictors and biotransformation, and elimination of the drug from the circulation (Malamed, 2013).

### **1.2.6.2 Allergy to local anaesthesia**

True allergy has been reported most often for ester local anaesthetics such as procaine and tetracaine (Gall *et al.*, 1996; Finder and Moore, 2002). Fortunately, the most common agents used in dentistry are the amide anaesthetics that possess very limited ability to induce hypersensitivity reactions (Finder and Moore, 2002). True allergy to LA can also be identified by skin tests; these tests need to be carried out by an allergy specialist.

It is very important to try to distinguish true allergic/anaphylactic reactions from other causes of cardiovascular collapse. Distinctive clinical features of anaphylaxis include pruritus and flat skin erythema, sometimes localised to the hands or feet, axillae or groin; 'hives' (urticaria) which are itchy welts; and angioedema, usually a

painless non-pruritic swelling occurring distant from the site of injection. However, importantly, some cases of true anaphylaxis can show only hypotension without any of these signs. Therefore, the absence of these features does not rule out a true systemic allergic reaction (Sambrook *et al.*, 2011).

Berkun *et al.* (2003) carried out a study to determine the prevalence of true LA allergy among the patients referred for suspected hypersensitivity. A total of 236 patients were included in this study. Skin prick and intradermal test results were negative for all subjects. No objective adverse reactions were observed during the challenge in all but one patient, who developed local erythema at the site of injection and later underwent an uneventful challenge with a different LA.

### **1.2.6.3 Methemoglobinemia**

Methemoglobinemia is a clinical syndrome caused by an increase in the blood levels of methemoglobin, secondary to both congenital (chronic) changes in haemoglobin synthesis or metabolism, or acute imbalances in reduction and oxidation reactions induced by the exposure to several chemical agents. Central cyanosis, unresponsive to the administration of oxygen, which can cause a reduction in oxygen delivery, is the main characteristic of Methemoglobinemia (Nascimento, 2008).

Cyanosis becomes apparent when methemoglobin levels are low, but symptoms of nausea, sedation, seizures and even coma may result when levels are very high. Prilocaine, articaine and benzocaine are best avoided in patients with congenital Methemoglobinemia (Finder and Moore, 2002).

#### **1.2.6.4 Paraesthesia**

Paraesthesia are one of the more general groupings of nerve disorders known as neuropathies. Paraesthesia may manifest as total loss of sensation (i.e. anaesthesia), burning or tingling feelings (i.e. dysesthesia), pain in response to a normally non noxious stimulus (i.e. allodynia), or increased pain in response to all stimuli (i.e. hyperesthesia) (Hass, 2006).

Prolonged anaesthesia or paraesthesia of the tongue or lip are known risks of surgical procedures such as extractions, but may also occur following nonsurgical dentistry (Haas, 2002; Malamed, 2013).

Persistent paraesthesia are most commonly reported after oral surgical procedures in dentistry. With the lingual nerve, being the most often affected, followed by the inferior alveolar nerve. Needle traumas, use of local anaesthetic solutions, and oral pathologies have been less frequently documented (Moore and Haas, 2010).

The true incidence of paraesthesia is unknown. Some lesions may resolve completely and patients return to normal function through spontaneous healing, whereas other injuries may be permanent, and patients may recover partially or not at all (Pogrel *et al.*, 1995; Pogrel and Thamby, 2000; Hillerup and Jensen, 2006).

The majority of cases resolve within eight weeks after the injection (Pogrel and Thamby, 2000, Haas 2002; Hillerup *et al.*, 2011). Although a few cases of recovery after several years have been reported, it is generally accepted that paraesthesia lasting longer than 6 to 9 months are unlikely to recover fully (Moore and Haas, 2010).

Pogrel and colleagues (1995) suggested three mechanisms for neurosensory disturbance:

- 1) Mechanical injury caused by a penetrating needle to the conductive structures of the nerve. However, the researchers found it difficult to understand how a needle that is smaller than 0.5 mm in diameter could cause such profound damage to the entire nerve, and they concluded that “direct trauma from the needle is probably not responsible for the nerve damage.”
- 2) Mechanical injury causing intraneural bleeding with subsequent hematoma and granulation tissue formation. Pogrel *et al.* (1995) have suggested that this theory is quite acceptable.
- 3) Neurotoxicity with degeneration of axon or myelin cellular structures, or both, due to local anaesthetics. The authors expect intra fascicular injections of local anaesthetic to affect the skin or mucosal area and sensory parameters supplied by that fascicle and not the whole nerve. It has also been suggested that alternative pathways for the breakdown of commonly used local anaesthetic agents, possibly results in the formation of aromatic alcohols around the nerves, which may in turn, result in the equivalent of an alcohol block that causes prolonged nerve damage.

Articaine and prilocaine have been reported as more likely than other anaesthetics to be associated with paraesthesia. In 1995, Haas and Lennon conducted a retrospective study evaluating the incidence of paraesthesia in Ontario, Canada between 1973 and 1993. The database accessed was from the insurance carrier that administered malpractice insurance to all licensed dentists in that province. It was concluded that there was an overall incidence of one paraesthesia out of every 785,000 injections. Compared with the other local anaesthetics, a statistically significant higher incidence was noted when either articaine or prilocaine was used.

In another study the cases of paraesthesia were evaluated by the Oral and Maxillofacial Surgery Department of the University of California in San Francisco. This study showed that 35% of the paraesthesia involved the use of lidocaine hydrochloride, versus 30% being associated with articaine hydrochloride (Pogrel, 2007).

Moore and Haas (2010) recommend that the use of 4% articaine or 4% prilocaine for the mandibular nerve block should generally be avoided. This conservative approach is recommended because there is no scientific indication that either agent (articaine or prilocaine) provides greater anaesthetic efficacy than the current gold standard 2% lidocaine with 1:100,000 epinephrine, for the inferior dental nerve block (IDNB). As always, dentists should carefully assess the risks and benefits of any drug they prescribe or administer (Moore and Haas, 2010).

Garisto and colleagues (2010) obtained reports of paraesthesia involving dental local anaesthetics from the U.S. Food and Drug Administration Adverse Event Reporting System; the period they looked at spanned from November 1997 through to August 2008. They used analysis to compare expected frequencies, on the basis of U.S. local anaesthetic sales data, with observed reports of oral paraesthesia. The obtained data suggested that paraesthesia occur more commonly after the use of 4% local anaesthetic formulations.

In general, during any LA administration, the dentist should have knowledge and understanding of the adverse effects and safety considerations associated with that LA. Furthermore, dentists should consider the results of these studies when assessing the risks and benefits of using local anaesthetics for mandibular block anaesthesia.

Although there may be controversy regarding its safety and advantages in comparison to other local anaesthetics, there is no conclusive evidence demonstrating neurotoxicity or significantly superior anaesthetic properties of articaine for dental procedures.

#### **1.2.6.5 Ophthalmologic complications**

According to Boynes et al. (2010), Characteristic ophthalmologic complications after intraoral local anaesthesia include; diplopia (double vision), ptosis (drooping of upper eyelid), mydriasis (dilation of pupil), ophthalmoplegia (paralysis of all muscles responsible for eye movements) and amaurosis (loss of sight). However, these symptoms are most often attributed to the anaesthetic solution reaching the orbit or nearby structures. The ophthalmologic complications in conjunction with intraoral local anaesthesia have an immediate to short onset, and disappear as the anaesthesia subsides (Boynes et al., 2010). The study by Aguado-Gil and colleagues (2011) concluded that, Ophthalmological complications are seldom a problem, and diplopia being the most common among them. Almost all of the papers studying the ophthalmologic complications suggested an intravascular injection of the anaesthetic solutions in the cases of IDNB or anaesthesia of the superior posterior alveolar nerve (Aguado-Gil et al., 2011)

#### **1.2.6.6 Drug interaction**

The systemic effects produced by combinations of local anaesthetics follow principles of summation. When adhering to dosage limits, guidelines for various agents should be regarded as additive. It is also essential that local anaesthetics be

respected as CNS depressants, and they potentiate any respiratory depression associated with sedatives and opioids (Becker, 2011).

In addition, practitioners must be alert to drug interactions when using local anaesthetics containing the vasoconstrictors epinephrine and levonordefrin. Earlier reports suggest that vasoconstrictors should be used with caution in patients taking nonselective  $\beta$  -adrenoreceptor blockers, tricyclic antidepressants, cocaine, and  $\alpha$ -adrenergic blockers (Finder and Moore, 2002).

### **1.2.7 Vasopressors**

Two main catecholamines have been used in LA formulations over the years: epinephrine and norepinephrine; epinephrine is far more widely used. These two compounds differ in the effect they have on the adrenergic system and on the effectiveness and toxicities of the LAs themselves.

Epinephrine and levonordefrin are the two catecholamine vasoconstrictors formulated with local anaesthetic agents in dental cartridges. The use of a vasoconstrictor can improve the safety of the formulation by slowing the systemic absorption of the local anaesthetic and decreasing the peak blood levels of the anaesthetic, thus reducing the systemic toxicity of the anaesthetic agent.

A low concentration of epinephrine 1:400,000 has shown to be sufficient for adequate pain control and haemostasis, while minimising the potential side effects caused by epinephrine. Therefore, minor effects on the cardiovascular system as well as a reduced intensity and duration of soft tissue anaesthesia, compared with other local anaesthetics, can be expected (Elad *et al.*, 2008). There is minimal stimulation of the cardiovascular system after sub mucosal injection of 1 or 2 cartridges of anaesthetic containing epinephrine or levonordefrin. However, when

excessive amounts of these adrenergic vasoconstrictors are administered, or when the agents are inadvertently administered intravascularly, cardiovascular stimulation, with clinically significant increases in blood pressure and heart rate, can occur (Moore and Hersh, 2010).

Although vasoconstrictors are rarely contraindicated, the general use of vasoconstrictor free local anaesthetic agents is considered to be controversial (Moore and Hersh, 2010).

#### **1.2.7.1 Articaine and epinephrine**

According to a study by Winther and Nathalang (1972), when articaine is used without adrenaline, it does not meet the requirements for local analgesia in dentistry. When 2% articaine is compared with 3% Mepivacaine, both without epinephrine, the difference in duration and frequency is statistically significant in favour of Mepivacaine. However, this difference is not significant when the comparison is made with 4% articaine.

Kämmerer *et al.* (2014) investigated 4% articaine in five different concentrations of epinephrine (1:100,000, 1:200,000, 1:300,000, 1:400,000 and without epinephrine), in buccal infiltration (BI) of right maxillary central incisor. The finding of the study showed that when using the epinephrine-free agent, time to recede was significantly shorter. Upon decreasing epinephrine concentration, the duration of pulpal anaesthesia and total anaesthetic efficacy declined. The shortest time of anaesthesia, the prolonged onset and lowest anaesthetic efficacy were seen for the solution without epinephrine. Additionally, soft tissue anaesthesia was significantly shorter without epinephrine. However, the differences of the local anaesthetic onsets between groups were not statistically significant. No association was found between

the local anaesthetic drug and cardiovascular parameters. Furthermore, with regard to the cardiovascular parameters, according to Pereira *et al.* (2013), there was a minimal incidence of significant differences throughout the clinical procedure during intraosseous injections of 4% articaine with 1:100,000 epinephrine or 4% articaine with 1:200,000 epinephrine. However, both solutions provided high anaesthetic efficacy (96.8% and 93.1% respectively).

Kämmerer *et al.* (2012) reported that when 4% articaine without epinephrine was used for dental extractions in the mandibular teeth after inferior alveolar nerve block anaesthesia, it was sufficient for dental extractions and showed less postoperative discomfort due to the shorter duration of anaesthesia compared to when 4% articaine with epinephrine (1:100,000) was used.

These results are in accordance with an earlier study by Daubländer (2012), who evaluated 4% articaine 1:400,000 epinephrine formulation in different injection sites and found a high success rate of efficacy in short dental procedures.

Santos (2007) reported that an epinephrine concentration of 1:100,000 or 1:200,000 in 4% articaine solution does not affect the clinical efficacy of this local anaesthetic. Furthermore, it is possible to successfully use the 4% articaine formulation with a lower concentration of epinephrine (1:200,000 or 5µg/mL) for lower third molar extraction with or without bone removal. These results are in accordance with the study by Tofoli *et al.* (2003).

Clinical studies (Costa *et al.*, 2005; Moore *et al.*, 2006; McEntire *et al.*, 2011; Pereira *et al.*, 2013) have demonstrated that, when used as a dental anaesthetic for maxillary infiltration and inferior alveolar nerve block anaesthesia. The 4 % articaine with 1:200,000 epinephrine formulations provide a comparable level of

pulpal anaesthesia to 1:100,000 epinephrine formulation, and both solutions produce a high success level of pulpal anaesthesia.

Furthermore, Costa and colleagues (2005), observed in their study that the 1:100,000 epinephrine formulation appears to have a slightly shorter onset and slightly longer duration of anaesthesia; however, these small differences in onset and duration characteristics were statistically and clinically insignificant. Kanaa *et al.* (2012) had reported in their findings that, lidocaine buccal infiltration was significantly more uncomfortable than articaine buccal infiltration. In addition, they have assumed that the difference might be the result of different epinephrine concentrations, even though this conclusion was not definite.

The overall result for anaesthetic success based upon meta-analysis by Paxton and colleagues (2009) showed no evidence that articaine hydrochloride with epinephrine 1:100,000 demonstrated statistically superior efficacy relative to epinephrine 1:200,000.

### **1.2.8 Local anaesthetic agents**

The development of safe and effective local anaesthetic agents has been possibly the most important advancement in dental science to occur in the last century. The agents currently available in dentistry are extremely safe and fulfil most of the characteristics of an ideal local anaesthetic (Moore and Hersh, 2010).

These local anaesthetic agents can be administered with minimal tissue irritation and with little likelihood of inducing allergic reactions. A variety of agents are available that provide rapid onset and adequate duration of surgical anaesthesia. They differ in potency and several pharmacokinetic parameters that account for differences in the

onset and duration of anaesthesia. The agents provide anaesthesia that is completely reversible, and systemic toxicity is rarely reported.

Selection of a particular agent must take into account the duration of the procedure planned and issues regarding vasopressor concentrations. Practitioners prefer the amide local anaesthetic agents to the ester agents (i.e. procaine and propoxycaine) because amides produce profound surgical anaesthesia more rapidly and reliably, with fewer sensitising reactions than ester anaesthetics. The availability of various formulations of lidocaine, mepivacaine, prilocaine, articaine and bupivacaine, permits a practitioner to select agents that can meet specific treatment requirements. The amide local anaesthetic agents currently available in dentistry are extremely safe and effective (Moore and Hersh, 2010). Figure 1-2 shows the chronological development of local anaesthetics.

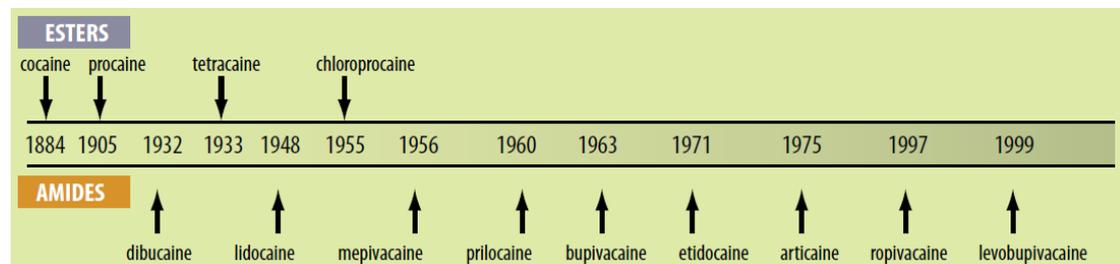


Figure 1-2: Chronological development of local anaesthetics

From: Malamed SF. *Handbook of Local Anaesthesia*, 6th edition, 2013, CV Mosby, St. Louis.

### 1.2.8.1 Lidocaine hydrochloride

Upon its clinical availability in 1948, lidocaine hydrochloride became the first marketed amide local anaesthetic. At that time, it replaced the ester-type local anaesthetic, procaine, as the drug of choice for local anaesthetics in dentistry. Lidocaine hydrochloride has maintained its status as the most widely used local anaesthetic in dentistry since its introduction. Proven efficacy, low allergenicity and

minimal toxicity through clinical use and research, have confirmed the value and safety of this drug. Thus, it became labelled the “gold standard” to which all new local anaesthetics are compared (Malamed, 2013). Lidocaine is formulated in cartridges as 2% lidocaine with 1:50,000 epinephrine, 2% lidocaine with 1:100,000 epinephrine, and 2% lidocaine plain. The 2% lidocaine with 1:100,000 epinephrine formulation is considered the gold standard when evaluating the efficacy and safety of newer anaesthetics (Moore and Hersh, 2010).

#### **1.2.8.2 Mepivacaine hydrochloride**

Mepivacaine has an important role in dental anaesthesia because it has minimal vasodilation properties and can therefore provide profound local anaesthesia without being formulated with a vasoconstrictor such as epinephrine or levonordefrin. The availability of a 3% mepivacaine formulation without a vasoconstrictor is a valuable addition to a dentist’s armamentarium. It is available in dental cartridges as 3% mepivacaine plain or 2% mepivacaine with 1:20,000 levonordefrin (Moore and Hersh, 2010).

Mepivacaine plain is often reported to have a shorter duration of soft tissue anaesthesia, making it potentially useful in paediatric dentistry in which children are known to chew their lips after dental procedures. However, one investigation suggests that although pulpal durations of mepivacaine plain are shorter than that of 2% lidocaine with epinephrine, the duration of soft tissue anaesthesia for mepivacaine and lidocaine with epinephrine are nearly identical (Moore and Hersh, 2010).

### **1.2.8.3 Prilocaine hydrochloride**

Prilocaine, like mepivacaine, is not a potent vasodilator and can provide excellent oral anaesthesia with or without a vasoconstrictor. It is available in preparations of 4% prilocaine plain and 4% prilocaine with 1:200,000 epinephrine. The formulation containing epinephrine has anaesthetic characteristics similar to 2% lidocaine with 1:100,000 epinephrine, with the 4% prilocaine plain formulation providing a slightly shorter duration of surgical anaesthesia. Prilocaine plain solution in dental cartridges has a somewhat less acidic pH. One of prilocaine's metabolic products has been associated with the development of Methemoglobinemia (Moore and Hersh, 2010).

### **1.2.8.4 Bupivacaine hydrochloride**

In the last few decades, the long-acting amide local anaesthetic bupivacaine has also found a place in dentists' armamentarium. This long-acting agent plays a valuable role in the overall management of surgical postoperative pain associated with dental care. The molecular structure of bupivacaine (1-butyl-2', 6'-pipecoloxylidide) is identical to mepivacaine except for a butyl (4 carbon) substitution of the methyl (1 carbon) group at the amino terminus of the molecule. The addition of a butyl group to the chemical structures of mepivacaine provides enhanced lipid solubility and protein binding properties. Although bupivacaine may provide adequate surgical anaesthesia, it is most useful for postoperative pain management. Clinical trials have shown that bupivacaine, having an elevated pKa of 8.1, has a slightly longer onset time than conventional amide anaesthetics. Onset times and profundity are optimised when preparations of bupivacaine include epinephrine (Moore and Hersh, 2010).

#### **1.2.8.5 Articaine hydrochloride**

Articaine was first clinically investigated in 1974 (Van Oss *et al.*, 1989). It was originally synthesised and prepared by Rusching and colleagues as Carticaine in 1969 and entered clinical practice in Germany in 1976. The name was changed to articaine in 1984 and was released in Canada. It entered the United Kingdom in 1998 and the United States in 2000, under the name of Septocaine (Septodont) (Malamed *et al.*, 2001).

Currently, articaine is available as a 4% solution containing 1:100,000, 1:200,000, 1:300,000, 1:400,000 or without epinephrine (Kämmerer, 2014). Articaine does not contain the benzene ring, instead it contains a thiophene group, which increases its liposolubility (allows the molecule to diffuse more readily through the nerve membrane), and is the only widely used amide local anaesthetic that also contains an ester group. The ester group enables articaine to undergo biotransformation in the plasma (hydrolysis by plasma esterase) as well as in the liver (by hepatic microsomal enzymes) (Melamed *et al.*, 2001). Over 90% of articaine is metabolised by plasma esterases, with the remainder being broken down in the liver. The solution's plasma half-life can be as low as 20 minutes and is excreted mainly by the kidneys (Oertel *et al.*, 1997).

As articaine is absorbed from the injection site into the systemic circulation, it is rapidly inactivated via hydrolysis of the ester side chain to articainic acid. Consequently, articaine has the shortest metabolic half-life (estimated to be between 27 to 42 minutes) of the anaesthetics available in dentistry. Articaine is lipid soluble, highly protein-bound (94%), and has a dissociation constant (pKa) of 7.8. Articaine has an intermediate-potency; it is a short-acting local anaesthetic with a fast onset of action (Oertel *et al.*, 1997).

Articaine does not seem to have a greater allergenicity than other available amide anaesthetic agents, probably because the ester metabolite is not the allergen. Reports of toxicity reactions after the use of articaine for dental anaesthesia are extremely rare (Moore and Hersh, 2010). The rapid inactivation of articaine by plasma esterases may explain the apparent lack of overdose reactions reported after its administration (Oertel *et al.*, 1997). Furthermore, from their review of the dental literature, Yapp *et al.* (2011) concluded that articaine is a safe and effective local anaesthetic drug to use in all aspects of clinical dentistry for patients of all ages, with properties comparable to other common local anaesthetic agents.

### **1.2.9 Reversal of local anaesthesia**

Recently there has been a renewed interest in the reversal of local anaesthesia. This is achieved by injecting the alpha-adrenergic antagonist phentolamine mesylate at the end of treatment, to oppose the effects of the vasoconstrictor (adrenaline) in the original local anaesthetic (Becker and Reed, 2012). The local injection of phentolamine has been shown to significantly shorten the time taken for a return to the normal sensation of the lip and tongue after dental anaesthesia. In clinical trials, phentolamine was injected in doses of 0.2 to 0.8 mg (0.5 to 2 cartridges), determined by patient age and volume of local anaesthetic administered. As a result median lip recovery times were reduced by 75 to 85 minutes (Yagiela, 2011).

It should be mentioned that a local anaesthetic reversal agent has been introduced that effectively reverses the influence of vasopressors on submucosal vessels (Becker and Reed, 2012). Phentolamine (OraVerse) is an alpha adrenergic receptor blocker, formulated in dental cartridges; manufactured in 1.7 mL dental cartridges, each of which contains 0.4 mg active drug. When it is injected into the identical site

where anaesthetic was administered, causing smooth muscle relaxation, vessels dilate, leading to enhanced absorption of local anaesthetic, which shortens the duration of anaesthesia (Malamed, 2013; Goswami *et al.*, 2014) However, it will likely receive limited use because of its expense and the fact that sustained anaesthesia is generally a benefit during the postoperative period, as it provides a source of pain management. However, it may be useful in the management of small children or patients with special needs who may be prone to self-inflicted injury while tissues remain numb (Malamed, 2013).

A consideration may also be given to the fragile diabetic or elderly patient for whom adequate nutritional intake may be hindered by prolonged numbness. Reversal may also be offered to the busy patient who must return to work and communicate effectively (Becker and Reed, 2012).

### **1.3 ANAESTHETIC EFFICACY**

The assessment of anaesthetic successfulness can be assessed subjectively by evaluating the patient response and behaviour. The first sign after anaesthetising the tooth is numbness of the area around the tooth, lip and/or tongue numbness in the case of Inferior Dental Nerve Block (IDNB). According to Malamed (2013), the success of mandibular block anaesthesia has traditionally been determined by the presence of a feeling of lip numbness. This can be assessed clinically by lack of mucosal responsiveness to a sharp instrument, however, a number of studies have now clarified that successful pulpal anaesthesia is not guaranteed when signs of soft tissue anaesthesia are present (Certosimo and Archer, 1996; Hannan *et al.*, 1999).

Using a more objective means of determining pulpal anaesthesia is important to assist the clinician and researchers in improving the clarity of clinical and research outcomes in the area of local anaesthesia in dentistry.

Different methods have been utilised to determine pulpal anaesthetic success. The electric pulp tester (EPT) is one of the objective means of measuring pulpal anaesthesia and has long been used to evaluate the sensibility of the dental pulp (Cooley *et al.*, 1984). This device stimulates A-delta fibers, normally indicating neural transmission and presence of innervation. Bjorn (1946) was the first to correlate a negative response to maximum output of electrical pulp stimulation to painless dental treatment. According to Evans *et al.* (2008) and Corbett *et al.* (2008), successful anaesthesia is commonly defined as the percentage of subjects who achieve two consecutive “80” readings on the EPT, within 15 minutes of anaesthesia administration, and continuously sustain this lack of responsiveness for some defined period. This is also in accordance with earlier studies by Dreve *et al.* (1987) and Certosimo and Archer (1996).

Currently, most investigations interested in determining pulpal anaesthesia utilise the EPT method. Even though the evaluation still depends on a patient’s response, the behaviour of the patient and the responses given by control teeth also require careful consideration (Lin and Chandler, 2008).

Clinical studies of various designs have investigated the efficacy of local anaesthetic solutions, especially lidocaine and articaine (with different concentrations) in clinical dentistry. Muschaweck and Rippel (1974) conducted an early investigation into the pharmacology and toxicology of articaine (0.05%–0.5% solutions) in animal experiments, with lidocaine (0.05%–0.5% solutions) as a comparison. This investigation found that when compared with lidocaine, articaine had 1.5 times higher anaesthetic activity in conduction anaesthesia infiltration, “markedly superior” efficacy in infiltration anaesthesia, equivalent efficacy in topical anaesthesia, and similar low toxicity to local tissues.

The first clinical trial in dentistry was conducted by Winther and Nathalang (1972) in Denmark; they tested the efficacy of articaine hydrochloride. Comparisons were made of 2% and 4% articaine hydrochloride, 2% lidocaine hydrochloride and 3% mepivacaine, all with and without epinephrine. The results showed that articaine hydrochloride in both concentrations with epinephrine was significantly superior to lidocaine and mepivacaine with respect to frequency, duration and extent of analgesia.

Malamed *et al.* (2000a) conducted three identical single-dose, randomised, double-blind, parallel group, active-controlled, multicentre trials, to compare the anaesthetic efficacy of 4 % articaine with epinephrine 1:100,000, with that of 2 % lidocaine with epinephrine 1:100,000, during simple and complex dental procedures. The primary efficacy parameter was the subjective evaluation of pain during the dental procedure, rated by both the subject and the investigators using a visual analogue scale, or VAS. The results indicate that there were no significant differences in VAS scores between subjects receiving articaine and those receiving lidocaine, either for subjects or for investigator ratings. Even though this study has some limitations, it was the study which granted the approval of articaine for sale and distribution as a 4% solution with epinephrine 1:100,000 under the brand name Septocaine in the USA.

According to Paxton and colleagues (2008), despite the variability of outcomes in the literature, meta-analysis showed a significant difference between articaine and lidocaine, suggesting an advantage, at least in some clinical situations, to the use of articaine. These results are supported by two further meta-analysis studies (Katyal, 2010; Brandt *et al.*, 2011). The findings of Katyal's (2010) study indicated that articaine is more effective than lignocaine in providing anaesthetic success in the first molar region, for routine dental procedures. Brandt and colleagues' (2011)

study pointed out that articaine has an advantage over lidocaine in respect of achieving pulpal anaesthetic success. In addition, when comparing the injection type, infiltration anaesthesia with articaine is superior to lidocaine, however, there is weak evidence for such differences in mandibular block anaesthesia.

Different studies have investigated the efficacy of articaine compared to lidocaine, and there was no difference found between 4% articaine and 2% lidocaine in healthy or inflamed pulp after IDNB injection (Malamed *et al.*, 2000a; Claffey *et al.*, 2004; Mikesell *et al.*, 2005; Tortamano *et al.*, 2009). Alternatively, pulpal anaesthesia was achieved in up to 92% of patients with uninflamed pulp when local anaesthetic solutions were administered by infiltration alone (Kanaa *et al.*, 2006; Meechan *et al.*, 2006; Robertson *et al.*, 2007; Jung *et al.*, 2008).

Furthermore, several investigations have shown that 4% articaine is effective in obtaining anaesthesia in maxillary and mandibular teeth (Malamed *et al.*, 2000a; Costa *et al.*, 2005; Uckan *et al.*, 2006; Robertson *et al.*, 2007; Evans *et al.*, 2008)

### **1.3.1 Mandibular anaesthesia**

Traditionally, local anaesthesia in the mandible has been delivered by means of one of the inferior alveolar nerve block techniques for example the Halsted, Gow-Gates or Akinosi-Vazirani methods (Moore and Hersh, 2010). In addition, infiltration techniques as well as periodontal ligament injections are different methods of delivering mandibular local anaesthetics. The periodontal ligament injection has been used for obtaining primary anaesthesia for one or two teeth or as a supplement to infiltration or dental nerve block techniques. This technique has an advantage of providing pulpal anaesthesia for 30 to 45 minutes without prolonged soft tissue anaesthesia. Nevertheless, its use should be avoided in primary teeth with a

developing permanent tooth bud as there have been reports of enamel hypoplasia in permanent teeth following periodontal ligament injection.

The following sections will discuss this in more details.

### **1.3.2 Inferior Dental Nerve Block**

Jung and colleagues (2008) conducted a crossover design study that compared the anaesthetic efficacy of IDNB to that of BI, in mandibular first molars using 4% articaine with epinephrine 1:100,000. The results of the study showed that 54% of the BI and 43% of the inferior alveolar nerve block were successful; the difference was not significant. The onset of pulpal anaesthesia was significantly faster with BI. This study concludes that BI with 4% articaine can be a useful alternative to an IDNB in achieving pulpal anaesthesia of mandibular first molars, with the advantage of having a faster onset. However, this study has some limitations.

Mikesell *et al.* (2005) carried out a prospective randomised double-blind crossover study on a healthy adult population with mean age of 28 years. They compared the degree of pulpal anaesthesia in IDNB using 4% articaine and 2% lidocaine, both with 1:100,000 epinephrine. The study found that there were no significant differences in terms of efficacy and onset. In addition, both local anaesthetics showed similar postoperative pain.

### **1.3.3 Buccal Infiltration**

There is increasing clinical research literature supporting the claim that articaine has superior diffusion properties and that anaesthesia can be prompted after BI in the mandible. However, the thicker cortical plate of the mandible is considered a barrier to such diffusion in the lower jaw.

Robertson and colleagues conducted a prospective, randomised, double-blind, cross over study to compare the degree of pulpal anaesthesia achieved by means of mandibular first molar BI using 4% articaine with 1:100,000 and 2% lidocaine with 1:80,000 epinephrine. The results indicated that 4% articaine was significantly better than 2% lidocaine in achieving pulpal anaesthesia of mandibular teeth; the success rate was higher in the first molar and premolar areas compared to the second molar. However, the pulpal anaesthesia in both local anaesthetics declined slowly over 60 minutes. When articaine formulation was used, successful pulpal anaesthesia ranged from 75- 92% compared to 45- 67% when lidocaine formulation was used (Robertson *et al.*, 2007).

The pulpal anaesthetic characteristics of six commonly used local anaesthetic formulations, when used for mandibular infiltration anaesthetic injections, were investigated in a randomised clinical trial. Using 0.9 mL of each solution, 2% lidocaine with 1:100,000 epinephrine (used as a standard comparator), 4% articaine with 1:100,000 epinephrine, 4% articaine with 1:200,000 epinephrine, 4% prilocaine with 1:200,000 epinephrine, 3% bupivacaine with 1:200,000 epinephrine, and 3% Mepivacaine without vasoconstrictor. When comparing anaesthetic formulations, the 4% articaine provided a greater level of pulpal anaesthesia after mandibular infiltration, as measured by means of EPT and the 3% bupivacaine provided the lowest (Abdulwahab *et al.*, 2009).

A prospective, randomised crossover study was carried out by Thakare *et al.* (2014). Patients were categorised into two groups; 4% articaine and 0.5% bupivacaine. A fixed volume of 1.4 mL of 4% articaine or 0.5% bupivacaine was infiltrated in the buccal vestibule (local infiltration) for extraction. The results showed that 4% articaine seemed to have better potency and efficacy in terms of onset of action and lower pain scores, with minimal pain or discomfort when compared to the

bupivacaine group. However, bupivacaine provides significantly longer duration of postoperative analgesia when compared with articaine.

The results of the study by Kanaa *et al.* (2006) (double-masked, randomised, controlled trial in healthy adult participants) showed that infiltration in the buccal sulcus opposite the mandibular permanent first molar could provide pulpal anaesthesia (as determined by no response to maximum stimulation from an EPT). The success rate of articaine was significantly higher (64%) when compared with lidocaine with a 39% success rate (Kanaa *et al.*, 2006).

In the anterior mandible, infiltration anaesthesia is considered the primary method of achieving pulpal anaesthesia. Different studies have evaluated various types of local anaesthetics including lidocaine and articaine, and success was reported to be achieved between 43% and 50% of the time (Yonchak *et al.*, 2001; Meechan and Ledvinka, 2002). In Brazil, Batista da Silva *et al.* (2010) carried out a prospective, randomised, double-blind, crossover study using incisive/mental nerve block to compare the anaesthetic efficacy of articaine and lidocaine in obtaining pulpal anaesthesia of mandibular premolars, canines and lateral incisors. In this instance, pulpal anaesthesia was defined as no subject response to two consecutive 80 readings. The conclusion was that articaine provides higher anaesthetic success (72% first premolar and 80% second premolar) than lidocaine (50% first premolar and 70% second premolar) even when used in small volume (in this study they used 0.6 mL with 1:100,000 epinephrine). However, this study was conducted on healthy volunteers and articaine is not recommended for long procedures. The anaesthetics duration was only 10 minutes with lidocaine and 20 minutes with articaine.

Nuzum *et al.* (2010) looked at the pulpal anaesthesia obtained with a labial infiltration compared to a combination of labial and lingual infiltration. Their study

used 4% articaine with 1:100,000 epinephrine in the mandibular lateral incisors. The findings of this study showed that the labial plus lingual infiltration significantly improved the success rate to 98% compared with a labial infiltration of the same articaine formulation, which provided a 76% success rate.

#### **1.3.4 Articaine for mandibular infiltration**

Meechan *et al.* (2011) conducted a randomised, controlled clinical trial to compare buccal and lingual infiltration for mandibular teeth using 4% articaine. Their results showed that the BI at the first permanent molar is more effective in obtaining anaesthesia for first molar and premolar teeth than lingual infiltration at the same region. It was suggested that the greater success in the BI compared with the lingual infiltration could be due to the mechanism of action of BI in the mandibular first molar region, which may involve diffusion through the mental foramen Corbett *et al.* (2008). The same results were obtained in Dressman and colleagues' study (2013), where the repeat infiltration at 20 minutes significantly increased the success rate (92%–94%) and the duration of pulpal anaesthesia for the premolars. On the other hand, the success rate ranged from 19% to 59% (Dressman *et al.*, 2013).

When comparing the local anaesthetic volumes, the results of a study by Martin and colleagues (2011) revealed that the anaesthetic efficacy of 3.6 ml 4% articaine with 1:100,000 epinephrine is better than 1.8 ml of the same anaesthetic solution in a primary mandibular BI of the first molar, with a statistically higher success rate (70% vs 50%) (Martin *et al.*, 2011). Conversely, when 4% articaine was used as supplementary BI with 1.8 and 3.6 ml volumes, the difference between the success rates of the two volumes was not statistically significant (62% and 64%, respectively). However, this study was carried out in patients with symptomatic

irreversible pulpitis and the initial injection was an IDNB of 4% articaine, which gave an overall success rate of 37% (Singla *et al.*, 2014).

### **1.3.5 Maxillary infiltration**

Infiltration anaesthesia is the technique of choice in the upper jaw. It provides pulpal anaesthesia by diffusion into the cancellous bone via the thin cortical plate of the maxillary alveolus.

Articaine has been reported to provide improved local anaesthetic efficacy (Schertzer and Malamed, 2000). Many studies and clinical trials have evaluated articaine and found it to be a safe and effective local anaesthetic agent. However, most of these trials did not show a superiority of articaine over lidocaine when used as maxillary infiltration to provide pulpal anaesthesia. Pulpal anaesthetic success has ranged from 64% to 100% (Donaldson *et al.*, 1987; Vähätalo *et al.*, 1993).

However, a study by Costa *et al.* (2005) has reported that the use of articaine resulted in a longer duration of anaesthesia in maxillary infiltrations than lidocaine. A similar conclusion was established in another randomised, double-blind, clinical study which demonstrated a higher rate anaesthetic success for articaine when compared with lidocaine in maxillary infiltration of the lateral incisor (88% success rate), but not the first molar lateral incisor (78% success rate) (Evans *et al.*, 2008).

When 4% articaine was used as buccal plus palatal injection to anaesthetise healthy upper canines, it showed no statistical difference when compared with 2% lidocaine using the same technique. However, this result was based on a small sample size (20 volunteers) and according to the author, pulpal anaesthesia may have reached statistical significance if a higher number of volunteers had been used (Oliveira *et al.*, 2004).

### **1.3.6 Studies on irreversible pulpitis**

Buccal infiltration with 4% articaine with 1:100,000 epinephrine, and 2% lidocaine with 1:80,000 epinephrine, produced similar levels of successful pulpal anaesthesia. Both anaesthetic solutions produced similar onset times of successful pulpal anaesthesia, and similar levels of pain-free treatment in patients attending with irreversible pulpitis in the maxilla. Pain-free treatment was completed more often in the tooth extraction group than in the pulp extirpation group; 2% lidocaine with 1:80,000 epinephrine was more uncomfortable than 4% articaine with 1:100,000 epinephrine when given as a maxillary BI. Furthermore, the percentages of pain-free treatment were similar in anterior, premolar and molar teeth (Kanaa *et al.*, 2012). Rosenberg *et al.* (2007) compared the efficacy of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine, as a supplemental anaesthetic in patients with irreversible pulpitis. The study found that articaine and lidocaine were equally effective in the reduction of pain on a visual analogue scale. Conversely, a study by Srinivasan *et al.* (2009) has concluded that 4% articaine with 1:100,000 epinephrine is more effective (with a statistically significant difference) than 2% lidocaine with 1:100,000 epinephrine, in producing pulpal anaesthesia when used as BI in maxillary posterior teeth with irreversible pulpitis. The anaesthetic success with articaine was 100% in both molar and premolar teeth compared to lidocaine success rates of 80% in premolars and 30% in molars.

The conclusion from a recent study by Rogers *et al.* (2014) reported that for mandibular molars with irreversible pulpitis, the IDNB success rate after one cartridge of 4% articaine with 1:100,000 epinephrine, was comparable to previous reports for 2% lidocaine IDNB. A supplemental BI of 4% articaine was significantly more effective (62%) than 2% lidocaine (37%) and the superiority of articaine was most evident in the second molars. The success rate of lidocaine dropped from 53%

in first molars to only 18% in second molars, with this difference classified as significant.

These results are in accordance with other studies, which look at irreversible pulpitis and provide similar results concerning success rate. A study by Matthews *et al.*, (2009) concluded that when the IDNB fails to provide profound pulpal anaesthesia (only 33% success rate), the supplemental BI injection of 4% articaine with 1:100,000 epinephrine would be successful 58% of the time for the mandibular posterior teeth, in patients presenting with irreversible pulpitis. In this study, the success rate for second molars was 48%, which was less than that for first molars, at 58%, and for the premolars, which produced a success rate of 100%. However, it is important to consider the small sample size in this study (Matthew *et al.*, 2009).

Another study reported that in patients with irreversible pulpitis, supplemental articaine infiltration along with an IANB (with 2% lidocaine) injection had significantly higher success rate than IDNB alone (success rate for IDNB alone 33%, with lidocaine 47%, with articaine 67%). However, none of the techniques provided acceptable success rates (Aggarwal *et al.*, 2009). Similar results were reported from another study by the same authors. The study was performed on mandibular molars with irreversible pulpitis; the comparison was between supplementary infiltration of articaine, and articaine plus ketorolac tromethamine; the success rates were 54% and 62% respectively (Aggarwal *et al.*, 2011).

In a recent study by Poorni *et al.* (2011) on mandibular molars with irreversible pulpitis, the efficacy of an IDNB with articaine or lidocaine showed similar success rates compared with a BI with articaine that had not been supplemented with an IDNB. Although BI and IDNB of 4% articaine were equally effective, BI can be

considered a viable alternative in IDNB for pulpal anaesthesia in mandibular molars with irreversible pulpitis.

A comparative study of 40 patients with irreversible pulpitis has been carried out which investigates articaine and lidocaine when used as IDNB. When comparing pulpal anaesthesia success as measured with the pulp tester, the lidocaine solution had a higher success rate (70%) than the articaine solution (65%). For patients reporting none or mild pain during pulpectomy, the success rate of the articaine solution (65%) was higher than that of the lidocaine solution (45%). Yet, none of the observed differences between articaine and lidocaine were statistically significant (Tortamano *et al.*, 2009).

Fan *et al.* (2009) compared the anaesthetic efficacy of IDNB using 1.7 mL of 4% Articaine with 1:100,000 epinephrine plus BI, and IDNB plus periodontal ligament (PDL) articaine injections (0.4 mL 4% articaine with 1:100,000 epinephrine for both techniques) in patients with irreversible pulpitis in the mandibular first molar. According to the VAS scores, all patients experienced no or mild pain with BI and PDL injections after the application of IDNB. Both injection combinations resulted in high anaesthetic success in patients with irreversible pulpitis in the mandibular first molar. Anaesthetic success occurred in 81.48% for IDNB plus BI (IDNB/BI) compared with 83.33% for IDNB plus PDL injection (IDNB/PDL injection). None of the observed differences between the two groups was significant (Fan *et al.*, 2009).

### **1.3.7 Articaine as a supplemental injection**

Several studies have looked at the use of mandibular infiltration as a means of supplementing inferior alveolar nerve block injections. Some investigations were

conducted in normal uninflamed teeth. Foster *et al.* (2007), had shown that adding a buccal or lingual infiltration of 1.8 mL of 2% lidocaine with 1:100,000 epinephrine to an IDNB did not significantly increase anaesthetic success in normal uninflamed mandibular posterior teeth. Haase *et al.* (2008) used asymptomatic subjects and added an infiltration of either articaine or lidocaine in mandibular first molars, after an IDNB with 4% articaine 1:100,000 epinephrine; the success rate was statistically higher in articaine, at 88%, compared with 71% in lidocaine.

A number of studies have been carried out in patients with irreversible pulpitis. Dou *et al.* (2013) investigated the effect of supplemental lingual infiltration of mandibular molars following an IDNB plus BI, in patients with irreversible pulpitis. The results showed no statistical difference between the two treatments and the supplemental lingual infiltration success was only 62.5%, compared with 70% for the BI.

Ashraf (2013) compared the anaesthetic success rate of BI injections of articaine and lidocaine when supplemented with an IDNB, in lower molars with irreversible pulpitis. Participants in the study had received the IDNB by using either 2% lidocaine with 1:100,000 epinephrine or 4% articaine with 1:100,000 epinephrine. The success rate after the administration of the infiltration injections after an incomplete IDNB using lidocaine was 29%, whereas for articaine it was 71%. The second molars showed higher success rates than the first molars and no statistical differences were detected in the success rates between the two anaesthetics after the block injections. These results are lower than the values reported by Kanaa *et al.* (2009) who found a 91% success rate for articaine infiltration anaesthesia in posterior mandibular teeth with irreversible pulpitis. However, Ashraf's (2013) results are higher than the values reported by Matthews *et al.* (2009) (58%) and Aggarwal *et al.* (2009) (67%).

Aggarwal *et al.* (2013) had commented on Ashraf's *et al.* (2013) paper and mentioned two key points; the first is that the clinician should consider administering a supplemental buccal infiltration of 4% articaine if an initial IDNB fails. This is important, since the other supplementary methods like intraosseous and intraligamentary injections may require special armamentarium and may have a short duration of action. The second point was there is no significant difference between articaine and lidocaine when used as an initial IDNB agent.

According to Bigby *et al.* (2006), there was an 86% success when the intraosseous injection of 4% articaine was used as a supplemental injection when the IDNB failed to provide profound pulpal anaesthesia in patients diagnosed with irreversible pulpitis of a mandibular tooth.

### **1.3.8 Articaine for teeth extraction and third molar surgeries**

A comparative study was made of the anaesthetic efficacy of 4% articaine versus 2% lidocaine, both with epinephrine 1:100,000, in dental block of the inferior alveolar nerve during the surgical extraction of impacted lower third molars. The results obtained suggest that 4% articaine offers better clinical performance than 2% lidocaine, particularly in terms of latency and duration of the anaesthetic effect. However, no statistically significant differences in anaesthetic efficacy were recorded between the two solutions (Sierra-Rebolledo, 2007). These results are in agreement with Bhagat *et al.* (2014) and Kambalimath and colleagues' study, however, they have reported that articaine showed better cardiac stability (Kambalimath *et al.*, 2013).

The same results as the above studies were observed between the tested anaesthetic solutions for postoperative pain control in third molar surgery (Silva *et al.*, 2012).

When 4% articaine was compared with 0.5% bupivacaine both with 1:200,000 epinephrine, when used in the surgical removal of lower third molars with or without osteotomy, a statistically significant difference was found between the time of onset (articaine:  $1.66 \pm 0.13$  minutes and bupivacaine:  $2.51 \pm 0.21$  minutes). Patients who received bupivacaine experienced a statistically significantly longer period of anaesthesia compared with those who received articaine. There was a statistically significant difference during osteotomy procedures with regard to haemodynamic parameters, especially diastolic pressure and mouth opening at suture removal. However, there was no difference regarding the intraoperative bleeding, heart rate, quality of wound healing, and the need for postoperative analgesics (Gregorio *et al.*, 2008).

Uckan (2006) investigated the efficacy of 4% articaine in the removal of permanent maxillary teeth without palatal injection; there was no statistically difference between permanent maxillary tooth removal with palatal injection (97.5%) and without palatal injection (96.8%). This indicated the possibility of performing the extraction with BI of 2 mL of 4% articaine to the buccal vestibule of the tooth, without the need for a second palatal injection. This finding is in accordance with the studies carried out by Somuri *et al.* (2013) and Grace *et al.* (2008).

#### **1.4 DIFFERENCE BETWEEN INFERIOR DENTAL NERVE BLOCK AND BUCCAL INFILTRATION**

Inferior dental nerve block is the standard method and the most frequent injection technique used for achieving local anaesthesia for restorative and surgical procedures on mandibular molars. Several clinical studies show that IDNB does not always result in successful pulpal anaesthesia. A failure rate ranging between 38%

and 77% has been reported (Rood 1976; Vreeland *et al.*, 1989; Chaney *et al.*, 1991; Cohen *et al.*, 1993; Childers *et al.*, 1996; Claffey *et al.*, 2004; Mikesell *et al.*, 2005). This was noticed especially in patients diagnosed with irreversible pulpitis (Aggarwal *et al.*, 2009; Matthews *et al.*, 2009; Tortamano *et al.*, 2009; Poorni *et al.*, 2011; Aggarwal *et al.*, 2011; Rogers *et al.*, 2014). In addition, a greater incidence of complications such as trismus, haematoma or paraesthesia has been associated with inferior alveolar nerve block as compared to mandibular infiltration. These results indicate that IDNB, even when performed by the most experienced clinician, does not always result in successful pulpal anaesthesia (Meechan *et al.*, 2006).

Meechan (1999) has described the causes that influence a local anaesthetic injection failure and these causes can be classified as:

1) Operator dependent

- Choice of technique and solution: This includes poor technique, administration of insufficient solution or the use of an inappropriate anaesthetic or method of administration.

- Poor technique: As far as conventional methods of local anaesthesia are, concerned poor technique usually relates to mandibular anaesthesia, specifically failed inferior alveolar nerve block injections. Variables such as needle insertion, placement, and applied pressure are involved in this technique.

2) Patient dependent

- Anatomical: accessory nerve supply, variable course of nerve, variation in foramen position, bifid alveolar nerve or bifid mandibular canal.

- Pathological: trismus, infection, inflammation, and previous surgery can all contribute to local anaesthetic failure.

- Psychological: fear, anxiety and apprehension

The use of IDNB has several disadvantages compared with the infiltration technique, especially with young patients and children, these include:

- Technique difficulty, especially with patients with special needs
- The long duration of numbness following dental treatment which allows for more time for self-injury and post-operative trauma such as lip, cheek and tongue biting
- Parents are required to spend more time undertaking close supervision and observing their children

As a result of all of the disadvantages associated with nerve blocks, it can be concluded that any local anaesthetic that would permit the use of infiltration in the mandible would be of great value in dentistry.

Infiltration anaesthesia has been used successfully to restore maxillary teeth but has been avoided in the mandibular molar regions because of denser bone that does not allow adequate dissemination of the anaesthesia. Nevertheless, Meechan *et al.* (2006) suggested that with the proper combination of formulation, technique and site, the efficacy of mandibular infiltration techniques would possibly eliminate the need for the routine use of inferior alveolar block anaesthesia for restorative procedures in the mandible. Abdulwahab *et al.* (2009) considered that the efficacy of anaesthetic delivered via mandibular infiltration is dependent on the local anaesthetic formulation administered. Nevertheless, 4% articaine has been shown to be more effective than 2% lidocaine in obtaining pulpal anaesthesia in the molar and incisor region after BI (Kanaa *et al.*, 2006; Jaber, 2009).

Avoidance of IDNB for restorative dentistry has a number of advantages. The infiltration is perceived as less stressful for both child patient and dentist. It also produces less unwanted soft-tissue anaesthesia for minimally invasive procedures.

In addition, infiltration techniques may be preferred in certain patient groups such as those suffering from haemophilia; IDNB is associated with greater risks for these patients and therefore infiltration techniques will reduce the chances of dangerous haemorrhages. This technique is more effective in the case of disabled children where dental nerve block can be difficult to undertake. This might be due to different reasons including lack of understanding or compliance, poor communication.

BI is safer and easier for patient management and treatment, especially with reluctant children (Dudkiewicz *et al.*, 1987; Corbett *et al.*, 2008).

Infiltration is a relatively simpler technique than other alternatives to mandibular blocks such as intraosseous and intraligamentary injections. Infiltration does not require the specialised equipment needed for intraosseous delivery, is less destructive to the periodontium, and avoids the large bacteraemia that follows intraligamentary injections (Meechan, 1992; Roberts *et al.*, 1997; Corbett *et al.*, 2008).

Furthermore, the use of infiltration techniques means the avoidance of trismus and nonsurgical paraesthesia as a result of damage from the needle to the inferior alveolar or lingual nerves (Harn and Durham, 1990).

Various authors have evaluated the anaesthetic efficacy of BIs with or without a primary IANB (Jung *et al.*, 2008; Aggarwal *et al.*, 2009; Matthews *et al.*, 2009; McEntire *et al.*, 2011; Kanaa *et al.*, 2012 ;Ashraf *et al.*, 2013). Whilst evaluating the efficacy of a primary BI, without an IANB, it has been demonstrated that a primary

BI of 4% articaine results in a higher success rate than BI of 2% lidocaine in asymptomatic molars (Jung *et al.* 2008; McEntire *et al.* 2011; Kanaa *et al.* 2012)

Moreover, articaine benefits from a shorter plasma half-life compared with other amide local anaesthetics. Additionally, infiltrations employ lower doses of local anaesthetics and therefore increase the safety of treatment (Corbett *et al.*, 2008).

## **1.5 PAIN**

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Champion *et al.*, 1998). There are multiple dimensions of pain including sensory pain aspect, like pain intensity, duration and location. In addition, there is impact of pain in aspects of everyday life including physical, social, and emotional aspect, as well as cognitive aspect of pain, which is related to the pain unpleasantness. Even though pain is a multidimensional concept, subjective intensity is most likely the component most often measured in clinical practice and pain management outcomes research (Champion *et al.*, 1998).

The presented results from Corbett and colleagues' study showed that, the discomfort of infiltrating 4% articaine with 1:100,000 epinephrine in the mandibular buccal sulcus, increases with the volume of anaesthetic solution. This is in contrast to data reported after lidocaine infiltration. There was no significant difference noted in injection discomfort between articaine BI (mean VAS 22.4 mm, SD 18.4 mm) and lidocaine IDNB (mean VAS 20.7 mm, SD 17.4 mm) in the study population (27 subjects) (Corbett *et al.*, 2008). In Abdulwahab and colleagues' study, the reported pain at injection was similar for all test anaesthetic formulations as compared with those for the 2% lidocaine. Although there was no statistical difference in pain at

injection, the findings suggest that the bupivacaine injection was the most painful and the prilocaine injection was the least painful (Abdulwahab *et al.*, 2009).

When 4% articaine was used as buccal, and buccal plus lingual infiltration in the lower incisors, there was no significant difference between the two sets; however, the pain rating was higher in the labial injection compared with the lingual one. In addition, there was a significant difference between both sets regarding the post-operative pain, which was greater in the buccal plus lingual infiltration group. In this study, there was no report of paraesthesia (Nuzum *et al.*, 2010). All mean pain ratings were in the mild categories when 4% articaine with 1:100,000 and 1:200,000 epinephrine concentrations were used as BI in the lower first molar. Although there were no significant differences in the pain of injection, there were significant differences between the two anaesthetic volumes for postoperative pain at each postoperative day (McEntire *et al.*, 2011). Kanaa and colleagues observed that 4% articaine BIs were more comfortable than 2% lidocaine infiltration; however, this result was not conclusive (Kanaa *et al.*, 2012).

## **1.6 TIME**

The results presented in Corbett's study provide evidence to support the view that a mandibular infiltration with 4% articaine with epinephrine can be as effective as an inferior alveolar nerve block over the 30-minute study period. The maximum duration of anaesthesia possible in this trial was 28 minutes. Six subjects achieved 28 minutes of continuous anaesthesia after BI and four subjects after buccal plus lingual infiltration. The mean duration of successful pulpal anaesthesia was 21.6 minutes (SD, 7.9 minutes) after buccal and 20.5 minutes (SD, 7.8 minutes) after buccal plus lingual infiltrations. The difference was not significant ( $t$  0.46,  $p$  0.65) (Corbett *et al.*, 2008). Although the trial period was not long enough to evaluate the

duration of anaesthesia, it appeared that pulpal anaesthesia with BI injections began to decline after 20 minutes, whereas it remained constant for 30 minutes with IDNB injections. Therefore, BI injections may not be appropriate for procedures that take longer than 20 minutes (Jung, 2008). In support of this, it has been shown that BI alone would induce anaesthesia for a short period of time (Robertson, 2007).

The results of the studies by several authors (Oliveira *et al.*, 2004; Costa *et al.*, 2005; Haas *et al.*, 2008) suggested that the duration of pulpal anaesthesia also lasts longer with articaine than with lidocaine. However, the duration of pulpal anaesthesia will decline over 60 minutes with either formulation. The time of onset of pulpal anaesthesia averaged 4.4 to 5.4 minutes for the initial infiltrations, with no significant difference between the formulations (Robertson *et al.*, 2007; Corbett *et al.*, 2008; Jung *et al.*, 2008; Pabst *et al.*, 2009; Martin *et al.*, 2011; McEntire *et al.*, 2011).

Using one cartridge of 4% articaine with 1:100,000 epinephrine, produced onset times for the mandibular first molar of 4.2 minutes, 6.6 minutes, 6.5 minutes, 4.5 to 6.2 minutes, and 4.7 minutes, respectively. There was no significant difference in duration of anaesthesia between the two drugs; however, articaine did perform better in this respect.

## **1.7 ANAESTHETIC SAFETY/ADVERSE EVENTS**

Several studies have discussed the safety and efficacy of articaine in adults and children. As early as 1989, Wright and colleagues carried out a retrospective audit in two paediatric clinics, to examine the records of children under 4 years of age. The children were divided into two groups, group 1 consisted of 64 children all of whom had received preoperative sedation, and group 2 which consisted of 147 children who were not sedated, of which 40 children had medical history (cardiovascular

problems, asthma, dermatologic problems, allergies, or following a course of antibiotics at the time of treatment). The outcome of this report showed that articaine was safe for both groups of children. 211 patients received a total of 240 doses of articaine without any reported adverse effects. This finding supports the use of articaine in children under 4 years of age (Wright *et al.*, 1989).

Haas and Lennon's retrospective report of paraesthesia over a 21-year period showed that, the two most commonly reported local anaesthetics when paraesthesia occurred were articaine (49%) and prilocaine, whilst only 5% of cases of paraesthesia were associated with lidocaine (Haas and Lennon, 1995). Another retrospective review of reported paraesthesia from 1999 to 2008, reported that higher concentration solutions such as articaine were associated with significantly greater frequencies of such complications (Gaffen and Haas, 2009). Hillerup and Jensen reported that 54% of the nerve injuries were associated with the use of articaine. The authors concluded that "during the two-year period mentioned, articaine produced a more than 20-fold higher incidence of injection injury when applied for mandibular block anaesthesia" (Hillerup and Jensen, 2006). These findings, however, could not be confirmed.

In a study by Pogrel (2007), he demonstrated that paraesthesia were not significantly more likely when articaine hydrochloride was administered. The same conclusion was made by Malamed and colleagues, who stated that, all the reported adverse events were mild to moderate except for one case of infection and one case of mouth ulceration, each of which was rated as severe in intensity. Both events occurred in the articaine group in male patients, and the only adverse event that occurred in the children group was an incidence of accidental lip injury (Malamed *et al.*, 2000a). Malamed stated, "There is absolutely no scientific evidence available to support the claim that articaine is associated with a greater incidence of paraesthesia than other

local anaesthetics” (Malamed, 2007). This is in accordance with the results of the Meta-analysis by Katyal (2010).

Adewumi *et al.* (2008) conducted a prospective study based on follow-up phone call questionnaires. They were observing the adverse events associated with using 4% articaine in children aged 4-14 who received dental treatment with different complexity. The follow-up time was three hours, five hours, 24 hours and 48 hours postoperative. The authors found that, the reported incidence of numbness was 40% after 3 hours and 11% after 5 hours. No reports of paraesthesia were observed at 24 and 48 hours, though it is important to bear in mind that approximately 25% of the data on paraesthesia at 24 and 48 hours was missing. Similar findings were reported in Ram and Amir’s study; parents were instructed to ask the child and to record the time the feeling of numbness disappeared. Parents were asked by phone after one, two, or more hours to report it, and were also asked about the occurrence of adverse effects. The authors found few adverse reactions were reported with both solutions and despite the greater duration of numbness with articaine, no significant differences were found in their frequency (Ram and Amir, 2006).

A number of studies have reported that the post injection complications were minimal, and included bruising and slight swelling at the injection site, pain or soreness at the injection site, headache and tooth sensitivity. There was no report of post-operative paraesthesia. Moreover, in Abdulwahab and colleagues’ study, they reported a total of 11 adverse reactions and these were not dependent on local anaesthetic formulation. All reported reactions were transient and resolved within seven days (Abdulwahab *et al.*, 2009).

There was no incidence of paraesthesia or any other side effect, allergic reactions, or complications observed (Dudkiewicz *et al.*, 1987; Dressman, 2013; Rogers, 2014; Thakare, 2014).

## **1.8 ARTICAININE IN CHILDREN**

The number of studies evaluating local anaesthetics in children have been increasing with time, with the main aim being to provide pain-free dental treatment. This will have apparent benefit to the patient whilst also helping the operator as treatment can be performed in a calm manner.

One of the first trials carried out in children to assess the effectiveness of infiltration anaesthesia was conducted by Dudkiewicz *et al.* (1987); in their study they restored 84 mandibular primary molars under infiltration anaesthesia, in 50 children ranging in age from 4 to 10 years. Articaine hydrochloride 4% was used as the anaesthetic solution and each injection was followed by a 10 minutes waiting period before undertaking operative dentistry. The authors concluded that the mandibular infiltration for conventional operative dentistry for primary mandibular molars is effective and safe, especially when articaine is used as the local anaesthetic due to its chemical properties.

Donaldson *et al.* (1987) conducted a single centre, clinical trial comparing 4% articaine with 4% prilocaine both with 1:200,000 epinephrine, in patients (adult 18-40 years old and children aged 6- 16 years old) requiring maxillary infiltration or mandibular dental nerve block for paired teeth with identical clinical conditions. Pulp tester was used to determine the anaesthetic efficacy. The conclusion was that both solutions, when used in similar concentrations and volume, provide similar onset and duration times. However, in both techniques the onset time in adults was approximately twice that for children.

Wright *et al.* (1991) also studied the effectiveness of infiltration anaesthesia in 66 children, 42-78 months old, who required conventional operative dentistry in the first or second mandibular primary molars. Three types of local anaesthetics were used, mepivacaine hydrochloride 2%, prilocaine hydrochloride 4%, and articaine hydrochloride 4%. Operative procedures were videotaped, and assessment of comfort and behaviour was made using the SEM scale (sound, eye and motor, used to measure comfort or pain) and the Frankl behavioural scale. 65% of the subjects experienced little or no pain during cavity preparation. It was also found that profundity of anaesthesia was not significantly related to the three variables examined: tooth location, chronologic age, or anaesthetic agent.

Wright *et al.* (1991) also looked at how variables such as age of the child, tooth location and type of local anaesthetic might affect the quality of anaesthesia when infiltration is used. The results of their study demonstrated that children who exhibit comfort at the time of injection are likely to exhibit no pain during successive procedures. There is also a high relationship between children behaving cooperatively and comfort during procedures.

Oulis *et al.* (1996) carried out a clinical trial (it was the first of its type) to investigate the effectiveness of mandibular infiltration compared with mandibular block in treating primary molars in children, and related it to the type of treatment performed using a crossover design. A total of 89 children participated in the study 1.7 mL of 2% lidocaine containing 1:100,000 epinephrine was used for both techniques. The conclusion from this investigation indicated that mandibular infiltration is an effective and reliable local anaesthesia technique for amalgam and SSC restorations but not reliable for pulpotomy in primary molars, both in primary and mixed dentition.

In a large, multicentre, clinical trial by Malamed *et al.*, (2000 a) a total of 70 subjects aged 4-13 years old were randomised into 2 groups (50 subjects in the 4% articaine with epinephrine 1:100,000 group and 20 subjects in the 2% lidocaine with epinephrine 1:100,000 group). The conclusion of this study indicated that articaine is as effective as lidocaine when measured on this gross scale. Articaine 4% with epinephrine 1:100,000 is a safe and effective local anaesthetic for use in paediatric dentistry. Time to onset and duration of anaesthesia are appropriate for clinical use and are comparable to those observed for other commercially available local anaesthetics (Malamed *et al.*, 2000 a).

The same results were observed in another study by Ram and Amir (2006) who compared 2% lidocaine with 1: 100,000 epinephrine and articaine 4% with 1: 200,000 epinephrine in 62 children aged 5-13 years. The results of their study showed that the duration of numbness of soft tissues was significantly longer for articaine than for lidocaine, and there was no difference regarding the efficacy of the anaesthesia or pain reaction. Similarly, these results are in accordance with the recent study by Arrow (2012), who investigated the efficacy of articaine when it is given as BI in 57 children aged 5-16 years. His findings were comparable to the findings of the majority of studies (Arrow, 2012). He concluded that while his findings suggest a higher proportion of LA successes with BI using articaine than lidocaine, the difference was not statistically significant. In addition, there was no difference in pain reporting from local anaesthetic administration with BI or IDNB. The success rate for mandibular infiltration and mandibular block was 85% and 95% respectively during operative and extraction treatment of mandibular primary canines (Yaseen, 2009). Moreover, the mandibular infiltration was not significantly less painful than the mandibular block. Although no lingual or intra papillary injection was given after mandibular infiltration, most children had adequate lingual

anaesthesia to allow pain-free dental treatment. This may be due to the diffusion of the local anaesthetic (Yaseen, 2009).

Ylimaz *et al.* (2011) compared 4% articaine and 3% prilocaine in a study comprising of 162 children (mean age 7.2 years) who required pulpotomy on primary molars. The study concluded that the local anaesthesia following mandibular nerve block is more effective than that following maxillary infiltration. However, the intensity of pain that was experienced by the children during administration of either prilocaine or articaine, and during some of the dental procedures after their administration was similar.

Odabas *et al.* (2012) evaluated the efficacy of 4% articaine as compared with 3% Mepivacaine in children with mean age 11.3 years old. It was reported that there is a significant difference in the duration of soft tissue numbness, which was high in articaine, however, both solutions provide similar efficacy with similar adverse events.

In a recent survey by Ashkenazi *et al.* (2014), of the 81 dentists who treated children, 64 (79%) reported successful rates of anaesthesia (1 carpule sufficed to achieve full anaesthesia in at least 90% of their patients). A positive statistically significant correlation was found between the length of the inserted needle, and self-reported achievement of full anaesthesia, with mandibular BI in 90% or more patients ( $p = 0.001$ ,  $R = 0.356$ ). Hence, practitioners who used shorter needles more often needed to inject more than one carpule. In their conclusion (Ashkenazi *et al.* 2014), they have stated that:

*“Shorter lengths of needle insertion and targeting the injection to the central most anterior quarters of the ramus were positively correlated with unsuccessful anaesthesia in children. In adults, the needle insertion length was*

*not correlated with successful anaesthesia. Routine waiting period of over five minutes was not associated with a greater rate of successful achievement of MBI in children''.*

Ashkenazi *et al.* (2014) reported that the higher success rate in children may result from the decreased density of the mandibular bone, which permits more rapid and complete diffusion of the analgesic solution. Moreover, the more inferior location of the mandibular foramen in children, facilitates transporting the analgesic solution into the mandibular foramen, by gravitation, even when the injection is performed more superiorly (Malamed, 2013).

Ashkenazi *et al.* (2011) also found that the mental foramen distance from the posterior border of the ramus increased significantly with age by 66% from the primary (mean of 7.75mm) to (mean of 12.9mm) (p0.001). Based on the available data, Malamed (2013) recommended injecting the mandibular block more posteriorly in children than in adults. Although Pinkham *et al.* (2005) mentioned that the mental foramen is located at the mid-line of the ramus and changes with age; however, they did not detail the change.

## **1.9 MANDIBULAR INFILTRATION EFFECTIVENESS IN CHILDREN**

Few studies have evaluated the mandibular infiltration effectiveness in children as an alternative to conventional dental nerve block. BI anaesthesia was found to be as effective as block anaesthesia in all situations, except when pulpotomies were performed in the mandibular second primary molar, where it proved to be unreliable regardless of age. Block anaesthesia was significantly more painful than BI anaesthesia, and behaviour of children aged 3 to 5 years old sometimes turned negative following the block injection (Sharaf *et al.*, 1997).

When comparing mandibular IDNB to mandibular BI in children, Oulis *et al.* (1996) and Sharaf *et al.* (1997) suggested that mandibular infiltration was less effective than a block for pulpotomy procedures. AL-Jumaili *et al.* (2009) recommended mandibular infiltration for amalgam restoration and to avoid it whenever possible for pulpotomy and extraction procedures in primary molars. Wright *et al.* (1987) suggested that mandibular infiltration would be more effective for treatments on first primary molars in comparison to second primary molars.

## **1.10 CONCLUSION**

The available literature indicates that 4% articaine with epinephrine is equally effective when statistically compared to 2% lidocaine with epinephrine in achieving mandibular and maxillary anaesthesia.

From the literature discussed previously, there was a statistically significant difference between both local anaesthetics during anaesthetising healthy teeth using infiltration or mandibular block. However, conversely, there was no statistically significant difference between the two when a mandibular nerve block was used in symptomatic teeth.

There is a lack of consensus concerning the clinical efficacy of articaine anaesthetic solutions used in children and this supports the need for a thorough review of available clinical data, and the formulation of recommendations regarding the appropriate use of local anaesthetics in paediatric clinical dentistry.

## Chapter 2

### SYSTEMATIC REVIEW

#### 2.1 ABSTRACT

##### **Anaesthetic efficacy of articaine versus lidocaine in children's dentistry: a systematic review**

**Aim:** To systematically review available evidence on the efficacy of two local anaesthetic solutions lidocaine and articaine used for dental treatment in children.

**Method:** A systematic search was conducted on Cochrane CENTRAL Register of Controlled Trials, MEDLINE (OVID; 1950 to June 2013), Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost; 1982 to June 2013), EMBASE (OVID; 1980 to June 2013), SCI-EXPANDED (ISI Web of Knowledge; 1900 to June 2013), key journals, and previous review bibliographies through June 2013. No restrictions were placed on years, language or publication status. Original research studies that compared articaine with lidocaine in children dental treatment were included and methodological quality assessment including assessment of risk of bias was carried out for each of the included studies.

**Result:** Electronic searching identified 520 publications. After the primary and secondary assessment process, only three studies were included in the final analysis. The RCTs included in this review investigated the efficacy of local anaesthetic solutions when given as a combination of both techniques, local infiltration as well as block anaesthesia. The data analyses showed superiority of articaine over that of lidocaine in terms of achieving anaesthetic success, although these results were not statistically significant.

**Conclusion:** Both articaine and lidocaine solutions presented similar efficacy. Articaine was found to have longer soft tissue anaesthesia than lidocaine. However, the number of adverse events reported following use of either solution was similar.

**Registration:** PROSPERO registration: CRD42013004620.

## 2.2 INTRODUCTION

Evidence based medicine has been characterised by its focus on obtaining high quality evidence through experimentation, particularly through the use of randomised controlled trials (RCTs), and the systematic examination of existing research.

There is an abundance of definitions of evidence-based practice. The most well-known definition is that put forth by David Sackett and colleagues: "Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values." (Sackett *et al.*, 1996).

A systematic review can be defined as "a review of a clearly formulated question that attempts to minimize bias using systematic and explicit methods to identify, select, critically appraise and summarise relevant research" (Needleman, 2002). These systematic reviews gained popularity in the 1980s as a scientific process to "identify, critically appraise, include and synthesize relevant research studies" and have gone on to hold an important place in aiding clinical decision-making in medicine. While a systematic review is generally developed to include representation, assessment and interpretation of all relevant research on a topic of interest, a meta-analysis serves to add a quantitative synthesis of clinical results to the systematic review. Meta-analysis evolved from the beginning of the twentieth century when Karl Pearson sought to analyse conflicting results on clinical studies related to inoculation against typhoid fever (Sutton *et al.*, 2000). When confronted with a number of outcomes, especially when in disagreement, Sutton pointed out, "Single evaluations and stand-alone studies add data to the knowledge base, but are rarely definitive in that they are often context specific and too small" (Sutton *et al.*, 2000). He therefore recommended bringing together the results of previous research in a systematic way to synthesise a more powerful outcome. This philosophy was

shared by a British epidemiologist, Archie Cochrane, who insisted in seeking the highest evidence from all randomised controlled trials. His focus led to the development of the Cochrane Collaboration in 1993 and set the stage for a global initiative to summarise research in all of health care. This practice sparked the movement of Evidence Based Medicine which was defined as the “conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” (Sutton *et al.*, 2000).

### **2.3 WHY SYSTEMATIC REVIEW IS IMPORTANT**

The need for a systematic review arises from the requirement of researchers to summarise all existing information about some phenomenon in a thorough and unbiased manner. This may be in order to draw more general conclusions about some phenomenon than is possible from individual studies, or may be undertaken as a prelude to further research activities (Kitchenham *et al.*, 2007).

The value of a good systematic review to clinical decision making is that it should minimise bias, provide a comprehensive and contemporary overview, be objective in its appraisal of quality, and above all be transparent to allow others to appraise the methods and quality of the review itself (Needleman, 2002). Figure 2-1 illustrate the Stages of any systematic review process, classically start by recognising and identifying the knowledge gap, and then formulate the research question and then systematically, step by step through the process as shown below, until the aim is reached and the finding is reported.

The advantages of systematic literature reviews are that the well-defined methodology makes it less likely that the results of the literature are biased, although it does not protect against publication bias in the primary studies. Furthermore, they

can provide information about the effects of some phenomenon across a wide range of settings and empirical methods. If studies give consistent results, systematic reviews provide evidence that the phenomenon is robust and transferable. If the studies give inconsistent results, sources of variation can be studied. In the case of quantitative studies, it is possible to combine data using meta-analytic techniques. This increases the likelihood of detecting real effects that individual smaller studies are unable to detect (Kitchenham *et al.*, 2007).

The major disadvantage of systematic literature reviews is that they require considerably more effort than traditional literature reviews. In addition, increased power for meta-analysis can also be a disadvantage, since it is possible to detect small biases as well as true effects (Kitchenham *et al.*, 2007).

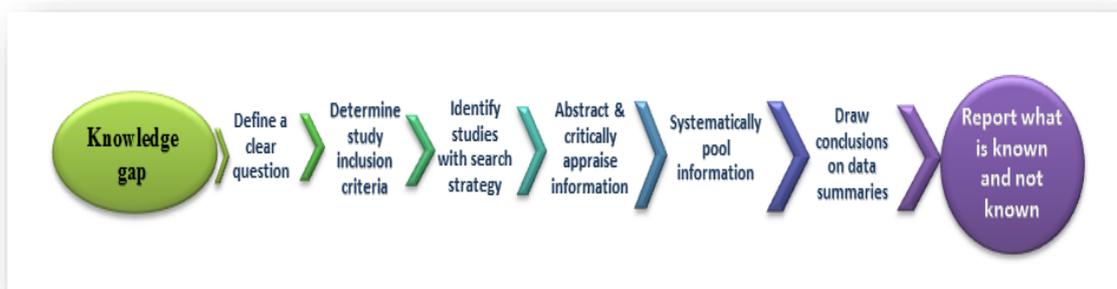


Figure 2-1: Stages in systematic review process

## **2.4 LITERATURE REVIEW**

### **2.4.1 Review of existing literature**

Local anaesthetic solutions have been utilised in clinical dentistry to alleviate or eliminate pain associated with invasive procedures as early as the 19th Century (Malamed, 2013). Since that time, a broad spectrum of local anaesthetics has been progressively developing.

Upon its clinical availability in 1948, lidocaine hydrochloride became the first marketed amide local anaesthetic. Lidocaine hydrochloride has maintained its status as the most widely used local anaesthetic in dentistry since its introduction. Proven efficacy, low allergies, and minimal toxicity through clinical use and research have confirmed the value and safety of this drug. Thus, it became labelled the “gold standard” to which all new local anaesthetics are compared (Malamed, 2013)

Despite the “gold standard” status of lidocaine hydrochloride, numerous reports and editorials have awarded articaine hydrochloride a superior reputation, primarily based on the notion that it possesses enhanced anaesthetic efficacy. The results of different studies demonstrated a common trend for articaine hydrochloride to outperform the “gold standard” lidocaine hydrochloride in dental applications.

Numerous publications have discussed topics regarding local anaesthesia in clinical dentistry; however, there has been no clear agreement on which local anaesthetic solutions provide the highest rate of success for the treatment of children’s teeth.

### **2.4.2 Conclusion**

No previous publication has systematically reviewed the existing literature to summarise the current best evidence regarding the success rates of local anaesthetic solutions in children dentistry.

### **2.4.3 Aims**

- 1.To systematically review available evidence on the efficacy of local anaesthetic solutions (lidocaine/articaine) used for local anaesthesia in children's clinical dentistry.
- 2.To compare the outcomes, benefits, and harms of using articaine local anaesthetic solutions to provide pulpal anaesthesia required for dental treatment in children.

### **2.4.4 Null hypothesis**

The null hypothesis is that no statistically significant difference exists between the anaesthetic efficacy of initial administration of 2% lidocaine hydrochloride and 4% articaine hydrochloride, both with epinephrine, in dental applications.

## **2.5 MATERIAL AND METHODS**

The following sections will illustrate the method adopted in order to achieve the aims and objectives of the research project. It include detailed description of the general outline of the study approach, as well as the research technique descriptions, the data collection methods, in addition to the ways in which data can be analysed.

### **2.5.1 Using protocols to guide the process**

The NHS Centre for Reviews and Dissemination (CRD) at York describes a protocol as follows: "The protocol specifies the plan which the review will follow to identify, appraise and collate evidence" (CRD, 2009, p 6).

A protocol is a useful tool for promoting transparency, transferability and applicability, with the main strength of developing a protocol being that it encourages the reviewer to be explicit about how the review will be carried out,

rather like action plans and other project management tools (CRD, 2009). Protocols outline what the reviewer intends to do and makes it possible for the review to be repeated later by others.

As such, a protocol was developed for this systematic review; this protocol was approved and registered in The NHS Centre for Reviews and Dissemination (CRD) at the University of York. (See Appendix 1).

Registration details:

CRD42013004620, The efficacy of articaine versus lignocaine in children's dental treatment, systematic review and meta-analysis

The systematic review protocol is available online from:

[http://www.crd.york.ac.uk/PROSPERO/register\\_new\\_review.asp?RecordID=4620&UserID=3172](http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=4620&UserID=3172)

### **2.5.2 PICO framework**

The PICO (Patient Population, Intervention, Comparison, and Outcomes) process is a technique used in evidence-based medicine to frame and answer a clinical question. It has been stated that there is a trend towards a higher precision of search results when a PICO template is used, thus improving the relevancy of search results (Schardt *et al.*, 2007). This technique was therefore implemented in this research.

### **2.5.3 Defining the scope of the question**

In this investigation, the original research question was of a broad scope. The population under consideration was all child patients receiving dental treatment in a clinical setting. The intervention included articaine local anaesthetic solutions approved for dental therapeutic use. The outcome was the achievement of profound anaesthesia of the dental pulp and soft tissue. As the question was narrowed, the

addition of the comparison component of the PICO question specifically aimed to compare the anaesthetic success associated with lidocaine versus that of articaine.

The PICO framework was used to formulate the following questions for a systematic review of the existing literature:

- ❖ In child patients receiving operative or extraction treatments, does using an articaine solution for local anaesthesia compared to lidocaine provide superior pulpal and soft tissue anaesthetic efficacy?

#### **2.5.4 Defining exclusion/inclusion criteria**

Studies were considered relevant to this review if they included specific defined characteristics as follow:

##### **2.5.4.1 Inclusion criteria**

The article was selected for inclusion in the review if it met the following criteria:

- The investigators evaluated the anaesthetic effect of local anaesthetic solutions of articaine comparatively with lidocaine, using volumes of at least 1.0 ml per administration and in combination with a vasoconstrictor, as initial application.
- The investigators evaluated interactions comparing articaine with lidocaine for maxillary or mandibular infiltration and inferior dental nerve block, using volumes of at least 1.0 ml per administration and in combination with a vasoconstrictor.
- The review concerned clinical trials that involved children human participants.
- It provided original data generated by means of a comparative design.
- The measure of local anaesthetic successes is clearly identified.

### 2.5.4.2 Exclusion criteria

The article was excluded if:

- It did not satisfy the above criteria
- It did not describe or define the methods for evaluating anaesthetic success
- It did not describe in detail the techniques for administering the anaesthetic solution.

<b>Criteria</b>	<b>Definition</b>
<b>Population</b>	Children patients (age <16 years), medically healthy, requiring routine dental treatments.
<b>Intervention</b>	<ul style="list-style-type: none"> <li>- Dental treatments involving maxillary or mandibular infiltration or dental nerve block anaesthesia administered manually were included.</li> <li>- Dental treatment including restorations, pulp treatment and extraction were included.</li> <li>- Trials studying computerised delivery routes were excluded, as they are not used routinely. Trials evaluating the less commonly used supplemental anaesthetic techniques after the routine infiltration or block anaesthesia were also excluded.</li> </ul>
<b>Characteristics</b>	Studies that directly compared similar dose of local anaesthetic lidocaine hydrochloride and articaine hydrochloride, both with epinephrine as vasoconstrictor.
<b>Outcome</b>	Anaesthetic success defined as none or mild pain measuring using standard or modified pain evaluation scale (e.g. VAS, FPS) during clinical treatment.

Table 2.1: Criteria for selecting studies in the systematic review

### 2.5.5 Assessment of anaesthetic success

Definition of anaesthetic success: “none” or “mild” pain measured using a standard VAS and W-B FRS during clinical procedures. The child should have a positive score in Frankl behaviour scale.

## **2.6 STUDY SELECTION PROCESS**

### **2.6.1 Searching procedures and database selection**

A comprehensive search strategy was constructed taking into account the PICO framework; population, intervention, comparators, outcome and study design. Computerised databases were originally searched in April 2013 for the Cochrane review and then updated in April 2014. Last update was carried out in April 2015. The included databases were: Cochrane CENTRAL Register of Controlled Trials, MEDLINE (OVID, 1950 to June 2013), Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost, 1982 to June 2013), EMBASE (OVID, 1980 to June 2013), SCI-EXPANDED (ISI Web of Knowledge, 1900 to June 2013). The electronic searches were complemented with a search of clinical trial registers of the reference lists of included studies and relevant systematic reviews, as well as Clinical.gov.com. Searching for theses and dissertations was also done through Proquest thesis and dissertations (an online research tool). Furthermore, forward citation tracking of included studies was also used to search for additional studies using the ISI Web of Knowledge.

In addition to publications located by this electronic search strategy, attempts to enhance the available references were made. Hand searches were made by reviewing the reference lists of relevant articles, clinical trials, and the tables of content of the journals containing most of the included studies for the last two years. No additional trials were located that could potentially contribute data to this review. Efforts were also made to locate unpublished, yet inclusion-worthy, research, however, unpublished studies were not located.

### **2.6.2 Electronic search strategies**

The MeSH database, the National Library of Medicine's controlled vocabulary indexing system, was used to search terms closely related to this study: articaine, articaine, lidocaine, lignocaine, local anaesthetics, anaesthetics, dental anaesthesia and anaesthesia. Based on the results from the electronic search, articaine and lidocaine were found to be the most appropriate and comprehensive Medical Subject Heading terms for the purpose of searching PubMed.

Keywords and subject index terms and MeSH were used to search for:

- Local anaesthesia, amid local anaesthetic.
- Dental, dentistry, dental anaesthesia.
- Articaine, articaine, septocaine, septanest, ultracaine, thiophine, artikent, bartinest, isonest.
- Primary dentition/teeth/tooth, deciduous dentition/teeth/tooth, baby tooth, baby teeth.
- Child, children, adolescent, young people, young person/s, young patient/s, preschool child/ren.
- Lignocaine, lidocaine, lignospan, lignospan special, xylocaine.
- Randomized control trial, control trial, control clinical trial/s.

### **2.6.3 Selection of studies**

Included studies within this review were limited to clinical trials involving human, paediatric population. No blinding was carried out regarding authors' names, journals and publication dates. One examiner (F. Alzahrani) read the titles and abstracts of all studies identified in the electronic search. This step was double-checked and validated by the study's supervisors. Whenever information was

lacking, the full-text article was obtained. Any unclear issue was solved by discussion with supervisors.

#### **2.6.4 Development of data abstraction form**

A data extraction form was designed and used as a framework for recording the study's information as presented in figures (2-2 to 2-5) below; more details see (Appendix 3).

The data recorded in the abstraction form included information regarding the quality of the included trials, as well as their outcomes. Information about study design including appropriate randomisation, allocation, blinding and standardisation of the procedures, as well as the evaluation procedures, were also reported on the form. Details of the study participants included the sample size and procedures of its calculation, mean age of participants, as well as age range, ethnicity, health status and any other information reported.

Treatment procedures were recorded for site of administered anaesthesia, whether it was documented as infiltration or block anaesthesia, as well as the arch anaesthetised, either maxilla or mandible. The type and amount of local anaesthetic used was also recorded. The dental treatment provided was identified as extraction, pulp treatment or restorative treatment and the type of teeth treated (primary or permanent teeth) was also recorded.

The outcomes were recorded for definition of local anaesthetic success, and the goal of anaesthesia was identified, being either an evaluation of pulpal anaesthetic effect or soft tissue anaesthetic effect.

### **2.6.5 Initial pilot data abstraction**

No piloting was done, as this is a PhD research with one researcher carrying out the review. However, all decisions were reviewed by the supervisors of the study and compared for reliability. Any disagreements were then resolved by means of discussion and consensus.

<b>DATA EXTRACTION SHEET</b>	
<b>General information</b>	
Article number	
Date of data extraction	
Title	
Details of publication	
Year	
• Volume	
• Pages	
Country of origin	
Institutional affiliation	
When was the fieldwork conducted	
Language	
Author	
Source	
Publication type	<input type="checkbox"/> Published <input type="checkbox"/> Unpublished <input type="checkbox"/> Thesis <input type="checkbox"/> Other
Data Extraction Sheet	

Research question	
Aim	
Hypothesis	
Study design	
Randomisation	<input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, describe it : _____
Blinding	Subject <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Operator <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Evaluator <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Statistician <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
Standardization	Number of operators <input type="checkbox"/> Not reported <input type="checkbox"/> Single <input type="checkbox"/> Multiple
	Attempt to standardize operators <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Number of evaluators <input type="checkbox"/> Not reported <input type="checkbox"/> Single <input type="checkbox"/> Multiple
	Attempt to standardize evaluators <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
Statistical analysis	Appropriate for study design <input type="checkbox"/> Not Clear <input type="checkbox"/> Yes <input type="checkbox"/> No
Data Extraction Sheet	

Figure 2-2: Data abstraction sheets 1-2

Treatment procedures		
	Treatment group	Control group
Arch anaesthetised	<input type="checkbox"/> Maxilla <input type="checkbox"/> Mandible <input type="checkbox"/> Combine (max & mand)	<input type="checkbox"/> Maxilla <input type="checkbox"/> Mandible <input type="checkbox"/> Combine (max & mand)
Technique used for application of LA	<input type="checkbox"/> Not specified <input type="checkbox"/> Infiltration <input type="checkbox"/> Periodontal ligament <input type="checkbox"/> IANB <input type="checkbox"/> Buccal infiltration - mand <input type="checkbox"/> Palatal infiltration- max <input type="checkbox"/> Other	<input type="checkbox"/> Not specified <input type="checkbox"/> Infiltration <input type="checkbox"/> Periodontal ligament <input type="checkbox"/> IANB <input type="checkbox"/> Buccal infiltration - mand <input type="checkbox"/> Palatal infiltration- max <input type="checkbox"/> Other
Type of LA used	<input type="checkbox"/> Articaine <input type="checkbox"/> Lidocaine <input type="checkbox"/> Other	<input type="checkbox"/> Articaine <input type="checkbox"/> Lidocaine <input type="checkbox"/> Other
Amount of LA used		
Treated tooth/teeth	<input type="checkbox"/> Primary <input type="checkbox"/> Permanente	<input type="checkbox"/> Primary <input type="checkbox"/> Permanente
Treated tooth/teeth	<input type="checkbox"/> Not specified <input type="checkbox"/> Central incisors <input type="checkbox"/> Lateral incisors <input type="checkbox"/> Canine <input type="checkbox"/> 1 <sup>st</sup> premolar <input type="checkbox"/> 2 <sup>nd</sup> premolar <input type="checkbox"/> 1 <sup>st</sup> molar <input type="checkbox"/> 2 <sup>nd</sup> molar <input type="checkbox"/> 3 <sup>rd</sup> molar	<input type="checkbox"/> Not specified <input type="checkbox"/> Central incisors <input type="checkbox"/> Lateral incisors <input type="checkbox"/> Canine <input type="checkbox"/> 1 <sup>st</sup> premolar <input type="checkbox"/> 2 <sup>nd</sup> premolar <input type="checkbox"/> 1 <sup>st</sup> molar <input type="checkbox"/> 2 <sup>nd</sup> molar <input type="checkbox"/> 3 <sup>rd</sup> molar
Type of dental treatment	<input type="checkbox"/> Extraction <input type="checkbox"/> Pulp therapy <input type="checkbox"/> Simple restoration <input type="checkbox"/> Moderate restoration	<input type="checkbox"/> Extraction <input type="checkbox"/> Pulp therapy <input type="checkbox"/> Simple restoration <input type="checkbox"/> Moderate restoration

Data Extraction Sheet

Outcome		
Initial Diagnosis of the Tooth	<input type="checkbox"/> Not specified <input type="checkbox"/> Vital <input type="checkbox"/> Irreversible pulpitis	
Definition of pulpal anaesthetic success	<input type="checkbox"/> Not reported <input type="checkbox"/> Negative EPT responses at 80 % of consecutive reading <input type="checkbox"/> Ability to perform treatment without pain using VAS scale <input type="checkbox"/> Ability to perform treatment without requiring re injection <input type="checkbox"/> No pain <input type="checkbox"/> Other _____	
Pulpal anaesthetic success	<input type="checkbox"/> VAS categorical <input type="checkbox"/> EPT <input type="checkbox"/> Others _____	
Pulpal anaesthetic effect	Onset	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported
	Duration	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported
	Success	<input type="checkbox"/> 30 minute <input type="checkbox"/> 60 minutes
Soft tissue anaesthetic effect	Onset	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported

Data Extraction Sheet

Figure 2-3: Data abstraction sheets 3-4

	Duration	<input type="checkbox"/> Reported _____		
	Success	<input type="checkbox"/> Not reported <input type="checkbox"/> 30 minute <input type="checkbox"/> 60 minutes		
<b>Participants</b>				
<b>Target population</b>	<input type="checkbox"/> Adult		<input type="checkbox"/> Children	
<b>Characteristic of population</b>				
<b>Number of participants</b>	Total :	Girls:	Boys:	
<b>Age</b>	Mean age:	Girls:	Boys:	
<b>Social class</b>				
<b>Geographic location</b>				
<b>Ethnicity</b>				
<b>Health status</b>				
<b>Other information</b>				
Data Extraction Sheet				

<b>Methodology of study</b>	
<b>Inclusion criteria</b>	
<b>Exclusion criteria</b>	
<b>Sample size calculation</b>	
<b>Randomisation</b>	
<b>Allocation</b>	
Data Extraction Sheet	

Figure 2-4: Data abstraction sheets 5-6



## **2.7 QUALITY ASSESSMENT**

The Cochrane Collaboration (Schulz *et al.*, 1995) advised that the determination and reduction of bias be the major approach in the assessment of quality. Within this review, quality measures were designed to reduce bias. Risk of bias assessment was performed using Cochrane Collaboration's tool on the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (Higgins and Green, 2011).

The quality assessment of the methodology for the included studies was carried out using pre-established criteria on the abstraction form, which was designed based on the Cochrane Collaboration's tool, in order to minimise errors and confront differences in criteria for classification. The assessment was for appropriate randomisation and allocation of subjects to the study groups, the blinding of subjects, operators and evaluators'. The assessment also included description of losses, the use of intention to treat analyses, assessment of standardisation of the procedures and evaluation procedures.

### **2.7.1 Randomisation**

Clinical trials were considered randomised if random sequences were generated by random numbers or tables, a tossed coin, or any other random sequence generation. If just the terms randomised or randomly allocated were used with no detailed information on the exact method, the trial was deemed 'unclear' as regards to the randomisation.

### **2.7.2 Allocation**

Allocation was considered to be concealed if measures of allocation concealment were described, such as the use of opaque, sealed and sequentially numbered envelopes, or if anaesthetic cartridges were indistinguishable, and sequentially numbered.

### **2.7.3 Blinding**

The examiners of each trial were deemed to be properly blinded if the outcome assessor could not know to which group the participants had been randomised. Blinding of participants and health care providers was also considered.

### **2.7.4 Outcome reporting**

This was assessed and incomplete outcome data and selective outcome reporting was noted.

### **2.7.5 Adverse event reporting**

Reporting of adverse events was recorded as being present if reported, or noted as 'not mentioned' if no description of side effects was included in the results.

### **2.7.6 The intention to treat analysis**

Intention-to-treat analysis: includes all randomised patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol (Fisher *et al.*, 1990).

## **2.8 STRATEGY FOR DATA SYNTHESIS**

In this systematic review, data synthesis was carried out using narrative synthesis (NS) “An approach to the synthesis of evidence relevant to a wide range of questions including but not restricted to effectiveness [that] relies primarily on the use of words and text to summarise and explain – to ‘tell the story’ - of the findings of multiple studies. NS can involve the manipulation of statistical data (CRD, 2009).

## **2.9 RESULTS**

The following sections will present the results and findings from the selected studies along with tables and graphs where appropriate.

### **2.9.1 Selection procedures**

Electronic searching identified 520 publications, after eliminating the duplicates there were 178 studies for primary assessment. In the primary assessment phase, title and abstracts were reviewed, and if the abstract did not contain enough detail to determine the quality or methods of a specific trial, it was included for more detailed review. A total of 156 studies were excluded because they did not meet the inclusion criteria (Appendix 4). Figure 2-6: below illustrate the selection process.

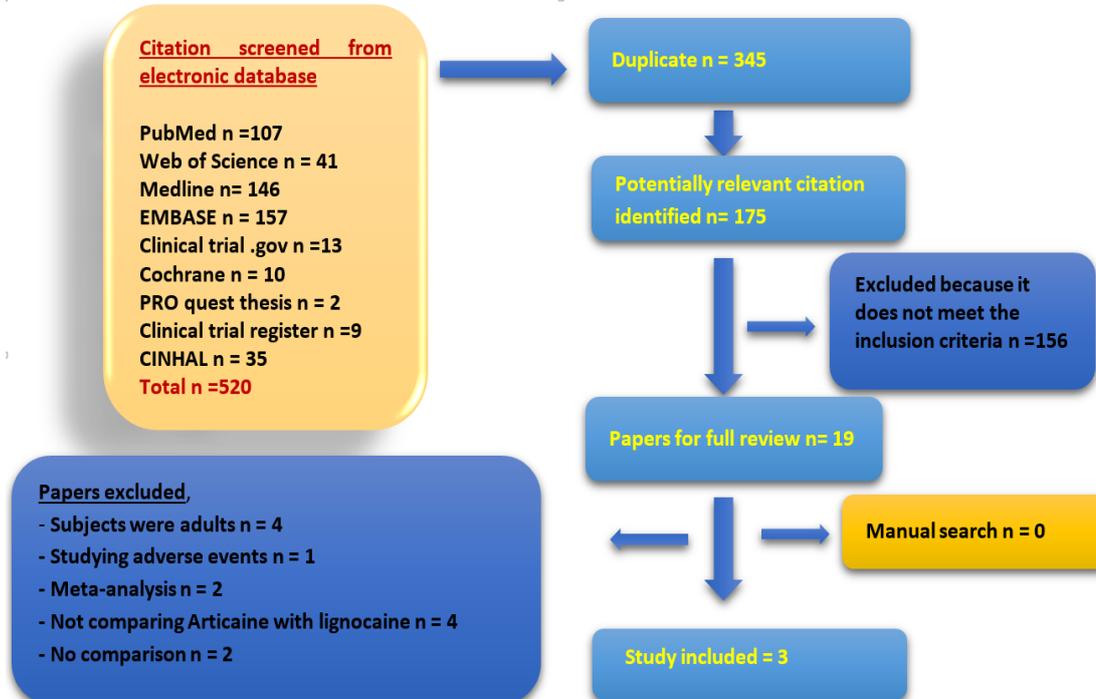


Figure 2-6: Study selection flowchart

Following the exclusions made at the abstract level, a total of 19 publications remained as potential articles of interest. Reference list screening for the remaining 19 studies revealed no relevant studies (Table 2.2).

Study	Included	Reason for exclusion
Abdulwahab <i>et al.</i> , 2009	No	Study subjects were adult population mean age was 24.9 years
Adewumi <i>et al.</i> , 2008	No	This paper was investigating adverse events
Arrow, 2012	Yes	
Bradley <i>et al.</i> , 1969	No	This study is comparing Lignocaine with Mepivacaine hydrochloride
Brandt <i>et al.</i> , 2011	No	Meta-analysis
Costa <i>et al.</i> , 2005	No	Study subjects were adult population
Donaldson <i>et al.</i> , 1987	No	This study compared Articaine with Citanest (Prilocaine)
Dudkiewica <i>et al.</i> , 1987	No	There was no comparison on this study; it was looking at articaine only.
Katyal, 2010	No	Meta-analysis
Malamed <i>et al.</i> , 2000a	Yes	
Malamed <i>et al.</i> , 2000b	Yes	
Malamed <i>et al.</i> , 2001	Yes	
Mikesell <i>et al.</i> , 2005	No	Study subjects were adult population (19-60)
Moore <i>et al.</i> , 2006	No	Study subjects were adult population (18-65) This study was looking at articaine only
Odabas <i>et al.</i> , 2012	No	This study was comparing Articaine with Mepivacaine hydrochloride in children.
Ram & Amir, 2006	Yes	
Robertson <i>et al.</i> , 2007	No	Study subjects were adult population (18-60)
Yassen, 2010	No	This study was looking at lignocaine only
Yilmaz <i>et al.</i> , 2011	No	Comparison of the efficacy of Articaine and Prilocaine

Table 2.2: Potential studies of interest for full assessment

All studies that appeared from their titles or abstracts to be studying articaine in children's dentistry, or where the abstract did not reveal a decision about the study design or subjects' age, were evaluated by secondary assessment of the full text of each study.

The results were summarised in tables and discussed by narrative review. Individual study details are presented in the characteristics of included studies' tables.

After secondary assessment of full articles, five studies were excluded because the study subjects were adults (Costa *et al.*, 2005; Mikesell *et al.*, 2005; Moore *et al.*, 2006; Robertson *et al.*, 2007; Abdulwahab *et al.*, 2009). Four studies were found to not be comparing articaine with lignocaine (Bradley *et al.*, 1969; Donaldson *et al.*, 1987; Yilmaz *et al.*, 2011; Odabas *et al.*, 2012). Two studies were meta-analysis (Katyayal, 2010; Brandt *et al.*, 2011) and a further two studies were non-comparative studies (Dudkiewica *et al.*, 1987; Yassen, 2010). One study was investigating adverse events (Adewumi *et al.*, 2008).

Following the secondary assessment, five original articles remained of the clinical studies evaluating the dental anaesthetic efficacy of both 4% articaine hydrochloride and 2% lidocaine hydrochloride, as initial local anaesthetics used in children's dentistry. However, two of these trials were reporting the same outcome for one large randomised control study (Malamed *et al.*, 2000; Malamed *et al.*, 2001), therefore, only three studies were included in the final analysis for this review (Malamed *et al.*, 2000b; Ram and Amir, 2006; Arrow, 2012) (Table 2.3).

<b>Author</b>	<b>Publication</b>	<b>Comments</b>
Arrow, 2012	Australian dental Journal	
Ram & Amir, 2006	Journal of paediatric dentistry	
Malamed <i>et al.</i> , 2001	Journal of American dental association	These three articles were related to the same study and was handled as one study in this review
Malamed <i>et al.</i> , 2000 a	Journal of American dental association	
Malamed <i>et al.</i> , 2000 b	Paediatric dentistry	

Table 2.3: Studies included in the final analysis

### **2.9.2 Study design of the selected articles**

The following sections will discuss the characteristic of the selected studies for this review along with quality assessment.

#### **2.9.2.1 Sample size**

The determination and sample size calculation was not reported in the study by Malamed *et al.* (2000b), neither was it reported in the study by Ram and Amir (2006). However, it was described in detail in Arrow's (2012) study.

#### **2.9.2.2 Randomisation**

Randomisation included both cross-over (matched pairs) and independent sample study designs. Cross-over study designs were defined as those studies where subjects received two experimental administrations, one with articaine

hydrochloride and one with lidocaine hydrochloride. There were two included studies of this type (Ram and Amir, 2006; Arrow, 2012).

Independent sample study designs were defined as those with each subject randomised to either the experimental group receiving articaine hydrochloride or the group receiving lidocaine hydrochloride. Only one of the included studies were of this study design type (Malamed *et al.*, 2000b)

The randomisation method was not clearly reported in the study by Malamed *et al.* (2000b). It has been stated that the randomisation was based on the dental procedures performed and was carried out to allocate the subjects in a 2:1 ratio (2 for articaine: 1 for lidocaine).

In Ram and Amir's (2006) study, the randomisation procedures were not clearly described nevertheless, the randomisation was based on local anaesthetic technique, either maxillary infiltration or mandibular block; however, it is not clear regarding how they randomised the local anaesthetic type.

In Arrow's (2012) study, the randomisation was in two stages; phase one, parallel randomisation for the local anaesthetic technique, in which each subject received the two types of local anaesthetic using the same injection technique, and the second phase was cross-over randomisation in which each subject received one local anaesthetic in each visit.

### **2.9.2.3 Allocation**

Allocation was considered concealed and adequate in the study by Arrow (2012) but it was not clear in the studies by Ram and Amir (2006); Malamed *et al.* (2000b).

#### 2.9.2.4 Blinding

Malamed *et al.* (2000b) failed to specifically report the operators' agreements or blinding for subjects, operators, evaluators and statisticians. The same was observed in Ram and Amir (2006), where only the chair side assistance was blind to the type of local anaesthetic. In Arrow (2012) study, Clinician, assistance and patients were blind to the local anaesthetic type but not to the technique (Table 2.4).

<b>Study</b>	<b>Arrow, 2012</b>	<b>Ram and Amir, 2006</b>	<b>Malamed <i>et al.</i>, 2000 b</b>
Blinding assessment	Clinician, assistance and patients were blind to the local anaesthetic type but not to the technique.	Only the chair side assistance were blind to the type of local anaesthetic	Not reported

Table 2.4: Assessment of blinding

#### 2.9.2.5 The intention to treat analysis

For the trials that employed a crossover design, (Arrow, 2012; Ram and Amir, 2006) it was noted that no losses occurred in Ram and Amir's (2006) study, and outcome data was available for all randomised subjects. Thus, all participants were included in this trial, and it was considered as an "intent to treat" analysis. However, in Arrow (2012), one patient from the Buccal Infiltration group did not attend the second visit; therefore, they have been excluded from the data analysis. Hence, this cannot be considered to have fulfilled the criteria for intention to treat analysis. There was lack of information about this part in Malamed *et al.* (2000b) study.

### 2.9.2.6 Statistical consideration

In both studies by Ram and Amir (2006) and Malamed *et al.* (2000b), there was no information provided regarding the statistical calculation apart from “because data did not meet the normality assumption, we used nonparametric test- Kruskal-Wallis to analyse the VAS data for the treatment group.” This was noted in a different paper, not the one selected for this review (Malamed *et al.*, 2000a). However, the statistical consideration was described in more details in the study by Arrow (2012).

### 2.9.2.7 Operators and evaluators

The number of operators and evaluators ranged from two operators/evaluators, as in Ram and Amir (2006), to six operators in Arrow (2012); the number of operators and evaluators was not specified in the study by Malamed *et al.* (2000b). Training and testing for interpreter agreement were inconsistently reported. Malamed *et al.* (2000b) failed to specifically report the operators’ agreements or blinding for subjects, operators, evaluators, and statisticians (Table 2.5).

Study	Arrow, 2012	Ram and Amir, 2006	Malamed <i>et al.</i> , 2000 b
Investigators	Six operators	Two operators	Not identified
Interpreter agreement	Not reported	Not reported	Not reported
Notes	There was no statistical significant difference between the clinician years of experience and the study outcomes based on Bivariate test.	An experienced paediatric dentist carried out the treatment in each centre	The studies used identical protocol

Table 2.5: Clinical operators and evaluators

#### **2.9.2.8 Age and gender**

Regarding age and gender, female subjects appeared to be represented similarly in all of the studies whereas male subjects had different representations.

In all included studies, all subjects were 16 years of age and younger with an age range from four to 16 years. One study that did not report the mean age of the subjects was that of Malamed *et al.* (2000b). The remainder of the studies reported the mean age of the subjects as 12.4 years in Arrow (2012) and 8.4 years in Ram and Amir (2006). See Table 2.12.

#### **2.9.2.9 Dosages of the local anaesthetic agents**

Various dosages of the local anaesthetic agents were utilised. In the study by Ram and Amir (2006), the maximum dose of local anaesthetic was administered, while in the other two studies the volumes ranged between 1.6 to  $2.5 \pm 0.43$  ml for articaine and from 0.78 to 2.6 ml for lidocaine depending on randomised procedures performed.

In the Malamed *et al.* (2000b) study, the volumes of both local anaesthetics were comparable, however higher mg/kg doses of articaine were used in both simple and complex procedures, and that was because of a higher concentration of 4% articaine compared to 2% lidocaine (Table 2.6). The same was observed in the Ram and Amir (2006) study, in which the local anaesthetics were in different concentrations.

In Arrow (2012), there were no statistically significant differences in the distribution of the variables for LA technique or LA type, except for anaesthetic dosage.

The mean dosage of local anaesthetic administered was 1.2 mg/ kg; range 0.3–3.6 mg/ kg. There was no statistically significant difference in dosage by LA technique but there was a statistically significant higher dosage with articaine.

Study	Arrow, 2012	Ram and Amir, 2006	Malamed <i>et al.</i> , 2000 b
Local Anaesthetic dose in ml	<ul style="list-style-type: none"> <li>• A 1.6 ml</li> <li>• L 0.78 ml</li> </ul>	<ul style="list-style-type: none"> <li>• Maximum dose was administered</li> <li>• A 5 mg /kg body weight</li> <li>• L 4 mg/kg body weight</li> </ul>	<ul style="list-style-type: none"> <li>• A simple 1.9 ±0.10</li> <li>• complex 2.5 ± 0.43</li> <li>• L simple 1.9 ± 0.23</li> <li>• complex 2.6 ± 0.00</li> </ul>
Notes			Patients received the lowest effective dosage

Table 2.6: Type and dose of local anaesthetics in each study

### 2.9.2.10 Tooth selection/type of treatment

Depending on the study, either one tooth or many teeth were evaluated per experimental administration. Typically, in the included studies, one tooth was targeted for a primary evaluation, and adjacent teeth may have been included for an alternative comparison.

In the Arrow (2012) study, a specific type of tooth was selected (only mandibular teeth) for which results were reported. The Ram and Amir (2006) study focused on combined arches, for which results potentially reflected a number of teeth. In Malamed *et al.* (2000b) there were no limitations to teeth evaluated, which opened the possibility for inclusion of any type of tooth.

Simple treatment included single extraction, routine operative treatment. The complex dental treatment included multiple extraction, multiple crowns and surgical procedures. See Table 2.7.

Study	Arrow, 2012	Ram And Amir, 2006	Malamed <i>et al.</i> , 2000 b
Tooth Location	<ul style="list-style-type: none"> <li>• Mandibular teeth</li> <li>• 2nd permanent molar</li> <li>• 1st permanent molar</li> <li>• 2nd deciduous molar</li> </ul>	Not specified  40 maxillary teeth 20 mandibular teeth	Not specified
Type of Treatment	<ul style="list-style-type: none"> <li>• Simple</li> <li>• Only simple operative procedures was done no extraction</li> </ul>	<ul style="list-style-type: none"> <li>• Simple complex</li> <li>• There was no specification to the type of dental treatment</li> </ul>	Simple / complex

Table 2.7: Complexity of dental treatment and tooth type

### 2.9.2.11 Routes of injections

In Ram and Amir (2006) and Malamed *et al.* (2000b), the routes of injections were inferior alveolar nerve block and buccal infiltration (mandibular buccal infiltration and maxillary buccal infiltration). Conversely, in the Arrow (2012) study, only mandibular injections have been administered. See Table 2.8.

Study	Arrow, 2012	Ram and Amir, 2006	Malamed <i>et al.</i> , 2000 b
Injection Route	Mandibular IDNB / Infiltration	Mandibular IDNB maxillary Infiltration	IDNB / Infiltration With no specification

Table 2.8: Route of injection in each study

#### **2.9.2.12 Pulpal status**

Pulpal status was not reported in these studies; however, the included studies imply the inclusion of teeth with normal pulps.

#### **2.9.2.13 Outcome reporting**

The outcome was reported as pulpal/soft tissue anaesthetic onset and duration, as well as anaesthetic success.

##### **2.9.2.13.1 Onset**

Arrow (2012) concluded that, there were no statistically significant differences in time to appearance of symptoms by local anaesthetic technique (t-test,  $p > 0.05$ ) and type (paired t-test,  $p > 0.05$ ). The same conclusion was also drawn from Ram and Amir (2006). Furthermore, in more than 80% of instances, onset time was immediate. The available results in this study showed that in both treatment sessions, the immediate onset time of local infiltration was 77.5% and after two minutes, it was 10%. In the mandibular block anaesthesia, the immediate onset was reported in 85.5% and after two minutes, it was 4.5% (Arrow, 2012). The onset of local anaesthetic was not reported in Malamed *et al.* (2000b). See Table 2.9.

Study	Onset time (mean time)			
	Articaine		Lidocaine	
	Pulp	Soft tissue	Pulp	Soft tissue
<b>Arrow, 2012</b>	Not reported	IDNB 129 seconds (lip). 85 seconds (tongue)  BI- 115 seconds (lip)	Not reported	IDNB- 119 seconds (lip). 104 seconds (tongue)  BI 170 seconds (lip)
<b>Ram &amp; Amir, 2006</b>	Not reported*	Not reported*	Not reported*	Not reported*
	*It was reported generally by the type of local anaesthetic injection technique, no specification to the type of local anaesthetic solution.			
<b>Malamed et al., 2000b</b>	Not reported*	Not reported*	Not reported*	Not reported*
	*It was not reported in all the three papers for this study.			

Table 2.9: LA onset time in each study

### 2.9.2.13.2 Duration of local anaesthesia

No significant difference was found in the duration of numbness between local infiltration and mandibular block, and between boys and girls for each local anaesthetic solution in Ram and Amir (2006). Nonetheless, the duration of numbness of soft tissues was longer for articaine than for lidocaine. This difference was statistically significant ( $P = 0.003$ ). The duration of local anaesthetic was not reported in both studies by Arrow (2012) and Malamed *et al.* (2000b). However, in Malamed *et al.* (2000b) the duration of the dental procedures was reported as follows: in articaine group the average time for simple procedures was  $16 \pm 2.46$  minutes and  $69 \pm 19.99$  minutes for the complex procedures. In the lidocaine group, it was  $19 \pm 5$  minutes for simple procedures and  $57 \pm 55.55$  minutes for the complex procedures. See Table 2.10.

Study	Duration time (mean time)	
	Articaine	Lidocaine
Arrow,2012	Not reported	Not reported
Ram & Amir,2006	a.± 00.74 hours (soft tissue)	3.01 ± 00.82 hours (soft tissue)
	*This difference was statistically significant	
Malamed <i>et al.</i> , 2000b	Not reported *	Not reported *
	*The reported time in this study was for duration of the dental treatment procedures (simple and complex)	

Table 2.10: LA duration time in each study

### 2.9.2.13.3 Anaesthetic success

The results of Arrow (2012) were presented in more detail and they demonstrated that adequate analgesia (successful) was achieved at both visits when IDNB technique was used with both types of local anaesthetics. However, local anaesthetic type was not associated with successful local anaesthesia, and there was no statistically significant association between local anaesthetic type and successful local anaesthesia.

Overall, for all BI administrations, the success rate for articaine with BI (71%) was higher than for lignocaine (64%), but the difference was not statistically significant.

There was however a statistically significant difference between IDNB and BI during dental treatment (higher levels of pain associated with BI); however, the difference was not statistically significant when comparing the two techniques of anaesthetic injection.

Participants with unsuccessful local anaesthetics were more likely to report moderate /severe pain. This association between pain reported during dental treatment and local anaesthetic success revealed high statistical significance. On the contrary, the association between observed and reported pain variables with local anaesthetics type were not statistically significant. In the Ram and Amir (2006) study there was no difference in subjective evaluation (Wong–Baker FPS) and in the objective evaluation (Taddio’s scale) in the technique of local anaesthesia, when

delivering maxillary infiltration or mandibular block. No significant difference was found when articaine or lidocaine was used during the first or second visit.

The study by Malamed *et al.* (2000b) concluded that VAS scores for patients and investigators indicated that articaine is an effective local anaesthetic when used in children; however, these values were not statistically significant. (P-value was 0.57 for patients and 0.42 for operators) (Malamed *et al.*, 2000). See Table 2.11.

Study	Pain rating		Significant	
	Articaine	Lidocaine		
Malamed <i>et al</i> (2000b)	mean VAS scores for articaine	mean VAS scores for lidocaine		
	Patients: 0.5 simple procedures 1.1 complex procedures  Operators: 0.4 simple procedures 0.6 complex procedures	Patients: 0.7 simple procedures 2.3 complex procedures  Operators: 0.3 simple procedures 2.8 complex procedures	p- value: 0.42   p- value :0.57	
Ram & Amir, (2006)	(Wong–Baker FPS) scores for articaine (time in	(Wong–Baker FPS) scores for lidocaine		
	After injection: 1.08 ± 0.79 After one hour: 0.95 ± 0.65 After two hours: 0.90 ± 0.68	After injection: 1.06 ± 0.73 After one hour: 1.03 ± 0.63 After two hours: 1.03 ± 0.81	No significant difference	
Arrow, (2012)	<b>CHEOPS</b>		p-value : 0.86	
	This scale was used during local anaesthetic administration only			
	no pain	47 patients	no pain	46 patients
	≥ one reaction	9 patients	≥ one reaction	8 patients
	<b>Faces scale during injection</b>		<b>Faces scale during injection</b>	
	No/mild pain	42 patients	No/mild pain	44 patients
	Moderate/sever	14 patients	Moderate/sever	12 patients
	<b>Faces scale during treatment</b>		<b>Faces scale during treatment</b>	
No/mild pain	40 patients	42 patients	37 patients	
Moderate/sever	15 patients	14 patients	18 patients	
<b>Parent report</b>		<b>Parent report</b>		
No behaviour change	34 patients	No behaviour change	33 patients	
≥ one behaviour change	11 patients	≥ one behaviour change	14 patients	
			p-value : 0.57	

Table 2.11: LA success rate in each study

#### **2.9.2.13.4 Adverse event reporting**

In all of the studies included in this review, there was good reporting of adverse events. There were eight reports of postoperative complications including lip-bite, cheek-bite, pain at injection site, tender tooth, and episodes of aching jaw. Tests of association between postoperative complications and LA technique and LA type were not statistically significant (Arrow, 2012).

Adverse events related to articaine and lidocaine were similar for the two solutions and included: accidental lip and/or cheek injury (three patients), post-procedural dental pain (four patients), and haematoma (one patient). Differences between the two solutions were not statistically significant (Ram and Amir, 2006).

There were no serious adverse events related to the study medication, however, at least one minor adverse event was reported. Adverse events noted in the articaine group were post-procedural pain (2%), headache (2%), injection site pain (2%), and accidental injury (2%). In the lidocaine group, the most common minor adverse event was post-procedural pain (10%) (Malamed *et al*, 2000b).

Overall, Table 2.12 summarised and compared the three reviewed studies including study characteristics, interventions, quality assessment and outcome reporting.

Variables		Studies		
		Arrow, 2012	Ram & Amir, 2006	Malamed <i>et al.</i> , 2000 b
Characteristics	Study methods	Cross-over Single centre	Cross-over Two centres	Parallel, active controlled group (Seven centres)
	Total number	57	62	50
	Gender distribution of patients	21 m 36 f	28 m 34 f	36 m 34 f
	Mean age	12.4 years	8.4 ± 2.3 years	Not reported
	Mean weight	52.6 kg	30.44 ± 8.80 kg	Not reported
	Range in years	5-16 years	5-13 years	4-13 years
	Number of patients	A 56* L 57	A 62 L 62	A 50 L 20
Interventions	Local Anaesthetic type	A 4% 1:100 000 L 2% 1:80 000	A 4% 1:200 000 L 2% 1:100 000	A 4% 1:100 000 L 2% 1:100 000
	Local Anaesthetic dose	A : 1.6 mg/kg L: 0.78 mg/kg	Maximum dose was administered A: 5 mg /kg body weight L: 4 mg/kg body weight	A: simple 1.9 ± 0.10 complex 2.5 ± 0.43 L: simple 1.9 ± 0.23 complex 2.6 ± 0.00
	Injection route	IDNB / Infiltration	IDNB / Infiltration	IDNB / Infiltration
	Tooth Type	2nd permanent molar 1st permanent molar 2nd deciduous molar	Not specified 40 maxillary teeth 20 mandibular teeth	Not specified
	Type of treatment	Simple	Simple / complex	Simple / complex
Quality Assessment	Random sequence generation	Adequate	Not reported	Not reported
	Allocation concealment	Adequate	Not reported	Not reported
	Blinding of examiners	Adequate	Adequate	Not reported
	Analysis of losses	ITA	Not applicable	Not applicable
Outcomes	LA success	Clearly identified	Not clearly identified	Not clearly identified
	Pain rating	Child Clinician Parent (Face Pain Scale – Revised)	Child Clinician (Wang – Baker FPS)	Child Clinician (VAS)
	Post-operative complication	Follow up phone call in 2, 4, 24 hours and one week	Follow up phone call in 1, 2 or more hours	Follow up phone call in 24 hours and one week
	others	Time onset Parent report of pain	Time onset	Time onset Safety: vital sings

Table 2.12: Characteristics of included studies

## **2.10 DISCUSSION**

In 1996, Sackett et al. described the systematic review of randomised controlled trials to be the “gold standard” for judging the effects of a treatment or intervention, stating that it is “so much more likely to inform us, and so much less likely to mislead us.” In fact, the Oxford Centre for Evidence-Based Medicine considered the systematic review of randomised controlled trials as the highest level of evidence from which to base treatment decisions, recognising that not all evidence is made accessible (Sackett *et al.*, 1996).

A protocol was developed with the aim to guide the process of conducting the systematic review and to encourage the reviewer to be clear about how the review was to be carried out. It is also a useful tool for promoting transparency, transferability and applicability (CRD, 2009).

The aim of this systematic review is to provide a comprehensive and current overview of the available evidence on the efficacy of local anaesthetic solutions (lidocaine /articaine) used for local anaesthesia in children’s clinical dentistry.

Extensive efforts were made to identify all relevant and comparable clinical studies in order to completely investigate, compare and draw conclusions on these two anaesthetic agents. By applying no limitation to the language as well as conducting interviews with experts to find unpublished studies, the scope of evidence was enhanced.

Studies included in this systematic review were subject to the inclusion criteria standards which were specifically set to regulate the quality of studies included for comparison. Despite this, inconsistencies in methodology and outcome measures with potential sources of bias were observed among the three studies. All included studies in this systematic review were published in peer-reviewed journals, therefore, publication bias was considered a risk; however, this was not assessed as

part of the systematic review. Publication bias has been defined as the trend of published studies to typically have significant/positive results where unfavourable results tend to go unpublished (Sjögren and Halling, 2002).

The quality of an RCT is dependent on all aspects of the study design and trial conduct. A few key features have been shown to have a discriminating effect in assessments of the scientific quality of a trial report (Schultz *et al.*, 1995).

The internal validity of an RCT is strongly related to reporting of adequate methodology for random allocation, double-blinding, patient follow-up and allocation concealment. It has been shown that trials with poor or inadequately reported methodology tend to exaggerate the treatment effects (Schultz *et al.*, 1995)

Although the CONSORT group recommends reporting details of sample size determination to identify the primary outcome and as a sign of proper trial planning, the results of this review revealed that reviewers and editors overlook the important of sample size determination. This view is supported by other researchers in different medical fields (Moher *et al.*, 1994; Freedman *et al.*, 2001; Charles *et al.*, 2009). In this review, two of the three studies (Malamed *et al.*, 2000b; Ram and Amir, 2006), did not have any reference to the sample size determination or how it had been calculated, which increased the risk of bias. It is possible however that the investigators performed them but simply did not report these calculations in the published report. This, however, seems unlikely, since previous studies have found that only rarely do authors perform calculations of sample size and not include them in the published report (Moher *et al.*, 1994).

Randomisation is of central importance in clinical trials. It is the only known way to eliminate selection bias from the trial and also insures against accidental bias. It produces comparable groups and eliminates the source of bias in treatment assignments. Finally, it permits the use of probability theory to express the

likelihood of chance as a source for the difference between outcomes (Rosenberger and Lachin, 2002).

In view of the central importance of randomisation, Malamed *et al.* (2000b) and Ram and Amir (2006), provide inadequate details of the steps taken to allocate participants to comparison groups. However, this was clearly reported in Arrow's study (2012).

Empirical evidence supports the view that inadequate random allocation leads to systematic errors in estimates of intervention effects, due to selection bias. Trials without allocation concealment tend to overestimate the treatment effects (Schultz *et al.*, 1995). Only one out of three RCTs appropriately reported allocation concealment (Arrow, 2012), this was a very low ratio and according to Moher *et al.* (1998), inadequately concealed trials exaggerate estimates of effectiveness by 37%.

Masking was typically reported as 'double-blind'. Double-blinding is related to ascertainment bias and when lacking, is associated with overestimation of treatment effects (Schultz, 1995). Nevertheless, two studies failed to specifically distinguish this for subjects, operators, evaluators and statisticians. Only one study (Arrow, 2012) adequately reported the blinding strategy.

According to Fisher, Intention-to-Treat Analysis is to include all randomised patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol (Fisher *et al.*, 1990).

For the trials that employed a crossover design (Ram and Amir, 2006; Arrow, 2012) it was noted that no losses occurred in Ram and Amir's, (2006) study, and outcome data was available for all randomised subjects. Thus, all participants were included in this trial, and it was considered as an "intent to treat" analysis. However, in

Arrow's (2012) study one patient from the Buccal Infiltration group did not attend the second visit; therefore, the patient has been excluded from the data analysis. Hence, this is not intention to treat analysis.

The Cochrane Collaboration advises that the determination and reduction of bias be the major approach in the assessment of quality of trials within a systematic review. Within this review, quality measures were designed to reduce bias. Language bias was eliminated by ensuring that all relevant studies were in English.

Although a range of local anaesthetic volumes were administered, these volumes were compared similarly as they were considered to be clinically reasonable anaesthetics. However, none of the included trials directly compared equivalent concentrations of articaine hydrochloride and lidocaine hydrochloride. As well as comparing different concentrations of LAs, the trials also covered two different methods for delivering LA. The two most common methods for delivering local anaesthetic solutions in clinical dentistry are infiltration and block anaesthesia (Malamed, 2013). These two means were considered within this review to be the primary routes of anaesthesia delivery.

The RCTs included in this review investigated the efficacy of local anaesthetic solutions when given as a combination of both techniques, local infiltration as well as block anaesthesia. There was a trend of superiority of articaine over that of lidocaine in terms of achieving anaesthetic success, although these results were not statistically significant.

The methodology for tooth selection for anaesthetic evaluation varied greatly within the studies in this review. In this review, either one tooth or many teeth were evaluated per experimental administration.

The main approaches for determining anaesthetic efficacy was through patients, with the patient giving a pain rating using a pain scale instrument during various

dental treatments. The pain scale used in all the trials was the faces pain scale; however, Malamed *et al.* (2000b) used the visual analogue scale (VAS) as another measure in his trial. This approach potentially reflected anaesthetic success and failure based on responses from pulpal, periodontal, or osseous origins (Brandt *et al.*, 2010). Moreover, the dental treatments covered were ones that would be associated with experiencing pain if profound anaesthesia was not achieved. Therefore, it was anticipated that reported pain related to anaesthetic failure, and lack of reported intraoperative pain was conversely associated with anaesthetic success.

The second approach was through operator evaluation, as in Ram and Amir's (2006) study in which the modified behaviour pain scale by Taddio *et al.* (1994) was implemented for objective evaluation of the patients' reaction during injection. The information was recorded by a trained dental assistant who was blinded to the type of treatment.

In Arrow's (2012) study, the dental clinical assistant administered the Faces Pain Scale independently of the treating clinician, and also recorded the behaviour of the child and rated the level of pain displayed using the Children's Hospital of Eastern Ontario Pain Scale, during LA administration and dental treatment.

VAS was used in the Malamed *et al.* study (2000b), immediately following the dental treatment in order to record the rate of pain experienced by the child. This scale included a smiley face to indicate that 'it did not hurt' and a frowning face to indicate 'worst hurt imaginable'.

The pain scale used in all of the trials was the faces pain scale, but with variations in each study. For example, Malamed *et al.* (2000b) used the visual analogue scale (VAS) with modifications to it by adding a smiley face to represent no pain and a crying face to represent extreme pain. In addition, the line was measured in

centimetres (0-10 cm). In the Arrow study (2012), the revised version of the faces pain scale was used. Anaesthesia was considered successful if the child rated it as no or mild pain, and considered as failure if the rating was moderate/severe pain. Whereas Ram and Amir (2006) adopted the Wong-Baker faces pain scale, which consists of six cartoon faces with each face being assigned a numerical value.

The reporting for local anaesthetic onset was not adequately addressed in two of the studies included in the trial. For example, in Malamed *et al.* (2000b) there was no reporting of the anaesthetic onset, while in Ram and Amir (2006) the information given was only related to the technique of injection, and there is no clear results for the local anaesthetic type apart from a singular statement; “No differences were seen between solutions in Onset time”. The results were reported in tables, which were difficult to interpret.

Malamed *et al.* (2000b) did not give a specific definition for the anaesthetic success; the efficacy of the local anaesthetic was determined in gross scale using the visual analogue scale. VAS scores for patients and investigator indicate that articaine is an effective local anaesthetic when used in children; however, these values were not statistically significant. (P-value was 0.57 for patients and 0.42 for operators).

A higher proportion of BI participants reported moderate/severe pain with dental treatment. The association of LA technique with a participant report of pain from dental treatment, may be explained by the observation that the report of pain from dental treatment was significantly associated with LA success,  $p = 0.005$ . There was also a statistically significant association between a participant report of pain on the faces pain scale for dental treatment and LA technique,  $p = 0.02$ ; (Arrow, 2012).

The overall success of LA in the study by Arrow (2012) was 84%, which was similar to the 85% success reported by Ram and Amir (2006). In Arrow (2012), there was also a 100% clinician judgement of LA success with IANB and 68% with

BI, irrespective of the type of local anaesthetic, and he attributed this finding to the fact that the majority of clinicians who participated in the study had at least 15 years clinical experience and in that time they have commonly used IANB in the treatment of mandibular posterior teeth in children, with BI being used less often. Therefore, the clinicians' skill levels for administering the IANB were likely to be high, while the skills for BI in the posterior mandibular region may be lower.

Adverse events were reported adequately in all of the included studies. These reported adverse events were all minors, with no reporting of paraesthesia. However, it was noted in this review that the children were healthy patients who are at less risk of having complications associated with local anaesthesia.

## **2.11 CONCLUSION**

Considering the present findings, the quality of RCTs was generally inadequate. Common methodological inaccuracies which increase the risk of bias of the trials in this review include lack of proper randomisation and allocation concealment, lack of power calculation, lack of intention-to-treat analysis and lack of blind. It is, however, promising that the recently included studies have improved reporting of some study details to enable quality assessment.

Articaine and lidocaine presented the same efficacy when used as infiltration or blocks for routine dental treatments. The effect of numbness of soft tissues was longer using articaine than lidocaine, and few adverse events were reported following the use of both solutions.

The results from this review indicate that articaine injections can cause slightly more post injection pain in the area injected than lignocaine, the difference was not statistically significant.

Ultimately, all the included studies had several limitations in reporting which indicated a need for a proper randomised clinical trial with standardised methodology to address these limitations.

## **2.12 LIMITATIONS**

The systematic review part of this study was conducted by a single reviewer. This may have resulted in an item receiving a score by one reviewer that may have not been selected by another. However, data abstraction was checked several times to avoid errors in data and decrease the likelihood of inaccuracy and bias. As there was no second reviewer this could not be qualified by inter-rater agreement.

Additionally, the results of this systematic review may be indefinite because of the small sample sizes and because children's behaviours are more difficult to control.

## **2.13 IMPLICATIONS FOR RESEARCH**

The outcome of this systematic review has highlighted a number of implications for future research.

- The importance of adequate reporting of the methodology in the RCT conduct and the quality of RCTs needs to be improved.
- Future research must address the methodological deficiencies associated with much of the clinical trials described in this review.
- Researchers are encouraged to be forward-thinking and to design research with standardised methodology and reporting to permit future synthesis.
- Extend research to look at artocaine in the treatment of hypo-mineralised teeth (MIH).

## Chapter 3

### RANDOMISED CLINICAL TRIAL

#### 3.1 ABSTRACT

**Anaesthetic efficacy of articaine hydrochloride versus lidocaine hydrochloride in children. An equivalence parallel prospective, randomised, controlled single centre trial**

**Aim:** The aim of this project was to carry out an equivalence parallel prospective, randomised, controlled study, in order to evaluate and compare the anaesthetic efficacy of mandibular infiltration using 4% articaine (1:100,000 epinephrine) with mandibular nerve block using 2% lidocaine (1:80,000 epinephrine) in the extraction and restoration of mandibular primary molars. In addition, we evaluated the response and reaction of children, in order to recommend the most effective and acceptable method of achieving anaesthesia for dental treatment of mandibular primary molars in children.

**Method:** In total 98 children aged 5–9 years old were randomly assigned into two groups: one group (treatment group) received mandibular infiltration combined with inter-papillary infiltration with 4% articaine with 1:100,000 epinephrine; the other group (control group) received an inferior alveolar nerve block with 2% lidocaine with 1:80,000 epinephrine. All local anaesthetic injections were given by a single operator, who had the role of assessing the presence/absence of pain as well as the child's behaviour during the injection and treatment procedures (using W-BFRS, VAS and Frankl Behaviour Scale). Each child received one treatment for one tooth only.

**Results:** During the injection phase the absolute differences between the two anaesthetic techniques using W-BFRS VAS and behaviour scales was zero (no difference), 0.060 (95% CI -0.110 to 0.230) and -0.080 (95% CI -0.190 to 0.030) respectively. During the treatment phase, the absolute difference were -0.020 (95% CI -0.180 to 0.140), -0.040 (95% CI -0.220 to 0.150) and zero (no difference). The equivalence margin was set at  $\pm 0.2$  and all comparisons showed equivalence of the two treatments except for the comparison of VAS during injection and W-BFRS during treatment with the 95% confidence intervals exceeding the equivalence margin.

**Conclusion:** The results indicated that both local anaesthetics (4% articaine used as BI and 2% lidocaine used as IDNB) provide similar efficacy. Likewise, the children behaviour during the dental treatment was very good and comparable in both treatment groups. The results indicates that it would be acceptable to carry out invasive dental treatment for mandibular primary molars with the administration of infiltration using 4% articaine instead of the traditional method of inferior dental block using lidocaine.

**Trial registration:** EudraCT number: 2011-004711-23

### **3.2 INTRODUCTION**

The randomized controlled trial is one of the simplest but most powerful tools of research. In the randomized controlled trial, the subjects are allocated at random to receive one of several clinical interventions. With the aim to examine the effect of interventions on particular outcomes such as death or the recurrence of disease (Meinert, 2012).

### **3.3 RATIONALE FOR THE PROPOSED STUDY**

Studies are available in the literature that have evaluated the anaesthetic efficacy of articaine for dental treatment on permanent teeth. Most studies have shown that articaine provides better analgesia with comparable safety levels to lidocaine, when used as infiltration or blocks for routine dental treatments in adults. However, as far as we are aware, there have been limited clinical studies conducted to evaluate and compare the anaesthetic efficacy of articaine delivered as infiltration, compared with lidocaine as a dental nerve block, during the dental treatment of mandibular primary molar teeth in children. The administration of an inferior nerve block in children for invasive treatment of mandibular teeth can be difficult, and can sometimes compromise the child's behaviour. An infiltration is relatively less problematic and easier for a child to cope with (Dudkiewicz, 1987).

Therefore, to contribute to a more profound knowledge about the use of articaine as a local anaesthetic for routine dental treatment in children, the purpose of this study was to evaluate and compare the anaesthetic efficacy of mandibular infiltration with 4% articaine with 1:100,000 epinephrine to mandibular block with 2% lidocaine with 1:80,000 epinephrine, in extraction and pulpotomy of mandibular primary molars in children aged 5–9 years old.

### 3.3.1 Aim

The primary aims of this study were as follows:

1. To evaluate and compare the anaesthetic efficacy of mandibular infiltration using 4% articaine (1:100,000 epinephrine) with the efficacy of mandibular nerve block using 2% lidocaine (1:80,000 epinephrine) in achieving adequate analgesia for extraction and pulpotomy of mandibular primary molars.
2. To evaluate the response and reaction of children when they receive the local anaesthetic injection. In addition, the occurrence of adverse events in treated children in order to recommend the most effective and acceptable method of injection for the treatment of primary teeth in children.
3. Explore children acceptance as well as parent satisfaction and experience of their child's dental treatment under local anaesthesia and their perception of the impact of this treatment on their child.

The secondary aims of the study were set in order to evaluate and compare the two local anaesthetics in terms of the following:

- 1) Safety of the LA, considering any adverse events associated with treatment.
- 2) Need for re anaesthesia.
- 3) Need for medication after the dental treatment.

### 3.3.2 Primary null hypothesis: the pain experience during local anaesthesia

**Null hypothesis:** A difference of at least  $\Delta = \pm 0.20$  exists, and the aim of the trial was to disprove this in favour of the alternative hypothesis that no difference exists.

In order to estimate the number of patients necessary for this trial; the power ( $1 - \beta$ ) of the trial should be 80%. The type 1 error risk ( $2\alpha$ ) should be 20%. The therapies would be considered equivalent if the confidence interval for the difference in proportion with sustained response falls entirely within the interval  $\pm 0.20$ .

**Alternative hypothesis:** In the dental treatment of mandibular primary molars, there is no difference in the pain experience between traditional mandibular infiltrations when using 4% articaine with 1:100,000 epinephrine, and the conventional technique inferior alveolar nerve block using 2% lidocaine with 1:80,000 epinephrine.

### **3.3.3 Trial objectives**

1. To assess and evaluate the pain during injection, and treatment by asking the child to rate their pain using the Faces Pain Rating Scale and Visual Analogue Scale (VAS). Also using Frankl behaviour scale to assess the child behaviour.
2. To assess the level of discomfort and numbness by asking the child to identify where they feel uncomfortable and numb (e.g. lip, cheek, tongue etc.).
3. To assess the acceptability of the treatment by both the child and parent using a designed questionnaire.
4. To assess the post-operative pain, pain at the injection site, as well as any adverse effects, such as the length of time for the local anaesthetic to wear off, any lip or cheek biting; this was checked by calling parents/guardians within 24 hours of the dental treatment.

5. To assess the need for reinjection through the observation of the child's discomfort (presence or absence of discomfort/pain), which includes hand and body tension, eye movements indicating pain, verbal complaints, tears, and hand and body movements.

### **3.4 ENDPOINTS**

#### **3.4.1 Primary Endpoint**

- Successful completion of treatment.

Success in this study was defined as no or mild pain during injection and treatment procedures. Pain was measured using W-BFRS and VAS as well as Frankl behaviour scale.

- Child's and Parents' perception of the treatment.

This will be assessed using mixed method approach in order to give more depth and knowledge to the data which cannot be accomplished by quantitative approach alone.

#### **3.4.2 Secondary Endpoint(s)**

- Adverse events reported.
- Need for re anaesthesia.
- Need for medications following the dental treatment.

### **3.5 MATERIALS AND METHODS**

The following sections will illustrate the method adopted in order to achieve the aims and objectives of the research project. It include detailed description of the general outline of the study approach, as well as the research technique descriptions, the data collection methods, in addition to the ways in which data can be analysed.

### **3.5.1 Ethical Approval**

Ethical approval was essential for this research. The related ethical issues along with the ethical process to gain the final ethical approval will be discussed further in the following sections.

### **3.5.2 EUdract Number**

The study has been registered with European Clinical Trials Database (EudraCT). summary of the trial protocol is available through the EU Clinical Trials Register (EU CTR). EudraCT number: 2011-004711-23.

### **3.5.3 National Research Ethics Service (NRES)**

Ethical approval was submitted to NRES, in order to obtain the necessary ethical approval to commence the study. This submission was via an Integrated Research Application System (IRAS).

The study was submitted and approved by the main Research Ethics Committee (REC); (Appendix 5). The committee requests minor changes (Appendix 7) to study forms namely, the patient's information sheet (PIS) (Appendix 19) and assent/consent forms (Appendix 20). In addition, the committee requested further information to the initial application about clarification of why non-English speakers are not being recruited into the study, as it was felt that these patients will have translation services provided (Appendix 8). It was explained to the committee that - In the Leeds Dental Institute we do value and respect the cultural and ethnic diversity of our local and national community. However, in our study it is necessary to limit subjects to English-speaking participants only as it is highly dependent on communication and reaction between the investigator and the child patient and we

needed to get immediate, direct feedback from the child and not through an interpreter, as it would affect the results of the study (Appendix9).

#### **3.5.4 Research and Development (R&D)**

Contact was made with the local R&D office in Leeds area at an early stage of conducting the study. The R&D form generated by IRAS and including sponsorship confirmation (Appendix 5) was submitted, along with the site-specific information form (SSI) for Leeds dental Hospital and all the supporting documentation (Appendix11).

#### **3.5.5 MHRA**

Since this study was a clinical trial of an investigational medicinal product (CTIMP) and to be conducted in the UK - that fall within the scope of the EU Clinical Trials Directive and the Medicines for Human Use (Clinical Trials) Regulations 2004. A Clinical Trial Authorisation was required for this clinical trial. The application form was part of the IRAS application form. The MHRA was contacted by the PI and the final approval was obtained (see Appendix 12).

#### **3.5.6 Pharmacy**

The study protocol and all the relevant documents were submit to the pharmacy department at the Leeds teaching hospital, including the SSI form and IRAS form; as part of clinical review process (Appendix 13).

### 3.5.7 Sponsor

University of Leeds had full legal responsibilities in accordance with the Clinical Trials Regulations. The sponsor confirmation letter (Appendix 10) and sponsor final approval form can be seen in Appendix 14.

### 3.5.8 Ethical Considerations

This clinical trial, which notably involves the use of an investigational medicinal product, has been designed and run in accordance with the Principles of GCP, as well as the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.

The trial was performed in accordance with the recommendations guiding ethical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Assembly, Helsinki, Finland, 1964, amended at the 48<sup>th</sup> General Assembly, Somerset West Republic of South Africa, October 1996. Informed written consent was obtained from the patients prior to randomisation/registration within the study. The right of a patient to refuse participation, without providing any reason for such, was respected. The patients were also free to withdraw from the study at any time without giving reasons and without prejudicing his/her further treatment. The approval numbers for the trial are given in Table 3.1

<b>Protocol number:</b>	DT11/9936
<b>IRAS project ID:</b>	82161
<b>EudraCT number:</b>	2011-004711-23
<b>REC reference:</b>	13/YH/0049
<b>MHRA Reference number:</b>	2286/0001/001-0001

Table 3.1: Study's approval numbers

### **3.5.9 Data Monitoring and Quality Assurance**

This research underwent regular monitoring and audit. Meetings were held with research supervisor on a monthly basis or more frequently when needed (Appendix 16a/ 16b).

Auditing was carried out by the Quality Assurance/R&D Leeds office. It involved periodic independent review of core trial processes and documents. Auditing was intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action if necessary. The processes reviewed was related to participant enrolment, consent, eligibility, and allocation to study groups; adherence to trial interventions and policies to protect participants, including reporting of harms; and completeness, accuracy, and timeliness of data collection.

### **3.5.10 Selection of patients**

The following sections will illustrate the selection criteria for the study participants.

#### **3.5.10.1 Inclusion Criteria**

- Children aged 5–9 years.
- Medically fit (ASA I,II).
- Requiring extraction /restoration (pulpotomy treatment) of primary mandibular molar teeth under local anaesthetic.
- A good understanding of English.
- Mentally capable of communication.
- Having a mandibular primary molar tooth that required extraction or pulpotomy. The tooth should have no history of infection

(abscess) or swelling and no evidence of periapical pathosis or soft tissue infection/inflammation near site of injection.

- Root resorption of the primary molar to be treated must be less than two-thirds of the root.
- Child must give assent prior to participation, as well as parental informed written consent.
- Body weight more than 20 Kg.

#### **3.5.10.2 Exclusion Criteria**

- Medically and mentally compromised children.
- History of significant behaviour management problems.
- Evidence of infection near the proposed injection site as this might affect the efficacy of local anaesthesia.
- Child did not speak or understand English.

#### **3.5.11 Sample size/power calculations**

This equivalence trial was designed to assess the efficacy between two types of the local anaesthetic used with different injection techniques i.e.; articaine as buccal infiltration (BI) and lidocaine as Inferior Dental Nerve Block (IDNB). The margin of equivalence,  $\Delta$ , was 0.20 and the range  $-0.20$  to  $0.20$  was predefined as an acceptable range of completion rates between the two types of local anaesthetics. The equivalence margin was based on clinically important differences obtained from previous studies. The sample size of 98 children was calculated to be sufficient with 80% power to establish equivalence and significance level 5%. Allowing for drop-off and failure to complete the trial, an estimated sample of 110 participants for the trial was required. We assumed a dropout rate of approximately 10%.

## **3.6 RECRUITMENT, CONSENT AND RANDOMISATION PROCESSES**

### **3.6.1 Recruitment**

Children were recruited from the Paediatric Dentistry Clinics at the School of Dentistry at the University of Leeds. They were approached by the clinical trial team and the principle investigator to assess their eligibility for treatment.

The screening process started by checking all the patients' notes attending for consultation and/or treatment in the period between November 2013 and March 2015 in order to identify the potential patients for the study. The collected information were related to the patients' age, medical history and treatment needed.

Children who fulfilled the inclusion criteria for the trial were approached by the principle investigator (PI) and a verbal explanation of the study, along with a patient information sheet (PIS) was provided for their consideration. A clinical and radiographic examination was carried out during the assessment phase.

#### **3.6.1.1 Storybook**

In this research, as well as securing the consent of the child's parent/guardian, attempts were made to secure the assent of the child. Notably, the assent of the child participants was achieved through the use of developmentally suitable approaches, taking the form of a specially designed storybook, which took the child through the study process, phase by phase, and described all what is involved (Appendix 17). This was approved by the local research ethics committee. The story begin in the dental reception area, when the dentist come out to call the child along with her/his parents. Then, child will sit on the dental chair (which is very similar to the real one). The child (patient) then was asked to set on the dental chair in a similar

position to the child in the picture. PI used tell-show-do technique and compared the picture in the story with the real one in the clinic. The PI pointed out the subjects in the picture and asked the child to point out the similar things that she/he could see in the clinic. The story described the dental treatment step by step, and it was used as a model for the child i.e. the child in the story was a 'superstar' child.

Using the 'super star' child as a model, was found to be very useful in this study, in terms of helping the child to exhibit appropriate behaviour during the dental treatment and reduce their anxiety. This finding is in accordance with many studies in dental literature. In Melamed study, Videos showing treatment similar to that about to be undertaken used prior to restorative work have shown greatly reduce disruptive behaviour in 5-9 year olds with little dental experience (Melamed, 1975).

### **3.6.2 Informing referring practitioners**

Once parents/children consent/assent had been obtained, a letter was sent to the patients' general dental practitioner, informing them of the patients' enrolment within the study (Appendix 18).

### **3.6.3 Patient Information Sheet (PIS)**

PIS were provided to parents/guardians. Children received an information leaflet specifically designed for children (Appendix 19). Following the provision of information, patients and their parents\guardians were given a minimum of one hour and up to one week, to consider participation, and were also given the opportunity to discuss the trial with their family and healthcare professionals before being asked whether or not they would be willing to take part in the trial. This process was documented clearly within the patients' dental records.

#### **3.6.4 Consent/Assent**

An informed, written consent (parents\guardians) and assent form for the patient (child) was obtained. The right of the patient's parents\guardians to refuse consent without giving reasons was respected. The process of obtaining written consent and assent was documented clearly in the patients' dental notes (Appendix 20a /20b).

#### **3.6.5 Randomisation**

Simple randomisation procedure was applied. A random number generator algorithm was determined by computer. Each number (0/1) determined the type of local anaesthetic to be used. A two legs randomisation log was created and used for the trial.

#### **3.6.6 Allocation concealment**

Sequentially numbered, opaque, sealed envelopes were used. These envelopes were opened in sequence only after participant details and consent were obtained (Appendix 21).

#### **3.6.7 Un-blinding**

The patients were blinded to the type of injection, and were not informed to which treatment group he/she belonged. Only partial information was given about the expected anaesthetic effect. The operator (investigator) was not blinded, and did know what type of local anaesthetic was given at the appointment visit. The outcome assessor was blinded to the type of local anaesthetic given.

### **3.6.8 Patients who withdraw consent**

Patients had the right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, and treatment failure following a prescribed procedure, protocol deviations, administrative reasons, or other reasons. If a patient decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. At the time of the patient's withdrawal, a complete final evaluation was made, comprising an explanation of why the patient was withdrawing from the study.

If the reason for the removal of a patient from the study was an adverse event, the principal specific event or test was recorded on the case report form (CRF) (Appendix 22).

## **3.7 TRIAL DESIGN**

This was a parallel prospective, equivalence randomised control trial comparing the anaesthetic efficacy of 4% articaine with 1:100,000 epinephrine to 2% lidocaine with 1:80,000 epinephrine, in the dental treatment of mandibular primary molars for children aged 5–9 years old.

The patients were randomly assigned into two groups: one group (treatment group) which received mandibular infiltration with 4% articaine with 1:100,000 epinephrine; the other group (control group) received inferior alveolar nerve block with 2% lidocaine with 1:80,000 epinephrine.

### **3.7.1 Trial protocol**

A protocol had been developed for this clinical trial. The protocol was developed following the SPIRIT (2013) checklist and in accordance with GCP (Chan *et al.*, 2013). It was followed throughout the clinical procedures and used as a reference guide for the clinical trial team (Appendix 2). The R&D office in Leeds had developed a standard operating procedure (SOP) to help maintain consistent clinical reporting as well as to maintain consistent processes at the site.

### **3.7.2 Operator (PI)**

Principle Investigator (PI), who is a postgraduate student in Paediatric Dentistry (Fatma Alzahrani) carried out this study. She was responsible for the management and integrity of the design, conduct, and reporting of the research project and for managing, monitoring, and ensuring the integrity of any collaborative relationships. Adhering to the guidelines for Good Clinical Practice (GCP), starting by developing the study protocol, applying for ethical approval from all the relevant parties, management of the clinical trial process and stages. This included:

- *Patient (participants) management:* patient screening and recruitment, obtaining consent/assent from the participants and parents/guardians, undertaking the dental treatment (local anaesthetic injection and extraction or restoration), administer the post-operative questionnaire to the participants and parents/guardians, supervise the dental nurse during giving the pain scales tools to the child (participant), arrange with the parents the follow up phone call in order to record any postoperative side effect or adverse reactions and data collection and recording of the clinical outcome.

- *IMPs' management*: this included maintenance of up-to-date records for the drug accountability; maintaining up-to-date records of the drug storage and temperature monitoring.
- *Data management*: this included maintaining accurate and keeping up-to-date the following documents: CRF, TMF, randomisation log, screening log, pharmacy log, delegation log, and investigator log (Appendix 22, 24, 25, 26, 27, 27, 29)
- *Reporting Adverse Events*: an adverse event log was developed in order to record all the adverse events that occur during the course of the clinical investigation (Appendix 30).
- *Communication*: this was done by having routine meetings between the investigator and study supervisors and clinical trial team as this was an important way to ensure effective communication among study team members. These meetings were very useful as part of regularity monitoring and raising any concerns that needed to take immediate action (Appendix 31).

### **3.7.3 Local anaesthetics**

#### **3.7.3.1 Drug accountability**

Drug accountability included: study local anaesthetics storage, handling, dispensing, and documentation of administration, return and/or destruction of the drug (local anaesthetics). Drug accountability was crucial for monitoring and ensuring clinical trial data integrity. A logbook was developed for this purpose in order to track each local anaesthetic dispensing unit, and site location, as well as by batch, label and expiration date, and patient allocation.

The principal investigator (PI) was responsible for maintaining adequate records of the disposition of the local anaesthetics, as well as ensuring proper security and storage of the local anaesthetics. The drugs accountability log was kept by PI in the Clinical Master File (CMF) - pharmacy section. The log contain the following information:

- Study identification information and numbers
- Protocol title and number
- Subject identification code
- Type of the local anaesthetic
- Batch number
- Expiration date

### **3.7.3.2 Drug supply and Storing**

Local anaesthetics used for this trial was ordered by the dental nurse who is usually responsible for the dental material supplies in the paediatric clinic. The local anaesthetics used for this trial were considered as an open- label study drug; which means they could be supplied and maintained in study inventory and could be dispensed to any patient scheduled to receive them. One batch of each local anaesthetic had been allocated to the trial once the trial had full approval to be initiated. At one stage of the trial, the local anaesthetic (4% articaine) was about to expire, therefore, it was replaced by a new batch. The remaining local anaesthetic was returned to the main drug storage cabinet (different to the trial drug cabinet) to allow other practitioner within the department to use it before it expired. This step was taken to ensure that there was no waste of material as the local anaesthetic used

for the clinical trial was the same as the one used in the department and from the same supplier (SEPTODONT Ltd).

The local anaesthetics used for this trial was securely stored in a temperature-controlled drug storage cabinet. Only the senior dental nurses had access to the cabinet. The PI was responsible for maintaining documentation, such as temperature monitoring logs (Appendix32), to verify that the medication was stored under the proper conditions.

### **3.7.3.3 Coordination with a Pharmacy Department**

This procedures were carried out according to the regulations governing the use of investigational drugs, i.e., MHRA regulations as the failure to account for and manage study drug was considered as noncompliance.

### **3.7.4 Pre-operative procedures**

*Information:* The participant and parent were provided with limited information with regard to the injection type and technique, in order to ensure the child's behaviour was not altered and his/her attention was not drawn to the injection. The information given included whether or not the tooth would be removed or saved, how the topical gel will be placed, and what the child should expect (numbness). All of this information was explained to the children verbally. For the younger age group and children with no previous dental experience, a storybook (designed by the principle investigator) was used to explain the dental procedures and help in behaviour guidance (see Appendix 17).

**Child weight:** Each child undergoing treatment was weighed on the day of treatment. The acceptable minimum weight was set at 20 kilograms in order not to exceed the maximum dosage for local anaesthetics.

**Radiographic examination:** This was carried out to confirm the dental clinical diagnosis.

### **3.7.5 Technique of local anaesthesia**

#### **3.7.5.1 Topical anaesthesia**

Lignocaine topical anaesthetic (10%) was applied for one minute to the dried injection site using cotton rolls prior to injection. Topical anaesthetic was used prior to injection so as to minimise the pain felt when administering the local anaesthetic. This was used according to the existing acceptable practice.

#### **3.7.5.2 Buccal infiltration injection**

Local anaesthetic used for buccal infiltration was Septanest 1:100,000 articaine hydrochloride 4% with adrenaline (epinephrine) injection 1:100,000 solution for injection—2.2 ml SEPTODONT Ltd.

The study used the Ultra Safety Plus, Sterile injection system with protective sheath, 30 G 10 mm—2.2ml. These are special safety needles, with a plastic slide to protect the needle and allow it to be unscrewed from the syringe.

The BI was administered at the buccal apex of the mandibular primary molar under treatment, and was combined with buccal intra-papillary infiltration in order to anaesthetise the lingual area. The injection rate was approximately 1 ml per minute.

### **3.7.5.3 Inferior dental nerve block**

Local anaesthetic used for dental nerve block was Lignospan Special, Lidocaine hydrochloride 2% and adrenaline (epinephrine) injection 1:80,000 solution for injection—2.2 ml SEPTODONT Ltd.

The injection was administered using special safety needles, with a plastic slide to protect the needle and allow it to be unscrewed from the syringe.

The system used was the Ultra Safety Plus, Sterile injection system with protective sheath, 30 G 25 mm or 27 G 35mm—2.2mL depending on the child's body build.

The dental nerve block was administered by the traditional inferior alveolar nerve block (IDNB) technique, as this is the best way to maximise the chances of achieving success (Meechan, 1999). The block was injected at a rate of approximately 1 ml per minute.

### **3.7.5.4 The amount of anaesthetic solution used**

The amount of anaesthetic solution used was recorded in ml. During the trial, a standard amount of one cartridge for each drug was used.

➤ **Articaine: maximum dose = 5 mg/kg.**

Therefore, for a 20 kg child a maximum dose of 100mg was used ( $5\text{mg} \times 20\text{ kg} = 100\text{mg}$ ).

4% articaine = 40mg/ml.

$100\text{ mg} / (40\text{ mg/ml}) = 2.5\text{ml}$ .

Accordingly, one cartridge of 2.2 mL is the maximum dose.

➤ **Lidocaine: maximum dose with adrenaline = 7 mg/kg.**

Therefore, for a 20 kg child a maximum dose of 140mg was used ( $7 \text{ mg} \times 20 \text{ kg} = 140 \text{ mg}$ ).

2% lidocaine = 20 mg/ml.

$140 \text{ mg} / (20 \text{ mg/ml}) = 7 \text{ ml}$ .

Accordingly, three cartridges of 2.2mL is the maximum dose.

### **3.7.5.5 The need for re-anaesthesia**

Prior to starting the treatment, patients were given 10 minutes to allow for the anaesthetic to reach optimum efficacy, this was based on clinical studies which showed that 6-10 minutes should elapse before any painful dental procedures including pulp treatment and extraction (Corbett *et al.*, 2008).

After this 10-minutes delay, if the child reported any symptoms of discomfort during treatment, the treatment was stopped and adequacy of local analgesia was assessed. After a five-minute wait, upon further assessment, if there were any signs of discomfort indicating pain, the presence of pain was recorded, the procedure discontinued, and the anaesthetic technique recorded as inadequate.

Subsequently, supplementation with another trial local anaesthetic and/or technique was administered to the child to facilitate the treatment. If the patient still showed any signs of pain or discomfort then the treatment was terminated and another appointment was made for another time. If there was a need to re-anaesthetise, the surgical zone was recorded, specifying the technique and the amount of anaesthetic solution used.

### **3.7.5.6 Operative treatment**

Rubber dam was used routinely and standard pulpotomy procedures were carried out. Tooth extraction was carried out using forceps and elevators if needed.

## **3.8 ASSESSMENT OF EFFICACY**

### **3.8.1 Pain assessment**

Pain was assessed after each stage of dental treatment; the effectiveness of anaesthesia was assessed by evaluating the presence or absence of pain during the injection, during labial and lingual probing for anaesthesia, whilst placing the rubber dam, during the use of the high and low speed hand piece, during the removal of the coronal pulp, during the pulpotomy procedure and during extraction.

#### **3.8.1.1 Wong-Baker Faces Pain Rating Scale (W-BFPS)**

Before starting any dental procedure, each child was introduced to the Wong-Baker Faces Pain Rating Scale (Figure 3-1) and the Visual Analogue Scale. This was to ensure that each child was familiar with the scales and understood what they would be asked to do. Immediately after the injection of the local anaesthetic, the children were asked to complete the W-BFPS for subjective evaluation of the feeling after injection (Baker and Wong, 1987).

Verbal instructions were given to the child on how to utilise the W-BFPS. The scale measures the unpleasantness or affective dimension of a child's pain experience. The values for this scale are presented in the form of six faces, ranging between zero and five, where zero is 'no hurt' and shows a happy face. Face number five shows crying and a sad face and relates to feeling as much hurt as you can imagine (It is not necessary for the child to be crying to feel this much pain), this was explained to the child as well to make sure they reported their pain as accurately as possible (Baker and Wong, 1987).

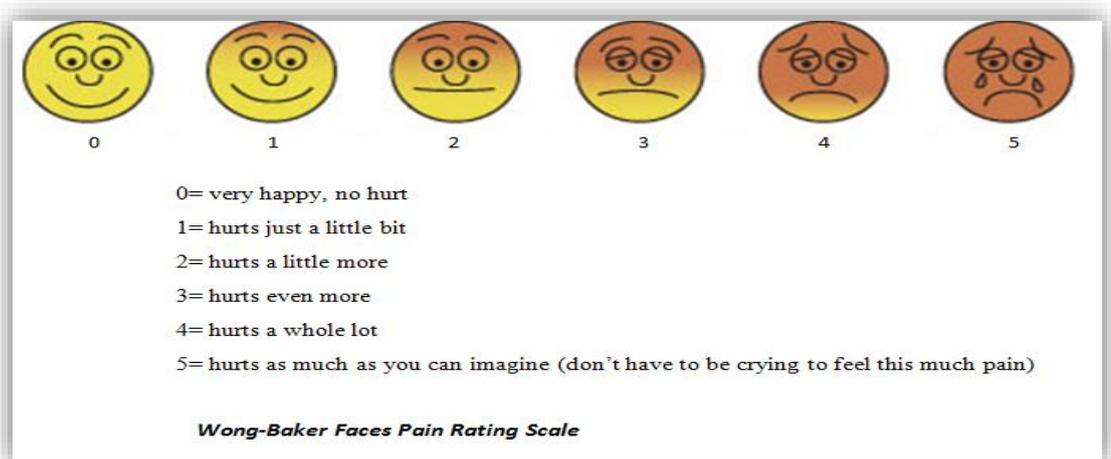


Figure 3-1: Wong-Baker faces pain-rating scale (W-BFPS)

### 3.8.1.2 Visual analogue scale (VAS)

The VAS is a 10 cm line with 'no pain' at one end and 'pain as bad as it could possibly be' at the other end, think it *hurts*."

Figure 3-2 .The children were asked to rate the level of pain that they were currently experiencing. The line was divided into ten lines to aid the child in reporting his/her pain level.

### 3.8.1.2.1 Description of the VAS to the child

In order to ensure that all children knew how to use the VAS a standard explanation was provided as follows:

*“Now I want you to make a mark on this line (point to VAS line) to tell me how much the magic wand hurts when we put your tooth to sleep (then when we wiggle your tooth or when we put the silver cap on). If you put a mark over here (point to the far left of the line) it means (putting your tooth to sleep/wiggling your tooth/fixing your tooth and having the silver cap) didn't hurt at all.*

*If you put a mark over here (point to far right of line) it means (putting your tooth to sleep/ wiggling your tooth/ fixing your tooth and having the silver cap) hurt as bad as the worst pain you can imagine. If you make a mark somewhere in the middle (point to range of middle of line) it tells me that (putting your tooth to sleep/ wiggling your tooth/ fixing your tooth and having the silver cap) hurt a middle amount. Remember that you can put your mark anywhere on this line and the closer to this end that you put it (point to the right end of the VAS line below), the more you think it hurts.”*



Figure 3-2: Visual analogue scale (VAS)

### **3.8.2 Assessment of lip/tongue numbness**

Children were asked to report any feeling of numbness (lip/tongue numbness) and the operator carried out soft tissue testing using a sharp instrument five minutes after the completion of the local anaesthetic administration; if numbness was considered sufficient, treatment was commenced.

### **3.8.3 Signs of discomfort**

Signs of discomfort included hand and body tension, eye movement indicating pain, verbal complaints, tears, and hand and body movements.

We did not use any observational scale to quantitate discomfort; either there was discomfort or not and this is translated as the presence or absence of pain. This was documented in the CRF.

### **3.8.4 Child's behaviour**

Distraction and conventional non-pharmacological techniques of behaviour management were used. Reframing techniques, i.e. using euphemistic phrases to explain the procedures to the children such as, 'jungle juice', 'magic wand' and 'putting the tooth to sleep', were used to describe the local anaesthetic, needle and feeling of numbness to all the children (McDonald *et al.*, 2011).

The child's behaviour was assessed during the injection of the local anaesthetic and during the treatment procedures, through the use of the Frankl behaviour rating scale immediately after each step, See Table 3.2.

<b>Rating</b>	<b>Categories of behavior</b>	<b>Level of acceptance</b>	<b>Influence on treatment</b>
<b>1</b>	Active physical resistance, protest, screaming. Refuse of treatment, crying forcefully, fearful, or and other overt evidence of extreme negativism.	Definitely negative No acceptance	Treatment cannot be carried out without physical control.
<b>2</b>	Crying, no cooperation, some evidence of negative attitude but not pronounced. (i.e., sullen, withdrawn)	Negative acceptance	Treatment cannot be carried out without undue delay. Raised hands interfering with the treatment.
<b>3</b>	Signs of resistance such as strained muscles. Reserved attitude. No answers but following direction with cooperation.	Positive Reluctant acceptance	Treatment can be carried out without undue delay. Raised hands but no interference with the treatment.
<b>4</b>	Relaxed, calm eyes, talking and showing interest in the procedure. Good cooperation	Definitely Positive acceptance	Treatment can be carried out immediately (after proper information).

**Table 3.2:** Frankl behaviour rating scale

### **3.8.5 Assessment of safety**

Following the treatment, the parents were given instructions in order to record the time that the feeling of numbness disappeared and to report any adverse event i.e. cheek and/or lip biting, or pain within 24 hours after the dental treatment.

A follow up phone call was made to the child's parent/guardian within 24 hours of the treatment to assess any adverse event or complications. Information about adverse events (AEs) was collected and recorded on the CRF.

### 3.8.5.1 Defining Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient during or following the administration of an investigational product, and which does not necessarily have a causal relationship with treatment. Therefore, an AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs.

### 3.8.5.2 Reporting AEs

Information about AEs—whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation—was collected and recorded on the CRF. Notably, a copy of all reported AEs was sent to the sponsor.

## 3.9 TRIAL SCHEDULE PROCEDURES

This part will demonstrate the clinical trial processes which was done through multiple phases as illustrated in the Figure 3-3 below. Further details about these practical tasks will be discussed in the following parts.

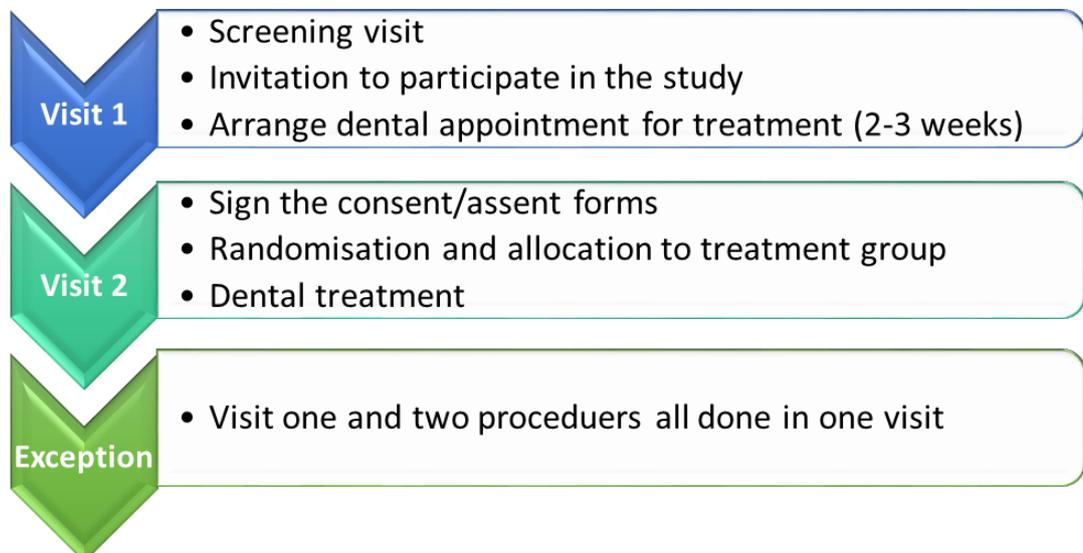


Figure 3-3: Clinical Trial Process

### **3.9.1 Patients screening**

Participant was seen for the first time in the new patient clinic at Leeds Dental Institute; whilst there a screening sheet was completed (see record case form) for each patient's notes (aged 5–9 years old). If the child fulfilled the inclusion/exclusion criteria, the child and parents/guardians were invited to participate in the study, and on their initial agreement, the study information sheet was provided to them, and an appointment for the treatment arranged for 2–3 weeks' time.

### **3.9.2 Patient's recruitment**

At the second visit, the consent form and the assent form was explained again and signed by the parents/guardians of the child and the patient (child), as well as by the principle investigator. The child was allocated randomly to one of the treatment groups, and the dental treatment was carried out by the principle investigator.

### **3.9.3 Special cases**

Some patients were seen in the screening visit, those patients needed a dental treatment on the same day, therefore; and to facilitate recruitment and to ensure the clinical team were acting in the best interests of the patient. They received their dental treatment on the same day; according to the study protocol and this was done in accordance with the randomisation table.

## **3.10 STATISTICAL ANALYSIS**

All collected data were entered into SPSS (Statistical Package for Social Sciences, Version 20) for Windows (SPSS Inc. Chicago, IL), software to analyse data. The first step was data cleaning to test data for missing values and checking for any

errors prior to starting data analysis. The screening and cleaning of the data is essential in order to perform accurate statistical analysis.

### **3.10.1 Descriptive analysis**

Data were tested for normality of distribution using Wilks Shapiro test. Following this step, descriptive statistics for patients and tooth characteristics by treatment group and overall were produced. Quantitative data were analysed using means and standard deviations and categorical data such as success rates were analysed using frequencies and proportions.

### **3.10.2 Univariate analysis**

Comparisons of patient and tooth characteristics between the two treatment groups were conducted using an independent t-test for normally distributed data. Comparisons of categorical data between the two groups were conducted using the chi-square test and z test for comparing two proportions. A  $P \leq 0.05$  was considered statistical significant.

### **3.10.3 Equivalence trials**

The statistical power of an RCT is the ability of the study to detect a difference between the groups when such a difference exists. In the equivalent trial, an equivalence, trial would use the 2-sided 95% confidence interval of the difference between the two trial arms (Piaggio *et al.*, 2012). Since proof of exact equivalence is impossible, a pre stated margin of equivalence is defined as the treatment effect being between  $-\Delta$  and  $+\Delta$ , in another word, a true (2-sided) equivalence approach;

in which a difference in either direction from the reference treatment is of importance (Piaggio et al., 2012). In equivalence trials, equivalence is demonstrated when the entire two sided  $(1-\alpha) \times 100$  CI lies within  $-\Delta$  and  $\Delta$  (CONSORT, 2012). In consequently, in this study, for the primary endpoints equivalence was demonstrated if the 95% confidence interval lied between -0.2 and 0.2. Figure 3-4, shows the criteria that is used to establish equivalence for equivalent trials.

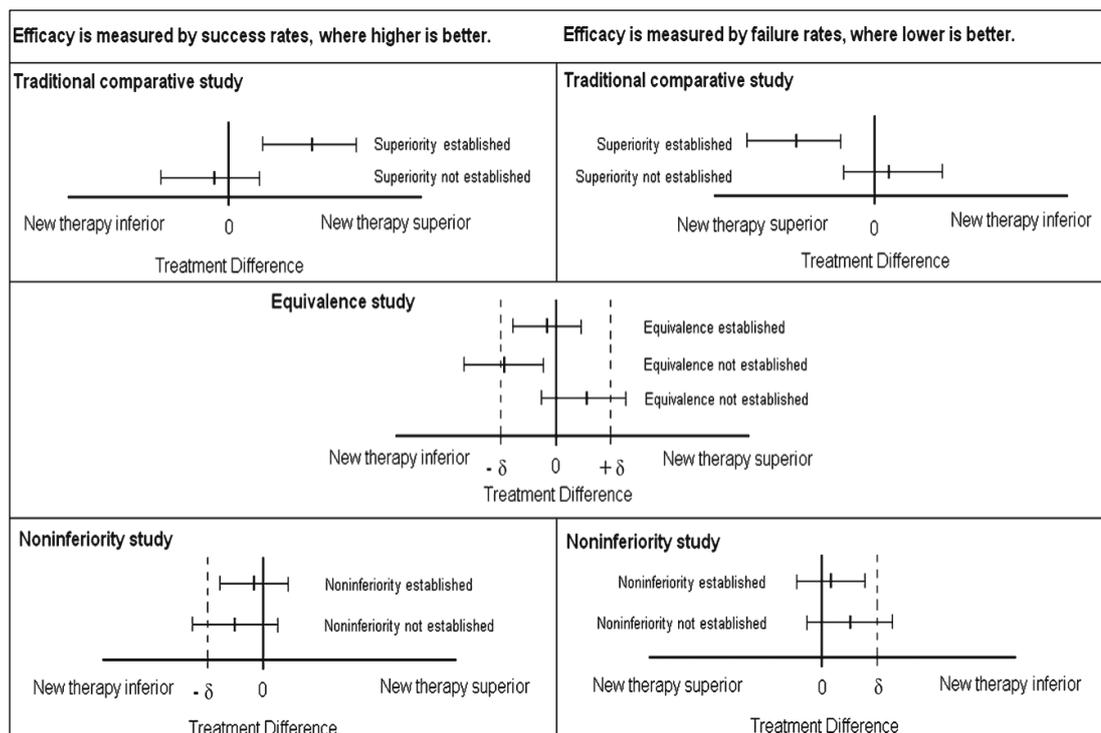


Figure 3-4: Two one-sided test and the equivalence margin ( $-\delta$  to  $+\delta$ ) in equivalence testing:

Adapted from Walker et al., 2011

The trial was designed as an equivalence trial for the primary outcome measure. The primary endpoint was completion of the treatment with no or mild pain. The analyses for the primary endpoints were on an intention-to-treat basis. There was no scheduled interim analysis, and the study reached the planned target. The other secondary outcomes were analysed for superiority.

### 3.10.4 Study variables

Study outcomes were classified as follows:

1. LA success coded as 0 = 'failure', 1 = 'success' 2 = no treatment.
2. Child report of pain for LA administration and for dental treatment;
  - faces pain scale coded as 0 and 1 = (1) success, 2-5 = (0) failure
  - VAS: coded as 'no or mild pain' 0-3 = (1) success and 'moderate to severe pain' 4-10 = (0) failure.
3. Child behaviour (based on Frankl behaviour scale) during dental injection and treatment was coded as: positive behaviour 3-4 = (1) success; negative behaviour 1-2 = (0) failure.
4. Need for re-anaesthesia Yes = 1 No = 0
5. Postoperative complications; 'none' = 0 soft-tissue injuries = 1 and 'other complications' = 2.

## **Chapter 4**

### **RESULTS**

The results of the study are presented in this section. The population sample was described followed by descriptive statistics of variables. Tables and figures were used to present the results where appropriate.

#### **4.1 STUDY SAMPLE**

A Total of 357 children who attended the Paediatric Dentistry Department at Leeds Dental Institute in the period between November 2013 and March 2015 were assessed for eligibility. Out of this total, 98 patients fulfilled the inclusion criteria and agreed to participate in the present study; they were subsequently recruited and then randomised in to one of the treatment groups. The distribution of the sample was precise, in which half of the sample 49 (50%) children were randomised to have one type of local anaesthetic. Figure 4-1 will demonstrate the study flow chart.

In articaine group, one child had local anaesthetic injection and then refused to have any further treatment. Conversely, in lidocaine group two children showed good motivation and agreed to participate in the study and then after been randomised, they refused to have any treatment. Those two children were referred to have their planned dental treatment under general anaesthesia. All patients were included in the analysis.

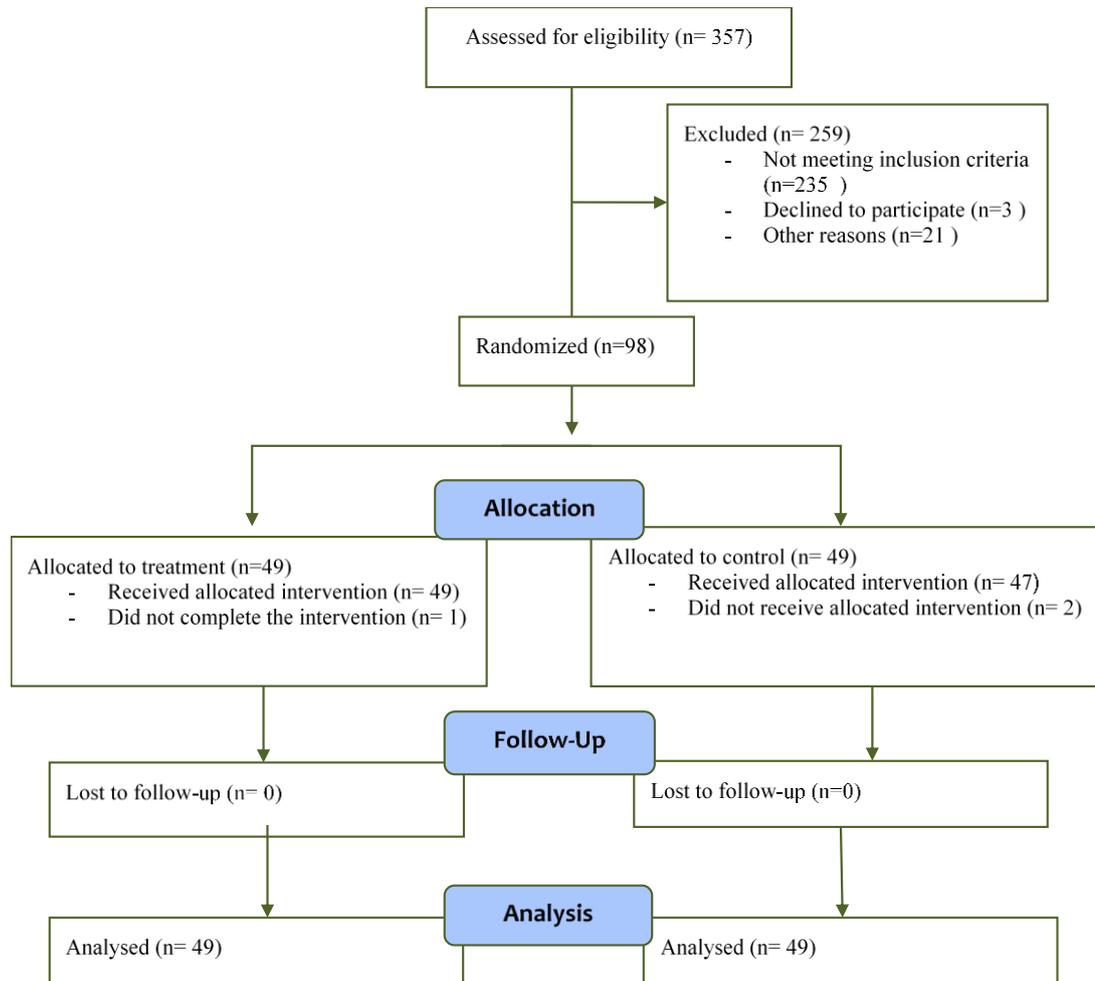


Figure 4-1: Trial flow chart

#### 4.1.1 Patient characteristics

Clinical and demographic characteristic of the randomised patients are summarised in Table 4.1. Key demographic features were evenly distributed between treatment groups. There were slightly more male (n= 53) patients than females (n= 47) with a mean age of 6.52 (SD = 1.19) years. The youngest patient was 5 years old and the oldest patient was 9 years old.

Approximately 76 (77.6%) of the children were in age group 5-7 years. There were 17 (17.3%) children at age eight years and only five (5.1%) were nine years old. The means ages for patients in the two treatment groups were comparable and they were no statistically significant difference between the mean ages. The BI group had a higher proportion of females, 53.1% compared to 38.8% in the IDNB group but the difference was not statistically significant (P=0.156).

Variable		IDNB	BI	P Value	Overall
Age	Mean (SD)	6.57 (1.24)	6.47 (1.14)	0.672	6.52 (1.19 )
	Gender			0.156	
Gender	Female	19 38.8%	26 53.1%	0.156	45 45.9%
	Male	30 61.2%	23 46.9%		53 54.1%
Local anaesthetic experience	Yes	31 63.3%	30 61.2%	0.835	61 62.2%
	No	18 36.7%	19 38.8%		37 37.8%
Tooth type	First primary molar	29 59.2%	23 46.9%	0.225	52 53.1%
	Second primary molar	20 40.8%	26 53.1%		46 46.9%
Treatment	extraction	36 73.5%	35 35.7%	0.269	71 72.4%
	Pulpotomy and SSC	10 20.4%	14 28.6%		24 24.5%

Table 4.1: Patient and tooth characteristics by treatment group

#### 4.1.2 Tooth type

Regarding the tooth type, 52 (53.1%) teeth were first primary molar and 46 (45.9%) were second primary molar. The lidocaine group had a higher proportion of first molars (59.2%) compared with the Articaine group which has higher proportion of second primary molars (53.1%) but the difference was not statistically significant (see Table 4.1).

### **4.1.3 Previous dental experience**

In relation to the local anaesthetic previous experience, 61 (62.2%) children had local anaesthetic at least once and 36 (36.7%) had previous extraction carried out under local analgesia. The Lidocaine had a slightly higher percentages of children with treatment experience (63.3%) compared with the Articaine group (61.2%) but the difference was not statistically significant as seen in Table 4.1.

## **4.2 TREATMENT EFFICACY**

In this section, the results for the primary endpoints will be presented: As described in section 3.3 of this thesis, the endpoint was analysed as an equivalence trial with an equivalence margin of  $\pm 0.2$ .

### **4.2.1 Local analgesia success during injection phase**

When W-BFRS was used to record the pain during the injection of local anaesthetics, Success rate was (63.3%) in both treatment and control groups.

When using VAS, the success rate was (73.5%) for Articaine group and (79.6%) for lidocaine group. Absolute difference of 0.060 (95% CI -0.110 to 0.230) was found.

Behaviour of the child during the injection of local anaesthetic was recorded, and the majority of the children showed positive behaviour for both study groups with success rate of 95.9% and 87.8% for articaine and Lidocaine respectively. Absolute difference of -0.080 (95% CI -0.190 to 0.030) was noted (see Table 4.2).

#### 4.2.2 Local analgesia success during treatment phase

During the treatment phase, success rate measured using W-BFRS was 70.8% and 67.3% for articaine and lidocaine respectively with absolute difference of -0.040 (95% CI -0.220 to 0.150).

VAS results showed almost similar success rate (81.6%) for articaine and (79.6%) for lidocaine. Absolute difference of -0.020 (95% CI -0.180 to 0.140) was found. Likewise, the children behaviour during the dental treatment was very good and comparable in both treatment groups. Success rate was 91.8% as shown in Table 4.2.

		Lidocaine n (%)	Articaine n (%)	Absolute difference (95% CI)	P value
<b>Injection</b>	<b>W-BFSR</b>	31(63.3%)	31(63.3%)	0.000 (-0.190 0.190)	0.347
	<b>VAS</b>	39 (79.6%)	36 (73.5%)	0.060 (-0.110 0.230)	0.191
	<b>Behaviour</b>	43 (87.8%)	47 (95.9%)	-0.080 (-0.190 0.030)	0.241
<b>Treatment</b>	<b>W-BFSR</b>	33 (67.3%)	34 (70.8%)	-0.040 (-0.220 0.150)	0.367
	<b>VAS</b>	39 (79.6%)	40 (81.6%)	-0.020 (-0.180 0.140)	0.841
	<b>Behaviour</b>	45 (91.8%)	45 (91.8%)	0.000 (-0.110 0.110)	0.264

Table 4.2: Success rates by type of local anaesthetic

The results from Table 4.2 indicated that the equivalence between the two types of local anaesthetics/techniques could be established for the primary endpoint, during the following:

- During injection phase, using W-BFRS and Behaviour scale
- During treatment phase, using W-BFRS, VAS and Behaviour scale

Considering the predefined equivalence range (0.2% to -0.2%), the absolute differences using behaviour scale; falls within this range, which indicate that both local anaesthetics are comparable in terms of children's acceptance. In addition, children coped very well during the local anaesthetic injection process. Figure 4-2 below presented more details related to the CI.

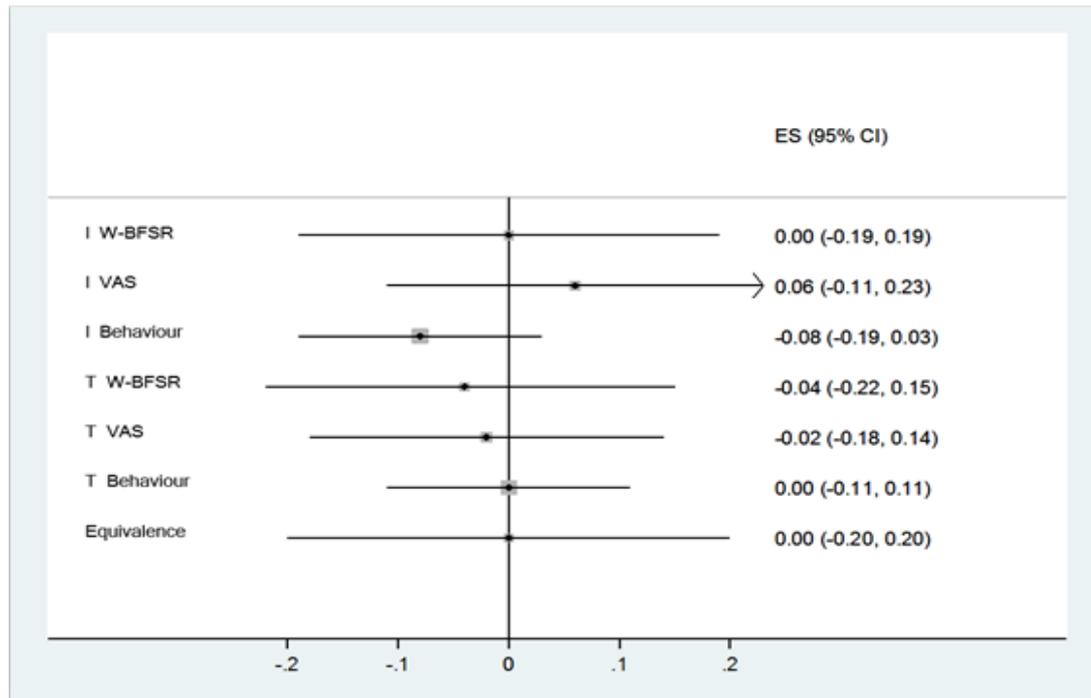


Figure 4-2: Anaesthetic efficacy on the 95% confidence interval.

The next section present the results for the secondary endpoints. As described in section 3.3.2, the aim of the secondary analysis was to investigate whether there was any association of need for re-anaesthesia, need for medication, and any adverse events with local anaesthetic type.

### 4.2.3 Need for re- anaesthesia

Three (6.1%) patients required re anaesthesia after articaine buccal infiltration comparing with only one (2.0%) patient for lidocaine IDNB. Table 4.3 presented the variable in which there was no statistically significant difference.

		Lidocaine n (%)	Articaine n (%)	P value
Re-anaesthesia	Yes	1 (2.0%)	3 (6.1%)	0.223
	No	46 (93.9%)	46 (93.9%)	

Table 4.3: Success rates by need for re anaesthesia

Figure 4-3 offered an extra illustration to this variable.

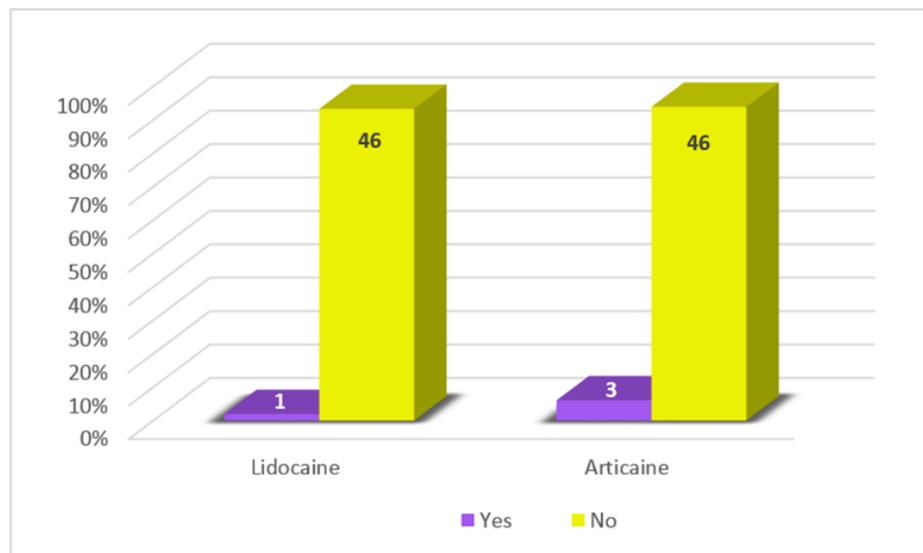


Figure 4-3: Success rates by need for re anaesthesia

### **4.3 TREATMENT/LOCAL ANAESTHETIC SAFETY**

Regarding the treatment safety, the potential adverse events associated with local anaesthetic administration and the subsequent dental treatment will be presented in the next section.

#### **4.3.1 Adverse Events**

There were six reports of postoperative complications associated with both treatment groups as described below:

One lip-bite associated with articaine BI; one case of cheek-bite associated with lidocaine IDNB; four cases reported post-operative pain after treatment with articaine BI. Only one serious adverse event occurred within the trial, patient attended with pain, had facial swelling after dental extraction of first primary molar. This patient needed antibiotic and analgesics. This event was considered to be unrelated to the intervention. There was no statistically significant difference between the two groups.

Additionally, Table 4.4 and Figure 4-4 below illustrated these findings.

		Lidocaine n (%)	Articaine n (%)	P value
Adverse events	Pain	0 (0.0%)	4 (8.2%)	0.310
	Soft tissue injuries	1 (2.0%)	1 (2.0%)	
	Others	0 (0.0%)	1 (2.0%)	

Table 4.4: Adverse events by type of treatment

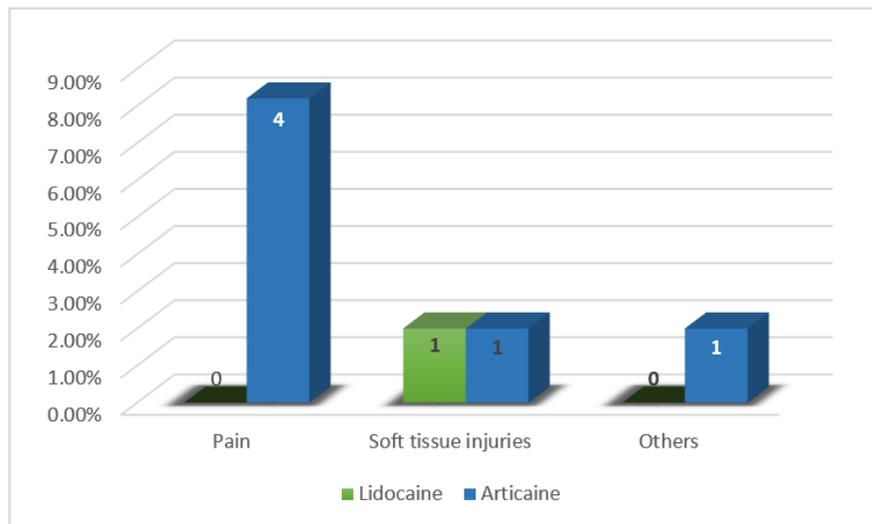


Figure 4-4: Adverse events by type of treatment

### 4.3.2 Need for medication

Some children feel mild pain or discomfort after the treatment. In case of a child feeling any post-operative pain or discomfort parents were advised to use an over the counter product such Paracetamol or Ibuprofen if needed. Paracetamol was used by six patients (12.2%), however, four patients did not really require the medication

(Paracetamol), and it was given to them by their mothers as reassurance only. One patient in articaine group had antibiotic (Amoxicillin 250mg/5ml) and Paracetamol (as described in the previous section). There was no statistically significant difference between the two groups (see Table 4.5 and Figure 4-5).

		Lidocaine n (%)	Articaine n (%)	P value
Medication	Ibuprofen	1 (2.0%)	2 (4.1%)	0.141
	Paracetamol	1 (2.0%)	6 (12.2%)*	
	Other	0 (0.0%)	1 (2.0%)	

Table 4.5: Medications taken by patients in each treatment group

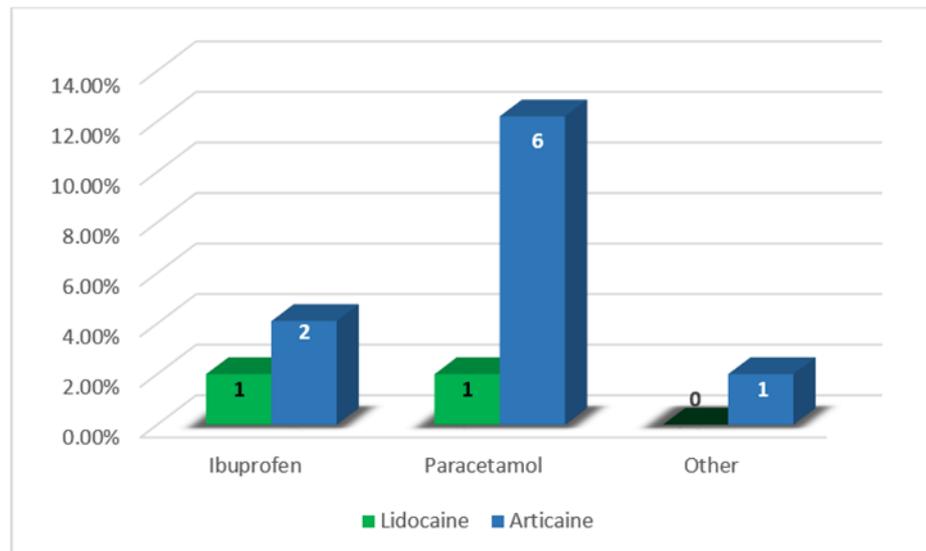


Figure 4-5: Medications taken by patients in each treatment group

## **Chapter 5**

### **DISCUSSION**

In this chapter, discussion of the most important components of the current study is presented.

Pain control is an essential part of any dental treatment especially in children. Studies in literature showed that there is strong relationship between pain and behaviour related problems in dentistry.

In this equivalence randomised clinical trial, comparative evaluation of local anaesthetic efficacy between 4% Articaine hydrochloride used as buccal infiltration with intrapapillary infiltration and 2% Lidocaine hydrochloride used as IDNB, was accomplished in children who required dental extraction or pulp treatment for the lower mandibular molars.

#### **5.1 STUDY DESIGN AND METHODOLOGY**

Based on the conclusion drawn from systematic review of existing evidence (discussed earlier in this thesis chapter two), research question was formulated and developed, as well as identification of specific participants, interventions and outcomes. Therefore, to answer the research question, the most appropriate study design is a randomised clinical trial. Randomised controlled clinical trials are the gold standard for intervention studies when feasible (Akobeng, 2005).

However due to their nature they tend to be expensive and time consuming to perform. ‘The RCT is a very beautiful technique of wide applicability, but as with everything else there are snags. When humans have to make observations there is always the possibility of bias (Higgins and Green, 2011).

Different classification has been described for the randomised clinical trial, classification based on hypothesis, including superiority trials, non-inferiority trials, and equivalence trials, the different in these categories is based on the methodology adopted and reporting process. The other way of classification is based on study design. The major categories of RCT study designs are: parallel group, crossover, cluster and factorial (Meinert, 2012).

According to Piaggio *et al.*(2006), equivalence and non-inferiority randomized controlled trials are the standard research methodology to demonstrate that a new treatment is equivalent or non-inferior to standard therapy (active-control) in term of efficacy (Piaggio *et al.*, 2006). Consequently, and to achieve the aim of this study, the most applicable approach would be implementing an equivalent parallel prospective, randomised, controlled study design.

### **5.1.1 Sample size and patients characteristics**

The participants in this study were similar to those in any trial that established efficacy of the reference treatment. For example, Oulis *et al.* (1996) had recruited 89 patients aged 3-9 years old in the study, which to investigate the effectiveness of mandibular infiltration compared with mandibular block in treating primary molars in children. The children who were selected for the present study were between the ages of 5-9 years (primary education age) with comparable characteristics.

According to Piaget, (cited in Casamassimo *et al.*, 2013), this age (6-12 years) is the concrete operational stage of cognition. Children acquire the ability to understand the constancies between length, mass, number and weight despite external differences (Casamassimo *et al.*, 2013). Thus, it could be argued that this age group

would have cognitive skills to comprehend some of the questions that were asked from them later in the study.

Children of this age group (6-12 years) are typically able to provide information about their experiences, with a limited ability to define abstract concepts (Kortessluoma *et al.*, 2003). In addition, this age group have either primary or mixed dentition, thus, the inclusion of this age group is acceptable.

### **5.1.2 Recruitment, consent and randomisation processes**

Children were recruited from the paediatric department at the School of Dentistry at the University of Leeds. Screening phase was continuous process throughout the clinical trial. It was started upon getting the sponsor approval and finished by recruiting the last patient in the trial. Consent and assent forms were explained to the participant and parents/guardian by the PI and the participants has the chance to ask and discuss the form or any other related concerns and then signed by the three parties. The PI enrolled the participants within the study and assigned them to their group based on the random number table.

According to Altman *et al.* (1999) randomisation has three major advantages. First, it eliminates selection bias in the assignment of treatments. Second, it facilitates blinding of investigators, participants and assessors to treatments or outcome evaluations. Third, randomisation increases the likelihood that changes in the dependent variable are attributable to the independent variables rather than extraneous factors or confounding variables (Altman *et al.*, 1999).

Concealed random allocation for the participants was achieved by using sequentially numbered, opaque, sealed envelopes prepared in advance by an independent party and opened in sequence only after participant details and consent were obtained. The

PI was blinded to the assignment before enrolment. Schulz and colleagues considered sealed opaque envelopes to be 'adequate' measures of concealment (Schulz *et al.*, 1995).

Once the envelopes were opened, the blinding of the operator (PI) was lost. The operators therefore was not blinded in this trial as the intervention administered to both groups cannot be blinded; although every effort was made as described previously to minimise bias. The patients were blinded to the type of injection, and were not informed to which treatment group he/she belonged. Only partial information was given about the expected anaesthetic effect.

### **5.1.3 Trial protocol**

The study protocol (Appendix 2) and all documents/forms were developed, discussed and amended in accordance with the good clinical practice (GCP) guidelines and using the template provided by the R&D office in Leeds. This was a long process and it required a number of months before finalisation of the protocol. According to study protocol, the trial team was consisted of the PI and study supervisors (MD, JT and TM), the team auxiliary which consisted of the dental nurses. The study was conducted in the dental clinic, children department at Leeds Dental Hospital.

The PI was the sole individual who carried out the dental treatment procedures, which included; consent/assent form completion, actual dental treatment i.e.: local anaesthetic injection and restorative/extraction procedures, as well as data collection throughout treatment and delivery of the questionnaire to both child and parent. The dental nurse who was assisting during the treatment delivered the VAS and W-

BFRS with the presence of the PI. The whole process took approximately between an hour to an hour and a half.

#### **5.1.4 Statistical Analysis**

Statistical analysis was carried out according to the ICH harmonised tripartite guideline, statistical principles for clinical trials - E9 guidelines (ICH E9, 1998).

This equivalence trial was designed to assess the efficacy between the two types of the local anaesthetic used with different injection techniques. The margin of equivalence,  $\Delta$ , was 20% and the range  $-20\%$  to  $20\%$ . The margin was based on clinically important differences using data from previous studies as described earlier in material and method section.

##### **5.1.4.1 Interim analysis (IA)**

Interim analysis (IA) is analysis comparing intervention groups at any time before the formal completion of the trial, usually before recruitment is complete, often used with "stopping rules" so that a trial can be stopped if participants are being put at risk unnecessarily (ICH E9, 1998).

Referring to the study protocol, there was no planning to do an interim analysis. As described by the CONSORT statement (2012), in this trial, there was less ethical need to stop the trial because the control group was already receiving the standard treatment and the experimental treatment was not appearing appreciably worse (Piggio *et al.*, 2012). In addition, undertaking an IA would damage the integrity of the trial and break the blinding and would not have added to the integrity of the trial.

#### **5.1.4.2 Intention to treat analysis (ITT)**

According to Fisher *et al.* (1990), ITT analysis includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.

This method of data analysis was adopted for this study in order to come over the two major complications usually encountered by RCTs, which are noncompliance and missing outcomes. This problem i.e. missing outcomes were faced in this study; in which three patients did not complete the trial as planned. By undertaking ITT analysis, there was no exclusion for any of the trial patient and therefore, the sample size was maintained, and thus, preserving the statistical power.

## **5.2 ASSESSMENT OF EFFICACY**

In this trial, the aim was to compare the efficacy of the two local anaesthetic each one with different injection technique, therefore, one of the most important thing is to understand and recognise the descriptions/meaning of this term. According to Marley (2000), *efficacy* is "the extent to which a drug has the ability to bring about its intended effect under ideal circumstances, such as in a randomised clinical trial". While *effectiveness* is "the extent to which a drug achieves its intended effect in the usual clinical setting" (Marley, 2000).

The primary end-point for this trial was successful completion of treatment. As has been mentioned earlier, the success in this study was related to the pain experience during injection and treatment procedures, in which the child should experience no or mild pain for the treatment to be successful.

### **5.2.1 Pain assessment**

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”. In order to assess children’s pain effectively, it will be essential to measure more than one dimension of pain experience. Because pain is subjective and multidimensional phenomena, self-report is the best way of assessment (Loeser, 2008). As described by Champion and co-authors, (1998), there are three approaches to measuring pain in children: self-report, observational or behavioural and physiological. The ideal would be a composite measure including self-report and one or more of these other approaches (Champion *et al.*, 1998). In addition, Pain perception in children is highly variable and unreliable due to poor communication. Thus, to achieve the aim of this study, the process of pain assessment included asking the child direct question- ‘how much does it hurt?’ - , using the pain rating scales VAS and W-BFSR (VAS and WBS are two different scales of measurement (continuous and ordinal, respectively) as well as direct observation of the child behaviour by both parents and the PI.

### **5.2.2 The use of VAS and W-BFSR scales**

There are currently more than 30 paediatric self-report pain intensity measures (Stinson *et al.* 2006). However, there is no accepted criterion standard (AAP and APS, 2001).

Based on systematic review by Tomlinson *et al.*, (2010) of faces scales for the self-report of pain intensity in children, there is no gold-standard pain scale. However, the systematic review identified four faces pain scales which have undergone extensive psychometric testing and have been used in the assessment of both acute

and disease-related pain in children: the Faces Pain Scale; the Faces Pain Scale–Revised; the Oucher Pain Scale; and the Wong-Baker Faces Pain Rating Scale (Tomlinson *et al.*, 2010). In this study, the W-BFSR was chosen because it has adequate psychometric properties, and it is easy and quick to use, and inexpensive to reproduce. The greatest strength of this scale may be its acceptability, given the consistent finding that the W- BFPRS was preferred by children (any age), parents, and practitioners when compared with other faces pain scales. The finding of Wong and Baker, (1988) support this argument by indicating that children age 3-18 years clearly prefer the faces scale over the other scales but that no one scale demonstrate superiority in validity or reliability (Wong and Baker , 1988). Khatri and Kalra, 2012, reported same findings. However, in this study the Wong-Baker faces pain rating scale (WBFPS) was found to be more sensitive as compared to visual analogue scale (VAS).

It is worth mentioning here that, the other faces pain scales with approved reliability and validity, is FPS-R. This scale shows excellent inter-scale agreement in children aged 4 to 12 years; however, it has been shown to have a low preference when children and adults are given a choice among faces scales (Stinson *et al.*, 2006, Tomlinson *et al.*, 2010). W-BFSR has been adopted for this study and has been used in similar studies (Ram and Amir, 2006: Odabas *et al.*, 2010) when comparing 4% articaine with 3% mepivacaine in children aged 7-13 years old. . In contrast, Arrow, (2012) used FPS-R when comparing same variables as the present study.

The most widely used pain assessment scale in acute pain research is the VAS. One of the strengths of using a VAS as a self-report measure is the range of choices available to the subjects for describing their perceptions (Stinson *et al.*, 2006, Tomlinson *et al.*, 2010). Conversely, Visual analogue scale use in children has

inherent difficulties. According to Pinkham *et al.* (2005), children do not have the same cognitive abilities as adults to quantify and qualify abstract phenomena, and younger children may not cognitively be able to use self-report measures of pain, such as the VAS. However, this can be limited through proper explanation (Pinkham *et al.*, 2005). As described earlier in the material and method section, the PI has explained the VAS to each child - using a standard transcript.

### **5.2.3 Cut off point in the scale**

There is no universally accepted cut-off points, however, most of the studies describing the cut-off point were in adult population with the majority of these studies were studying chronic pain and/or cancer pain. Most of the clinical studies which measured the pain associated with local anaesthetic injections in children as well as in adults, did not provide a good evidence or rationale of using the cut of point if it was used in the first place. In a recent study by Arrow (2012), there was no rationale provided for these cut off points when using the modified faces pain scale. There was no reference to this in Ram and Amir (2006) study as well as Malamed *et al.*, (2000b) study.

After comprehensive search in the pain literature, the results of Jones *et al.*, (2007) study, were adopted in order to establish the cut of point in the scales that have been used at this study i.e. VAS and W-BFRS. Even though, the study by Jones *et al.* (2007), was on adult population- more specifically nursing home residents-, it was the most recent and comprehensive study(to our knowledge), to show the relationship between the different pain scales tools and cut-off points. Another important issue worth mentioning here is that, Jones *et al.*, (2007) , had used numeric rating scale, FPS-R , and verbal descriptor scale (Jones *et al.*, 2007). It is

thus necessary to clarify that, the cut- off point developed for this study needed further investigation and exploration. Indeed, there is still need for more studies to establish defined cut offs related to age and gender in pain scales .The Figure 5-1, illustrates the scales and cut- off points for this study.

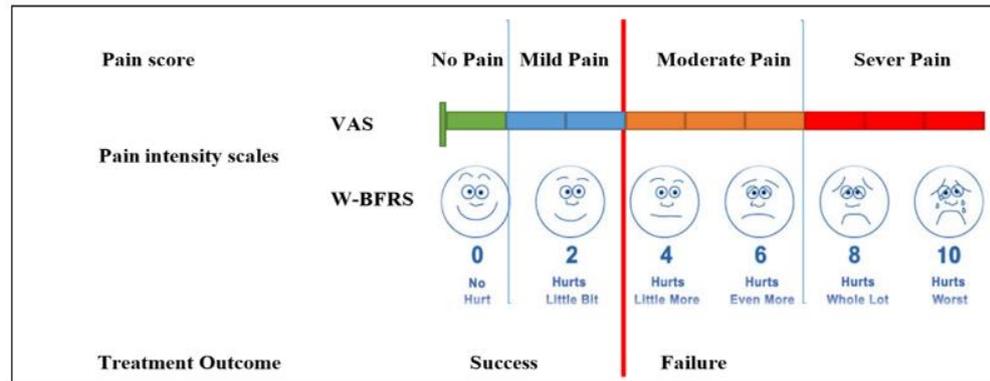


Figure 5-1: Cut off point in the scales used in the trial

#### 5.2.4 Observation scale

Using observational measures to complement self-report measures of pain intensity is important to gain boosted and more accurate results. This was achieved by direct observation of the child behaviour by both parents and the PI. Parents' observation will be discussed in the following chapter.

#### 5.2.5 Child's behaviour

The child's behaviour was assessed during the injection of the local anaesthetic and during the treatment procedures, using the Frankl behaviour rating scale (Frankl *et al.*, 1962) immediately after each step.

Dental fear and anxiety are common problems in dentistry and particularly in paediatric dentistry (Welbury *et al.*, 2012). Therefore, behavioural rating play a significant role in dentistry as they may provide an aid to classify behaviour and cooperation of child patients as well as important in evaluation of treatment (Klingberg, 2008).

The Frankl scale is probably the most frequently used behaviour-rating scale in dental literature, even though, there are other available scales e.g. Venham rating scale and Houpt rating score and global rating scale (Hosey and Blinkhorn, 1995). The advantage of using Frankl behaviour rating score is its ease of use and brevity. However, a limitation of this scale is that it does not provide sufficient clinical information regarding the uncooperative behaviour of the child. To overcome this problem, a section in the CRF for each patient was added on in order to record discomfort including any observational comments.

Fear of dental treatment and dental anxiety are prevalent in most children. They have negative impact on their quality of life and on the quality of the dental treatment they could receive both in terms of the nature of the dental treatment that is likely to be performed and the limiting of attendance for treatment (Newton *et al.*, 2012). A study by Krekmanova *et al.* (2009), has clearly underline that dental anxiety is a reinforces of pain perception. Therefore, in this study, the treatment strategy was based on behaviour management techniques which include, conventional non-pharmacological techniques e.g. tell show do technique, distraction, enhancing control (use of a stop signal), and reframing techniques, i.e. using euphemistic phrases to explain the procedures to the children such as, 'jungle juice', 'magic wand' and 'putting the tooth to sleep', were used to describe the local anaesthetic, needle and feeling of numbness to all the children (McDonald, 2011).

By implementing this strategy, the children showed more cooperative behaviours and this can prevent further development of behavioural or anxiety problems.

The relationships between anxiety/pain and anxiety/success of a dental appointment have been reported in the dental literature. Anxiety plays an important role in the pain reaction of children, and was found to be more determinative in pain perception than the injection devices preferred. There is a strong relationship between a child's dental anxiety and successful dental treatment (Klingberg, 2007); and also between anxiety and pain. Painful dental operations cause fear, whereas fear and anxiety increases the amount of perceived pain (Wellbury *et al.*, 2012).

Variation in the IANB injection speed can produce a significantly different outcome and slow IANB is deemed more comfortable than rapid injection (Kanaa *et al.*, 2006). Therefore, all study injections were standardised to be given at a rate of approximately 1mL per minute. However, Hargreaves and Keiser (2002) suggested that rapid injection may enhance spread and efficacy of local anaesthetics.

Whitworth *et al.*, (2007) found that the speed of injection for buccal infiltration in incisive/mental nerve block had no significant influence on the anaesthetic's success or duration of anaesthesia for individual teeth. Slow injection of 2.0mL of 2% lidocaine with 1:80.000 epinephrine (60 seconds) was significantly more comfortable than rapid injection (15 seconds).

According to Malamed, (2013) there is a growing trend towards the use of smaller-diameter (higher-gauge) needles on the supposition that they are less traumatic to the patient than needles with larger diameters (Malamed, 2013). In this trial, all the injections were performed using 30 G needle. Although in clinical demonstrations performed in adult patients using 25, 27, and 30 gauge needles, no patient was found

who could correctly determine the gauge of each needle; the author advised that a 30-gauge needle be used in any infiltration injection. (Lehtinen, 1983).

Many studies have shown pain reduction with smaller needle diameters. A well-designed randomized controlled trial using an automated injection device to standardize injection parameters demonstrated a significant decrease in pain reported with 30-gauge needles than with 25-gauge needles (Nielsen *et al.*, 2006). The use of a smaller gauge needle also forces the injector to slow the rate of injection, which has also been shown to decrease the pain experienced.

### **5.3 TREATMENT EFFICACY**

In order to establish the comparison of the local anaesthetic efficacy, confidence intervals (CI) were used as well as the P value. However, according to Altman, (1995), in reporting the results of equivalent trials, “if only one is to be reported, then it should be the CI, as the p value is less important and can be deduced from the CI; p values tell us little extra when CIs are known”. This has been demonstrated in the Table 4.2 in which both values were recorded.

The validity of clinician determined success of LA was supported by multiple independent observations that were likely to have valid association with LA success (participants’ report of pain experience and parent report of child’s behaviour and operator observation). Garra *et al.*, (2010) had conducted a prospective, observational study of children ages 8–17 years with pain presenting with the aim to compare mean VAS scores across mean W-BFRS scores. Agreement between the WBS and VAS was excellent ( $\kappa = 0.90$ ; 95% confidence interval [CI] = 0.86 to 0.93).

### **5.3.1 Local analgesia success**

The results drawn from W-BFRS showed that both local anaesthetics showed equal success rate (63%) with respect to the pain measured during local anaesthetic injection, however, this equality was not conclusive when the pain was measured during dental treatment using the same scale, even though, there was no statistical difference between the two groups with P value = 0.367.

Equally important, the results from VAS showed higher success rate for lidocaine group (79.6%) comparing to articaine group (73.5%) during local anaesthetic injection. Despite the fact the absolute difference was 0.060, the upper margin of the CI was 0.23 (more than predetermined margin = 0.20) which indicate in-conclusive results, there was no significant difference between the two groups (P value = 0.191). Furthermore, children behaviour was found to be equal in both groups with high success rate for articaine group (95.9%) during injection phase.

This is the first equivalence randomised clinical trial (to our knowledge) comparing articaine with lidocaine in children population, with success rate of articaine buccal infiltration ranged from 63.3% to 95.9%. However, the findings, which indicate equality is supported by other study with the respect to the different methodological approached used. Ram and Amir (2006), and Arrow (2012) used superiority approach to find the difference in the efficacy of both local anaesthetics, the results of both study indicate high overall success rate for articaine as buccal infiltration, which was 84.4% and 84% respectively. Arrow (2012) demonstrated that, the success rate was 71% in BI using articaine.

In an adult population, and as was discussed earlier in chapter two, when articaine formulation was used as BI, successful pulpal anaesthesia ranged from 75- 92% (Robertson *et al.*, 2007) and it was up to 64% in Kanaa *et al.*, (2006).

Supplementary anaesthesia was administered in three patients in this study, one patient in lidocaine group, received a repeat IDNB as the first one was not effective as the patient did not report any sign of lip numbness, and still could feel pain on placement of rubber dam clamp. The other two patients were in articaine group, both had lidocaine IDNB as supplementary LA. One patient was anxious when she came for the dental appointment; however, she had exhibited a positive behaviour at her previous dental visits. Patient's mother related her daughter behaviour to restless/sleepless in previous night as she was having a party. The second patient attended her third appointment for treatment; the clinical examination and diagnosis based on clinical signs and symptoms indicated that she needed pulpotomy and SSC for her lower second primary molar. However, after having LA and placement of rubber dam, the patient started crying on pulpal penetration, the treatment was stopped at this point and further assessment was made. The tooth was hypermic, hence, the treatment plan was changed, and the tooth was extracted at the same visit. The number of patients requiring supplementary LA is much smaller in the present study compared with that reported by Ram and Amir (2006) in which nine patient out of 62 required supplementary anaesthesia.

The post-operative assessment and reporting of adverse events were based on the subjective evaluation of the parents/guardian. The information were gathered through a follow up phone call within 24 hours of dental treatment. Parent were asked specific questions related to their child post-operative pain, any soft tissue injuries i.e. lip and/or cheek biting, any prolonged numbness, need for medications, and any other observation reported by parents/guardians.

### **5.3.2 Adverse Events**

Few adverse event were reported in this study; two soft tissues injuries, four cases of post-operative pain and one facial swelling after dental extraction of first primary molar. This rate of occurrence is similar to that reported by Malamed *et al*, (2000b); Ram and Amir, (2006); Adewumi *et al.*, (2008) and Arrow, (2012). In one patient facial swelling was reported as an adverse event after articaine. However, the incident of pain and facial swelling was unlikely associated with LA type or administration technique, but more probably due to extraction technique.

#### **5.4 POTENTIAL BIAS IN THIS STUDY**

- Within any clinical trial, there is a risk of participation bias; however, every effort was made to reduce such bias by appropriate patient's selection during screening phase. Despite this, in this trial two patients refused to have any treatment as part of the study as well as having any other treatment under local anaesthetic. Therefore, they were then scheduled to have planned dental treatment under general anaesthetic. In an effort to minimise the risk of bias both patients were included in the outcome analysis i.e. ITT.
- There may be an effect attributed to inter personal relation between the dentist (PI) and patient - the child might have expressed positive replies to the questionnaire in order to please the dentist. Therefore, the pain measuring scale (W-BFRS and VAS) was given by the dental nurse.
- Although there is no universally accepted lower age limit for the self-reporting of pain, children are limited in their ability to understand sequential ordering. However, we did assess the child behaviour prior to enrolment in the study as this is likely to have great influence on the study results. Fear and anxiety may bias pain reporting and interfere with attempts at measuring pain intensity.

## **5.5 PROBLEMS ENCOUNTERED**

The study encountered several difficulties and will be discussed below:

### **5.5.1 Ethical approvals**

At first stage the study required approval of the R&D Leeds office as discussed earlier, this process along with the protocol development took 15 months. Ethical approval was then obtained from National Research Ethics Service (NRES) and MHRA. The last stage was the sponsor approval letter, which included the site-specific information form (SSI), for Leeds Dental Hospital and the pharmacy approval letter. Due to requiring approval from multiple authorities the planned start date of January 2013, was postponed to November 2013.

### **5.5.2 Participants**

Recruitment of participants in the study was slow during the first six months. Only 22 patients (22.4%) of the required sample were recruited in the trial out of 148-screened patients in a 6 months period.

Several factors were identified that hampered patients accrual;

1. Restricted eligibility criteria for the study, the majority of the patient seen at Leeds Dental Hospital were referred by their general dentist either because they needed comprehensive dental treatment under general anaesthesia or inhalation sedation or due to dental anxiety and dental behaviour management problems. It was not easy to identify those patients who presented with behaviour management problems immediately, therefore, if there was suspicion about the child behaviour, the recruitment were delayed; so that the child behaviour could be assessed during different treatments appointment. This

assessment was carried out by PI directly while the child was having the dental treatment or retrospectively from the child's dental note.

2. Strong parent's preference of having the child's dental treatment under general anaesthetic (GA). This can be due to the fact that parents think this is in the best of interest of their child. In addition, treatment under GA does not requires multiple dental visit to the dentist as the treatment under LA; thus, reducing the time-out of school for children and even sometimes, it reduces time-out from the working time for the parents.
3. Leeds Dental Hospital is a teaching hospital which means large number of patient are treated by students (undergraduate and postgraduate students). In this very competitive environment, the students are under pressure to finish the required dental cases as well as to gain more clinical experience. The inclusion criteria for this study represent the ideal and the most suitable patients for any student; therefore, the patients' recruitment was complex and needed extensive time, more tolerance and understanding.
4. Patients' attendance: during the period of this study, the percentage of patients who missed their appointment were high. In the first six months of the clinical trial, 14 (63.6%) out of the 22 patients recruited for the trial had missed at least one appointment. This had a negative impact on the study's recruitment proces.

### **5.5.3 Study design with regard to dental visits**

During the protocol writing stage, and in accordance with GCP, the participant should have at least 24 hours after providing them with the information sheet, in order to consider participation. Even though, this has been implemented in the recruitment of the majority of the patients, it was not good option for whom it was required to carry out the dental treatment on the same screening visit. Therefore, a substantial amendment was asked for from the REC committee in order for us to be able to recruit patients who were given the information sheet and were consented on the same day. The approval was granted based on the information provided by PI. This process helped with the patients' recruitment. Consequently, the dental visit time was longer (15-30 minutes) as the PI gave the information on one-to-one bases so that all the parents/patient could have all the information needed to provide valid consent/assent.

Reading and completion of the information sheet may have slightly prolonged the appointment time, for those attending the dental clinic, but anecdotally, this did not present a problem, as most individuals in both study and control groups completed the forms while waiting for another dental appointment.

## **5.6 CONCLUSION**

Based on W-BFRS and Behaviour scale, the difference in efficacy of success rates between articaine hydrochloride BI and lidocaine hydrochloride IDNB were well within the equivalence range and within the estimated 95% CI for intention-to treat analyses. Therefore, equivalence between the two types of local anaesthetics/ techniques can be established for the primary endpoint.

Conversely, the difference in efficacy between the two local anaesthetics - during local anaesthetic injection - based on VAS results, was not within the equivalence range. However, during the treatment procedures and using the same scale (VAS), the equivalence was established.

Overall, the results pointed out that it would be acceptable to carry out invasive dental treatment for mandibular primary molars with the administration of infiltration with intrapapillary infiltration using 4% articaine instead of the traditional method of inferior dental block using lidocaine, which many children find difficult to cope with.

## Chapter 6

### EXPLORATION OF CHILDREN AND THEIR PARENT'S SATISFACTION AND THE EXPERIENCE OF THE CHILD'S DENTAL TREATMENT UNDER LOCAL ANESTHESIA

#### 6.1 ABSTRACT

**Qualitative exploration of children and their parent's satisfaction and experience of the child's dental treatment under local anaesthesia**

**Background:** It is important to understand children acceptance as well as parents' perception and satisfaction of their children's dental treatment. This will assist the dentist, and dental team in providing the dental treatment in way that is more acceptable for the children as well as the parents.

**Aim:** The study aimed to assess and explore the child's experience associated with dental injection, and to compare the two different techniques that were used (buccal infiltration and inferior dental nerve block). This comparison was in terms of children's acceptance as well as parents' satisfaction of their child's dental treatment under local anaesthesia and their perception of the impact of this treatment on their child.

**Method:** Concurrent mixed method data collection strategies were used. The qualitative and quantitative data were collected from the same participants as well as in the same timeframe. Thematic analysis was performed on the semi-structured interviews.

**Result:** 42 (56%) of the participants in the qualitative part of the study, were in articaine group while 31 (41%) were in lidocaine group. Only two of the participants (3%) had received both local anaesthetics. Parent's responses to the questionnaire,

reflected their opinion based on their observation of the dental treatment. Majority of the parents were happy about the treatment in general. The children's responses were very positive as well.

The questionnaire/interviews with the children, parents, along with the dentist's comments, allowed the development of three major themes addressing the aims and purposes of the study. The three major themes that emerged were: Firstly, "Experience of the anaesthetic procedures", secondly "Ease vs difficulty of the dental treatment" and finally the third major theme was "Perception of the dentist approach during the treatment".

**Conclusion:** Considering the findings from the survey, along with the results from the questionnaire/interview, it was established that, the reactions of the patients to both the local anaesthetics were very similar. Parents/children reported a high degree of satisfaction with the treatment outcomes. The satisfaction expressed by parents/children can have a positive impact on children's future dental treatment.

## **6.2 INTRODUCTION**

There are three types of research methods: qualitative, quantitative and mixed methods (Creswell, 2007).

Qualitative research is concerned with developing explanations of social phenomena. That is to say, it aims to help us to understand the world in which we live and why things are the way, they are. It is concerned with the social aspects of our world and seeks to answer questions about:

Why people behave the way they do; and the meanings they attach to their experiences, actions and interactions

Quantitative research has traditionally dominated much of healthcare research, particularly dentistry. However, qualitative approaches, which are common within social sciences, are recognised as contributing to understanding of health and healthcare. Qualitative research methods remain excellent ways of helping to identify peoples' thoughts, feelings, attitudes, perceptions and preferences. In addition, it can provide useful technique for exploring the diffusion of evidence into clinical practice (Newton, 2000). Both paradigms would claim to be scientific in that they are seeking explanations that go beyond the uniqueness of individual experiences and employ systematic approaches to information gathering. What is critical is that qualitative and quantitative research are based on different conceptions of the nature of the social world (ontology) and different ways of understanding that social world (epistemology). Both qualitative and quantitative researchers would question these binary conceptions and you would also find differences between researchers working in these difference paradigms (Bryman, 1988).

Both approaches have a place in healthcare research because they are each capable of addressing different research questions and therefore contributing to different aspects of clinical practice (Stewart *et al.*, 2008). They differ, both philosophically and practically, from quantitative methods, but can also be used alongside those methods. They can produce unique, detailed, personal accounts, and identify patterns of variation and what shapes these, which can be used to improve our knowledge and understanding on a variety of issues that are of interest and importance to dentistry. According to Bryman (1988), Whilst quantitative research may be mostly used for testing theory, it can also be used for exploring an area and generating hypotheses and theory. Similarly, qualitative research can be used for testing hypotheses and theories even though it is mostly used for theory generation (Bryman, 1988).

### **6.3 MIXED METHOD / TRIANGULATION RESEARCH METHOD**

This method involves the combination of qualitative and quantitative methods. Creswell describes this approach as one which "the data collection involves gathering both numeric and text information so that the final database represents both quantitative and qualitative information". Creswell argue that giving types of mixed-methods research names has certain advantages (Creswell, 2003).

Bryman (1988) argued for a 'best of both worlds' approach and suggested that qualitative and quantitative approaches should be combined. However, Bryman also had suggested that multi-strategy research is more commonly practised in some disciplines than others, based on the finding of his research (Bryman, 2006).

#### **6.4 STRENGTH VS. WEAKNESS**

Each of the various features of both research types may be viewed as a strength or as a weakness. This depends on the original purpose of the research. However, each can benefit from the combination of both research type. Here, we have given the examples of the foremost strength/weakness of these two types of research. For example, one common criticism levied at qualitative research is that the results of a study may not be generalisable to a larger population because the small size and participants not being chosen randomly. However, the original research question may have sought insight into a specific subgroup of the population, not the general population because the subgroup is “special” or different from the general population and that specialness is the focus of the research. The small sample may have been required because very few subjects were available such as is the case with some ethnic groups or patient groups suffering from an uncommon condition. In other words, in qualitative research, the researchers are aiming for theoretical generalisability but the generalisations are not intended to be universalist explanations i.e. explanations are rooted in context – time, place and circumstance. The researchers seek to understand the contexts in which things happen as they do (Tashakkori and Teddlie, 2003).

The strong point about the quantitative research is that the generated result can be generalizable. This is basically dependant on the selection of a representative sample, as well as the data collection procedures, which should be carried out in standardise manner, in order to allow statistical comparison. However, the challenging issue with quantative research is the need for large sample size, in order to obtain adequate data related to the research question. This is contrasting the qualitative approach, in which the sample size is not problematic (Tashakkori and Teddlie, 2003).

The following presented the common comparisons between qualitative and quantitative approaches.

	<b>Quantitative</b>	<b>Qualitative</b>
<b>General framework</b>	<p>Seek to confirm hypotheses about phenomena</p> <p>Instruments use more rigid style of eliciting and categorizing responses to questions</p> <p>Use highly structured methods such as questionnaires, surveys, and structured observation</p>	<p>Seek to explore phenomena</p> <p>Instruments use more flexible, iterative style of eliciting and categorizing responses to questions</p> <p>Use semi-structured methods such as in-depth interviews, focus groups, and participant observation</p>
<b>Analytical objectives</b>	<p>To quantify variation</p> <p>To predict causal relationships</p> <p>To describe characteristics of a population</p>	<p>To describe variation</p> <p>To describe and explain relationships</p> <p>To describe individual experiences</p> <p>To describe group norms</p>
<b>Question format</b>	Closed-ended	Open-ended
<b>Data format</b>	Numerical (obtained by assigning numerical values to responses)	Textual (obtained from audiotapes, videotapes, and field notes)
<b>Flexibility in study design</b>	<p>Study design is stable from beginning to end</p> <p>Participant responses do not influence or determine how and which questions researchers ask next</p> <p>Study design is subject to statistical assumptions and conditions</p>	<p>Some aspects of the study are flexible (for example, the addition, exclusion, or wording of particular interview questions)</p> <p>Participant responses affect how and which questions researchers ask next</p> <p>Study design is iterative, that is, data collection and research questions are adjusted according to what is learned</p>

Figure 6-1: Comparison of quantitative and qualitative research approaches.

From: Tashakkori & Teddlie, 2003

## 6.5 QUESTIONNAIRE

A questionnaire is a written document to gather information irrespective of mode of administration. There are different types of questionnaire; it can be structured in which the same questions will be asked in the same way to all the participants. Questionnaire can be a closed question or open question. In the closed question, the

respondent can make choices among a set of answers in a given question. Usually answers to a closed question will provide **quantitative data**. The open question allows the respondent to answer the question how they like and with as much detail as they want. Open questions usually provide **qualitative data** (Tashakkori and Teddlie, 2003).

## 6.6 DATA COLLECTION

According to Creswell (2007), the most common approaches of data gathering in qualitative research are interviews, observations, and review of documents. The procedures of data collection can be categorised into four main domains: observations, interviews, documents, and audio-visual materials (Creswell, 2007). It can be seen from Table 6.1, the differences when collecting data in both qualitative and quantitative during different phases of the researches.

Qualitative Data Collection	Phases in the Process of Research	Quantitative Data Collection
<ul style="list-style-type: none"> <li>• Purposeful sampling strategies</li> <li>• Small number of participants and sites</li> </ul>	Sampling	<ul style="list-style-type: none"> <li>• Random sampling</li> <li>• Adequate size to reduce sampling error and provide sufficient power</li> </ul>
<ul style="list-style-type: none"> <li>• From individuals providing access to sites</li> <li>• Institutional review boards</li> <li>• Individuals</li> </ul>	Permissions	<ul style="list-style-type: none"> <li>• From individuals providing access to sites</li> <li>• Institutional review boards</li> <li>• Individuals</li> </ul>
<ul style="list-style-type: none"> <li>• Open-ended interviews</li> <li>• Open-ended observations</li> <li>• Documents</li> <li>• Audiovisual materials</li> </ul>	Data sources	<ul style="list-style-type: none"> <li>• Instruments</li> <li>• Checklists</li> <li>• Public documents</li> </ul>
<ul style="list-style-type: none"> <li>• interview protocols</li> <li>• Observational protocols</li> </ul>	Recording the data	<ul style="list-style-type: none"> <li>• Instruments with scores that are reliable and valid</li> </ul>
<ul style="list-style-type: none"> <li>• Attending to field issues</li> <li>• Attending to ethical issues</li> </ul>	Administering data collection	<ul style="list-style-type: none"> <li>• Standardization of procedures</li> <li>• Attending to ethical issues</li> </ul>

Table 6.1: Phases in the data collection process for qualitative and quantitative research. From

## **6.7 QUALITATIVE DATA ANALYSIS**

Miles and Hubberman (1994) as well as Smith and Firth (2011), considered different types of qualitative data analysis:

- Socio-linguistic methods that explore the use and meaning of language such as discourse and conversation analysis;
- Methods that focus on developing theory, typified by grounded theory;
- Methods that describe and interpret participants' views such as content and thematic analysis.

The qualitative descriptive approaches such as, content analysis, and thematic analysis are appropriate when reasonably low level of interpretation is needed.

## **6.8 REASONS FOR CARRYING OUT THIS RESEARCH**

Exploring patient/parents satisfaction with dental care may provide useful information to those attempting to understand or to predict patient behaviour, and to those who are evaluating dental providers (Davies and Ware 1981).

It is important to understand parents' satisfaction of their children's dental treatment, as this will assist the dentist and dental team in providing the dental treatment in way that is more desirable for the children as well as the parent. Hawkins and Moore, (2002) stated that parents are expected to offer subjective impressions rather than professionally informed opinions or objective observations. The parent's impression was based on their understanding of how their child acts and behaves. What is 'normal' for them as opposed to the professionally derived observations of the dentist (i.e. both different but both shaped by different ways of 'knowing'). According to Guralnick (1989), because parents are responsible for their child, they

should have a voice in program evaluation, which is in this study, the dental treatment provided (Guralnick, 1989).

There are differences between clinicians' and the public's evaluation of oral health, as well as the evaluation of dental treatment provided. Parent's thoughts and ideas might add to our knowledge and by doing this qualitative study, we are aiming to reduce this gap and see the dental treatment from parents' point of view, also as experienced by the child.

Given the evidence available to us today with respect to the potential impact of parents' satisfaction on dental treatment, it is important to assess level of parents' perception and their overall satisfaction of dental treatment for their children. Moreover, understanding parents' perception of their children's oral health and dental treatment procedures as well as the factors that motivate these perceptions can help dentists to overcome barriers that parents encounter in accessing dental care for their children. Same concept was applied in the current study for children as well.

However, as far as we are aware, there has only been limited information on children's acceptance and parents' perception/satisfaction with dental treatment, particularly dental treatment carried out under local anaesthesia.

### **6.8.1 Aim**

The main aim of this study was to explore children's acceptance as well as parent's satisfaction and experience of their child's dental treatment under local anaesthesia and their perception of the impact of this treatment on the child.

This sub study was based on the main study; in which the aim was to view the efficacy of local anaesthetic from multiple perspectives. The integration of this sub study within the main study was to enhance and enrich the meaning of a singular perspective (i.e. the quantitative findings) and to develop a more complete

understanding of a dental treatment under local anaesthetic. Furthermore, the study was aiming to assess and explore the child's experience associated with dental injection and compare the two different techniques that have been used (IDNB and BI) to evaluate which one is more acceptable with less pain and distress.

### **6.8.2 Objectives**

The objectives of this sub-study were to:

- Evaluate parents' perceptions of patient outcomes following dental treatment under local anaesthesia and to assess their satisfaction with that modality of treatment.
- Explore the children's point of view in relation to the treatment provided and dental experience.
- Examine the factors associated with acceptance of the dental treatment from the parent's as well as children's prospective.
- Consider the extent to which the local anaesthetic and dental treatment affected the children, in terms of acceptance/avoidance of treatment.

## **6.9 RESEARCH DESIGN AND METHOD**

In order to achieve our study objectives, we used a mixed methods design. Mixed methods research is defined as "The type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of breadth and depth of understanding and corroboration" (Johnson *et al.*, 2007).

The choice of mixed methods design depends on timing, weighing and mixing of both the quantitative and qualitative components (Creswell, 2007). Based on the present study's objectives we decided to take the sequential explanatory mixed methods approach. This design consists of two phases, starting with the quantitative component and followed by a qualitative part that aims at providing an in-depth understanding of the quantitative findings. A mixed-methods design was used, as this approach is useful in gaining dual perspectives of dentistry and provides valuable insights that contribute to overall treatment evaluation. The following diagram (Figure 6-2) described the different mixed methods designs.

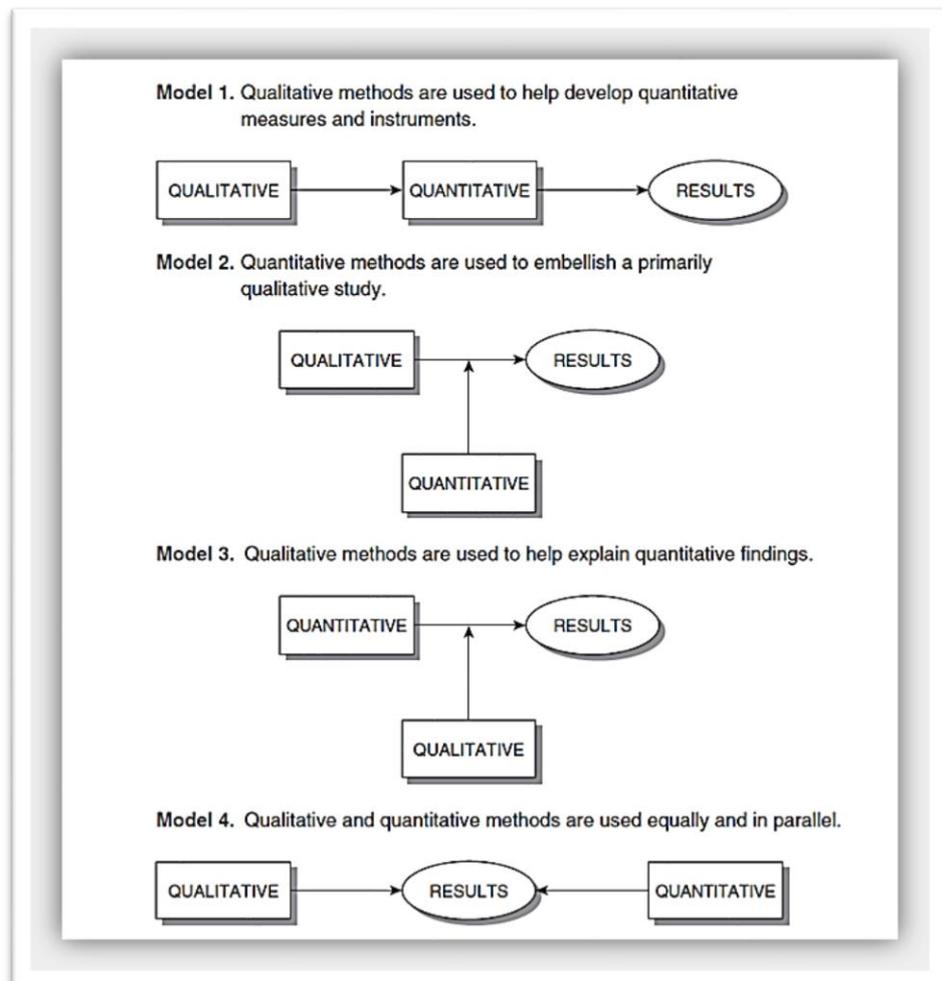


Figure 6-2: Mixed method approaches. Form Tashakkori & Teddlie 2003

Researchers have been conducting mixed methods research for several decades, and referring to it by an array of names. Early articles on the application of such designs have referred to them as multi-method, integrated, hybrid, combined, and mixed methodology research (Creswell and Clark, 2007).

In this approach, quantitative and qualitative data are connected between the two phases and the final interpretation of the study findings is based on both quantitative and qualitative results. Since the quantitative part of the study provided the basis for the qualitative element, our design is mainly quantitative with an embedded qualitative component.

### **6.9.1 Questionnaire Methods**

The methodology described by Adamson and colleagues ‘**questerviews**’ was implemented in this study; in which, both structured self-completion questions and semi- structured interviews were integrated together in order to explore research questions and enhance the meaning of each component (Adamson *et al.*, 2004).

#### **6.9.1.1 Structured questionnaire**

In this study, specially designed and validated structured questionnaire was administered to the parent after the dental treatment, in a quiet open-spaced area within the paediatric dentistry clinic in the Leeds Dental Institute (see Table 6.2). Validation of the questionnaire was carried out by asking qualified professionals within the school of dentistry, in order to evaluate the effectiveness of the questionnaire, in terms of whether the questions measured what it was supposed to measure, and whether the questions were clear and understandable. Furthermore, the structured questionnaire was piloted. The questionnaire was given to 10 children/parents who attended the LDI for routine dental treatment. This step was

done to check that the questionnaire’s design was appropriate to be used and also to identify and amend questions as needed. Nevertheless, based on piloting the questionnaire, no major changes was carried out. The pilot questionnaire included a question about the overall impression and comments of the respondents about the questionnaire in general.

**The structured questionnaire covered the following topics:**

- Overall satisfaction with dental treatment provided.
- Parent’s perception about the dental treatment carried out for their child.
- Previous dental experience.
- Child behaviour during the treatment.
- Child behaviour after dental treatment.
- Their personal experiences.

Statements	Response				
	Strongly agree	Agree	No opinion	Disagree	Disagree Strongly
The dentist explained very well why my child needed dental treatment.					
I have no concerns about how the local anaesthetic works.					
I think the local anaesthetic is doing a good job at helping my child to cope with the treatment					
My child coped well with having the local anaesthetic.					
The dental team were kind and helpful during my child’s treatment.					

Table 6.2: parent’s questionnaire

Children’s perspectives of dental treatment on that visit were assessed qualitatively, through asking the children about their experiences and perceptions of dental treatment and quantitatively through using the ‘visual analogue scale’ and W-BFRS. Questions asked to the children will be illustrated in the following Table 6.3.

QUESTIONS	Response		
	Positive 	Neutral 	Negative 
What do you think about numbing your tooth?			
Are you glad to have your tooth fixed /extracted?			
How did we look after you when you had your treatment?			
How friendly were we when you came to see us?			
How well did the dentist explain everything about treating your tooth?			
Was it ok having your tooth fixed / extracted?			

Table 6.3: Children’s questions about attitudes and experiences of dental treatment

### 6.9.1.2 Open-ended, semi-structured interview

The questionnaire was supported by open-ended, semi-structured interviews with the parents. The interview, even though very limited, provided opportunities to ask questions that could not be included in the questionnaire and also aided in exploring the rationales behind the children’s/parent’s answers, which enabled us to develop a richer understanding of these attitudes and behaviours. In another words, parents and children were asked to elaborate on their responses, however, we should

acknowledge here that, this involved limited exploration of issues but did allow parents and children to express issues that were important to them in an open way.

**The interview with parents was open-ended, semi-structured interview and it covered the following topics:**

- What do you think about your child's experience during the dental treatment?
- Is there anything you would like to say about your child having local anaesthetic?
- Is there anything you would like to say about your child treatment in general?
- What do you think your child found easiest?
- What do you think your child found hardest?
- Would you be happy for your child to have dental treatment again?
- Do you think you would consider treatment under general anaesthesia?

These questions were presented and discussed with parents and children; in order to ensure that all participants had considered the concepts of the research objectives. Children were encouraged to provide their responses through conversation, and some of them draw what they thought it might represent their feelings.

### **6.9.2 Description of the sample**

This part has been discussed in detail in the previous chapter; however, for the purpose of clarification, more details will be specified in the following paragraph.

The participants were children and parents whose children had recently undergone dental treatment under local anaesthesia as part of the main RCT. Parents were asked to complete a single page questionnaire that sought their perceptions of treatment outcomes that were related to quality of treatment such as pain, feelings,

and the inability to cope with dental treatment. Parents were asked to indicate whether they observed improvement, no change, or worsening of the child behaviour. In addition, the children who had the dental treatment were questioned as well.

### **6.9.3 Data collection procedures**

The qualitative and quantitative data were collected from the same participants as well as at the same timeframe.

### **6.9.4 Data analysis**

In this study, concurrent mixed method data collection strategies were selected to validate the quantitative data with qualitative data, in which the qualitative data was more about elaborating and expanding on the questionnaire responses.

### **6.9.5 Qualitative Data Analysis**

To reach the objectives of this study, the method adopted here was based on describing and interpretation of the participant's views. A thematic content analysis was conducted. Data were extensively read and re-read many times in order to get familiar with the data as well as the pattern. The responses were then transcribed. A set of preliminary concepts or themes was generated. Each of these themes was linked to data from the main study such as child gender, age and previous dental experience; this provided a wider context in which to view the data.

## **6.10 FINDINGS**

This part will present and illustrate the overall results of the quantitative analysis and qualitative analysis. As demonstrated above, the open-ended questions were given to all the study participants both children and parents. The valid responses were gathered from 96 participant (two children refused to have any treatment, therefore, they did not answer the questions).

The open-ended questionnaire/ interview was given to all the 96 children/parents who had the dental treatment. However, after initial exclusion for answers with very limited information, further exclusion was carried out after reading the full records and responses. This process produced 75 transcripts.

### **6.10.1 Quantitative Analysis**

Parents were interviewed at the end of their child's dental treatment by the PI; and were asked to complete a single page questionnaire that sought their opinions and satisfaction with the treatment outcomes that were related to their child the dental treatment provided. At the same time, children were interviewed as well. In the following sections, parents and children responses will be presented.

#### **6.10.1.1 Parent satisfaction with the dental treatment**

This section will illustrate the findings based on parent's responses to the questionnaire, which consisted of six questions as illustrated in table (6.2). The parents were asked to select the most appropriate answer that reflect their opinion based on their observation of the dental treatment; which was provided to their child. The following paragraphs will explain the questions and the parents' response to each question.

**6.10.1.1.1 The dentist explained very well why my child needed dental treatment.**

Majority of the parents 56 (57.1%) agreed that the dentist explained very well the need for dental treatment. About thirty-nine of the parents (39.8%) have strongly agreed with this statement. Only one parent did not answer this question in Lidocaine group, because the child did not have any treatment and was referred for treatment under general anaesthetic (P value: 0.357; Pearson R: 0.101). See Table 6.4.

	No Treatment	Strongly Agree	Agree	No Opinion	Total
<b>Lidocaine</b>	2 4.1%	18 36.7%	28 57.1%	1 2.0%	49 100.0%
<b>Articaine</b>	0 0.0%	21 42.9%	28 57.1%	0 0.0%	49 100.0%
<b>Total</b>	2 2.0%	39 39.8%	56 57.1%	1 1.0%	98 100.0%

Table 6.4: The dentist explained very well why my child needed dental treatment

**6.10.1.1.2 I have no concerns about how the local anaesthetic works.**

Parents were requested to give a response to the question stating that ‘I have no concerns about how the local anaesthetic works’ and 66 (67.3%) of them agreed about this statement; in contrast only two parents gave the response of disagree and three parents gave no opinion (P value: 0.177; Pearson R: 0.104). See Table 6.5.

Type of local anaesthetic	No Treatment	Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree	Total
<b>Lidocaine</b>	2 4.1%	14 28.6%	29 59.2%	3 6.1%	1 2.0%	0 0.0%	49 100.0%
<b>Articaine</b>	0 0.0%	10 20.4%	37 75.5%	0 0.0%	1 2.0%	1 2.0%	49 100.0%
<b>Total</b>	2 2.0%	24 24.5%	66 67.3%	3 3.1%	2 2.0%	1 1.0%	98 100.0%

Table 6.5: I have no concerns about how the local anaesthetic works

**6.10.1.1.3 I think the LA is doing good job.**

Majority of parents 58 (59.2%) agreed that local anaesthetic is doing good job for their children; and this response was equal for both types of local anaesthetics. In addition, 35 (35.7%) parents strongly agreed on this statement with almost similar distribution between groups 19 (38.8%) in Articaine group and 16 (32.7%) in lidocaine group. One parent in each group gave no opinion. In addition, one parent in lidocaine group disagreed with this statement (P value: 0.516; Pearson R: 0.102). See Table 6.6.

	No Treatment	Agree	Strongly Agree	No Opinion	Disagree	Total
<b>Lidocaine</b>	2 4.1%	29 59.2%	16 32.7%	1 2.0%	1 2.0%	49 100.0%
<b>Articaine</b>	0 0.0%	29 59.2%	19 38.8%	1 2.0%	0 0.0%	49 100.0%
<b>Total</b>	2 2.0%	58 59.2%	35 35.7%	2 2.0%	1 1.0%	98 100.0%

Table 6.6: I think the LA is doing good job

**6.10.1.1.4 My child coped well with having the local anesthetic.**

The parents' response to this statement in total was 61 (62.2%) agree and 28 (28.6%) strongly agree, with almost comparable response for both groups. Three parents gave no opinion response, one parent in lidocaine group, and two parents in articaine group. Four parents did not agree with this statement, three parents in lidocaine group and one in articaine group (P value: 0.479; Pearson R: 0.101). See Table 6.7.

	No Treatment	Agree	Strongly Agree	No Opinion	Disagree	Total
<b>Lidocaine</b>	2 4.1%	30 61.2%	13 26.5%	1 2.0%	3 6.1%	49 100.0%
<b>Articaine</b>	0 0.0%	31 63.3%	15 30.6%	2 4.1%	1 2.0%	49 100.0%
<b>Total</b>	2 2.0%	61 62.2%	28 28.6%	3 3.1%	4 4.1%	98 100.0%

Table 6.7: My child coped well with having the local anaesthetic

**6.10.1.1.5 The dental team were kind and helpful during my child's treatment.**

Almost all parents gave a positive answer to this statement for both local anaesthetic groups. The response rate was 50 (51.0%) for strongly agree response and 45 (45.9%) for agree response (P value: 0.342; Pearson R: 0.100). See Table 6.8.

	No Treatment	Agree	Strongly Agree	No Opinion	Total
<b>Lidocaine</b>	2 4.1%	23 46.9%	23 46.9%	1 2.0%	49 100.0%
<b>Articaine</b>	0 0.0%	22 44.9%	27 55.1%	0 0.0%	49 100.0%
<b>Total</b>	2 2.0%	45 45.9%	50 51.0%	1 1.0%	98 100.0%

Table 6.8: The dental team were kind and helpful during my child's treatment

**6.10.1.2 Children satisfaction with the dental treatment**

This section of the research was in the form of a questionnaire - consisted of five questions- given to the children and the requested response was to tick the most appropriate choice they thought it reflected their situation from the following options: positive, neutral and negative. The following paragraphs will illustrate the questions and the children's response to each question.

**6.10.1.2.1 What do you think about numbing your tooth?**

The majority of the children gave a positive response, 59 children (60.2%) for both groups. However, 31 children (31.6%) recorded the neutral response and only six children (6.1%) recorded not being happy about numbing their teeth (P value: 0.511; Pearson R: 0.100). See Table 6.9.

	No Treatment	Positive	Neutral	Negative	Total
<b>Lidocaine</b>	2 4.1%	30 61.2%	14 28.6%	3 6.1%	49 100.0%
<b>Articaine</b>	0 0.0%	29 59.2%	17 34.7%	3 6.1%	49 100.0%
<b>Total</b>	2 2.0%	59 60.2%	31 31.6%	6 6.1%	98 100.0%

Table 6.9: What do you think about numbing your tooth?

**6.10.1.2.2 How did we look after you when you had your treatment?**

The majority of children gave a positive response to this statement with 79 (80.6%) in total. Only two children in each group gave negative response (4.1%) and there was no significant difference between the two groups (P value: 0.522; Pearson R: 0.101). See Table 6.10.

	No Treatment	Positive	Neutral	Negative	Total
<b>Lidocaine</b>	2 4.1%	37 75.5%	8 16.3%	2 4.1%	49 100.0%
<b>Articaine</b>	0 0.0%	42 85.7%	5 10.2%	2 4.1%	49 100.0%
<b>Total</b>	2 2.0%	79 80.6%	13 13.3%	4 4.1%	98 100.0%

Table 6.10: How did we look after you when you had your treatment?

**6.10.1.2.3 Are you glad to have your tooth fixed/extracted?**

More than two third (84.7%) of the children were happy to have the planned dental treatment. Relating to the neutral and negative responses, almost similar answers were recorded, seven (7.1%) and six (6.1%) children retrospectively (P value: 0.390; Pearson R: 0.101). See Table 6.11.

	No Treatment	Positive	Neutral	Negative	Total
<b>Lidocaine</b>	2 4.1%	40 81.6%	4 8.2%	3 6.1%	49 100.0%
<b>Articaine</b>	0 0.0%	43 87.8%	3 6.1%	3 6.1%	49 100.0%
<b>Total</b>	2 2.0%	83 84.7%	7 7.1%	6 6.1%	98 100.0%

Table 6.11: Are you glad to have your tooth fixed/extracted?

**6.10.1.2.4 How friendly were we when you came to see us?**

There was a general agreement in this question with 94 (95.9%) children who gave a positive answer. Only two patients (2.0 %) respond negatively (one in each treatment group) (P value: 0.360; Pearson R: 0.100). See Table 6.12.

	No Treatment	Positive	Negative	Total
<b>Lidocaine</b>	2 4.1%	46 93.9%	1 2.0%	49 100.0%
<b>Articaine</b>	0 0.0%	48 98.0%	1 2.0%	49 100.0%
<b>Total</b>	2 2.0%	94 95.9%	2 2.0%	98 100.0%

Table 6.12: How friendly were we when you came to see us?

**6.10.1.2.5 How well did the dentist explain everything about treating your tooth?**

The children participated in this study showed good understanding about the planned dental treatment, this can be seen by the high number of children 82 (83.7%) who gave a positive answer to this question. Of the total 11(11.2%) children

gave neutral response while only three (3.1%) children gave negative response (P value: 0.362; Pearson R: 0.095). See Table 6.13.

	No Treatment	Positive	Neutral	Negative	Total
<b>Lidocaine</b>	2 4.1%	42 85.7%	4 8.2%	1 2.0%	49 100.0%
<b>Articaine</b>	0 0.0%	40 81.6%	7 14.3%	2 4.1%	49 100.0%
<b>Total</b>	2 2.0%	82 83.7%	11 11.2%	3 3.1%	98 100.0%

Table 6.13: How well did the dentist explain everything about treating your tooth?

**6.10.1.2.6 Was it ok having your tooth fixed/extracted?**

Approximately two third of the study sample 71 (72.4%) gave positive answer. On the other hand, 15 (15.3%) children were neutral about the treatment outcome; compared with nine (9.2%) children who did not like the treatment (P value: 0.888; Pearson R: 0.101). See Table 6.14.

	No Treatment	Positive	Neutral	Negative	Total
<b>Lidocaine</b>	2 4.1%	34 69.4%	8 16.3%	5 10.2%	49 100.0%
<b>Articaine</b>	1 2.0%	37 75.5%	7 14.3%	4 8.2%	49 100.0%
<b>Total</b>	3 3.1%	71 72.4%	15 15.3%	9 9.2%	98 100.0%

Table 6.14: Was it ok having your tooth fixed/extracted?

### **6.10.2 Qualitative analysis**

A thematic analysis was performed on the parents' responses to the open-ended, semi-structured interview along with the PI's comments on children behavior as well as the children responses who were the target sample of the study. Upon sharing their perceptions of the treatment outcomes related to quality of the procedure such as pain, feelings, and the inability to cope with dental treatment, a thematic analysis was conducted.

The findings were presented for the collected data. Emergent themes were described and findings discussed in relation to participant's views. Comments regarding how themes related to participants' age, gender, and previous treatment were identified as appropriate. Quotes were presented to demonstrate the themes that appeared during the analyses.

Three major themes were identified, these were as follow:

- 1) Experience of the anaesthetic procedures
- 2) Ease vs difficulty of the dental treatment
- 3) Perception of the dentist approach during the treatment

#### **6.10.2.1.1 First major theme 'Experience of the anaesthetic procedures'**

The first major theme was considered as one of the three most vital findings of the qualitative portion of the study. Overall, it was established that giving the local anaesthetic is a distinctive experience with diverse outcomes. This is explained below, in more details.

**6.10.2.1.1.1 Acceptability of having local anesthesia injection and how do the children react to it**

There was a wide range of views about how the local anaesthetic was accepted by the children. While some participants found the injection procedure an acceptable experience, others found it a difficult practice.

Parents' positive comments about their child's reaction to having the local anaesthetic are illustrated below:

One mother described that the anesthetic went better than she expected:

*"It went better than I thought." P43.*

A different mother shared similar response about local anaesthetic:

*"Was good he was not complaining or crying... It was ok. Even though I was expecting him to cry" P70.*

Some parents described their child's first dental treatment experience, being successful, especially with having local anaesthetic.

*"It was the first time my son had this and I was concerned, however he responded well to it... I liked the dental staff and their reassurance toward my son." P48.*

Quite a lot of parents admitted that the local anaesthetic was tolerable and helped in avoidance of pain during the dental treatment.

*"Having the anesthetic made it more comfortable than general" P31.*

*"I think it was good thing to have helped him with the treatment." P40.*

*"I think it seems working well" P62.*

*"Fantastic, it worked fantastic to help my child" P71.*

*“Everything was fine with the anesthetic she was in no pain at all” P 72.*

*“Helps to avoid the pain”P73.*

*“It helped my child to receive treatment with no pain, improves her attitude” P87.*

Conversely, more parents expressed other views, and considered having local anaesthetic injection as the hardest part of the treatment.

*“my son did not like having the injection at all. He knew it because it was going to hurt. If there was any way to numb without injection, that would be marvelous” P 27.*

*“He doesn't like injections as he remembers them hurting when he was younger... he told me that he is not scared as before and he is happy to come next time for the last extraction!” P37.*

One mother described how she thought her child found the local anaesthetic injection, initially it seemed difficult but had to continue because there were no other options available:

*“It's hard but what option do we have? After all he was well looked after and seemed okay.”P61.*

Another father admitted that his child has personal issues with anesthesia due to experience:

*“He doesn't cope with it very well due to personal issues”P52.*

When the father was asked to give more details about this personal issue, he commented:

*“ well, it was last year when he needed his tooth out... he was in pain and could not sleep for about two nights... we took him to the local dentist who*

*was very aggressive and he took his tooth out...it was not pleasant experience ''P52.*

This patient managed to have the first extraction under local anaesthesia with no complications with a very low pain score. However, he was very anxious in the subsequent visits; then refused to have any further injection/treatment under local anaesthesia. Therefore, the remaining dental treatment was carried out under general anaesthetic.

A different mother also commented that the actual injection and process of anesthesia was hard and they would only return if necessary:

*“The actual injection/anesthetic was the hardest ... this is not something I would ever put her through unless essential” P47.*

Similarly, another parents described that the needle for the anesthesia was the hardest part:

*“The needle to numb her mouth....”P69.*

*“The injection to numb his tooth” P66.*

The vast majority of the parents (94.9%) felt that LA is doing a good job. This can be seen through the positive comments from the questionnaire. Most of the parents had expressed their understanding of ‘good job’ based on the child reaction or coping with the treatment. , for example:

*“I think it was good thing to have helped him with the treatment” P40.*

Another parent who was the only one gave strongly disagree to the above statement had expressed his feeling based on his child’s negative reaction during dental treatment

*“I think she was in pain, not sure if she was numb” P12.*

#### **6.10.2.1.1.2 Mother anxiety**

Even though some children showed good behaviour and were cooperative during the local anaesthetic injection and subsequent dental treatment, mothers were very anxious and sometimes been a negative influence to the child

*“she needed her treatment, and I was happy that she was okay.... P69.*

*“however, mother was very anxious...” D69.*

*“she was very brave and coped better than I thought she would...”P92.*

*“having local anaesthetics scares me...first time that he will experience to have anaesthetic” P42.*

Example of a very anxious mother during her child’s dental treatment:

*“I have to ask her to set back on her chair and try to be quite many times”D45.*

Comparably, some parents were calm and very supportive to their children. This facilitate the treatment and make it easier for the child as well as for the dentist.

#### **6.10.2.1.1.3 Local anaesthetic safety**

Although most of the participants did not show any concerns about the local anaesthetic safety, one mother commented on this issue,

*“I don’t have a problem with the anesthetic. As long as there are no health implications and my child has pain free treatment. I am fine with it” P32.*

#### **6.10.2.1.2 Second major theme ‘‘ Ease vs difficulty of the dental treatment’’**

The second major theme was the evaluation of the parents’ responses and reaction of children when they have the dental treatment and how this associated with the final treatment outcome.

##### ***6.10.2.1.2.1 Fear or anxiety but will be happy to come back***

More than half of the parents admitted that their children found the dental treatment ‘‘scary’’. However, some of them commented on their children good reaction and being happy at the end of the treatment.

One mother contended that her son was scared but did not feel pain because of the anesthesia:

*‘‘He was scared, not really painful he was happy at the end, happy to have the tooth out’’ P35.*

*‘‘I think my daughter coped very well with the treatment, only thing is she might have been scared’’ P24.*

*‘‘She made a fuss on taking the tooth out, I think it was the sensation rather than pain’’ P20.*

Child 63 commented:

*‘‘my treatment today was scary but I was a brave girl my tooth is out...’’  
(Eight years old, girl).*

Child 68 commented:

*‘‘It was really scary but I am fine now’’ (Six years old, girl).*

However, the child gave a very low pain score and was very cooperative during the treatment procedures.

Another patient who showed good motivation and was very cooperative was scared of the sound of extraction:

*“This sound of my tooth... cracking sounds ...scared me...but I am fine now” C59 (seven years old, boy).*

Patient 28 was scared about tooth extraction, his mother had commented on this:

*“The tooth was very large and I think it scared him”.*

Only one mother had mentioned that **“fear/anxiety”** was the hardest part of the treatment P 70.

#### ***6.10.2.1.2.2 Putting the crown/extraction as the hardest part but was happy with the outcome***

Another important issue that had been experience by both parents as well as the children was the actual dental treatment, either tooth extraction or restorative treatment which was pulpotomy and SSC. Almost quarter of the respondents, (parents and children) agreed that the most difficult part was the treatment itself. Even though, the children agreed that the treatment was difficult, they were happy to try again and come for another treatment.

When comparing the two treatments, fifteen parents shared the response that the experience of tooth extraction was the most difficult part of the treatment, compared with only seven parents who thought that putting the crown on the treated tooth was the hardest part.

*“Hardest when the doctor was about to take the tooth out. She scares him about the “big push” P42.*

*“The actual extraction of the tooth was a little uncomfortable, but the rest was fine” P65.*

When viewing the responses about the restorative treatment, none of the parents nor the children had commented on the drilling procedures or the pulpotomy procedure, the main complaint was about putting the crown on the tooth, mainly due to the pressure during the crown cementation.

*“Putting the silver cap on the tooth...” P51.*

*“Putting the crown in place and pressing down to it...” P97.*

*“When the dentist put the princess crown on the tooth” P71.*

#### ***6.10.2.1.2.3 Difficult long process but happy with the results***

Another sub-theme that emerged under the treatment procedures was describing the long treatment time as the hardest part of the treatment. Quite few parents (Nine parents) had mentioned this; however, almost all of them were happy about the overall treatment outcome.

*“Having to keep his mouth open for a long time....getting restless... Yes, happy to get the treatment again” P48.*

*“Staying in a chair for 90 minutes.... Yes, happy to come back”P73.*

*“Keeping his mouth open all the time...” P78.*

*“Sitting down for long time was the hardest for my daughter”P79.*

One mother stated that she thinks the hardest part was:

*“Keeping his mouth open for long time” P33.*

On the contrary, dentist comments on this:

*“He was very happy, and very ready for treatment today. He wants to have another silver tooth! He slept at the end of treatment, I think he was feeling*

*very comfortable... this is not uncommon, to have child sleeping during dental treatment ” D33.*

#### **6.10.2.1.3 Third major theme “ Perception of the dentist approach during the treatment ”**

The third major theme was related to the management of the treatment and procedures, this included dentist behaviour and assessment as well as the teamwork and how that might affect the final treatment outcome.

##### ***6.10.2.1.3.1 Explaining the treatment procedures***

*“The child told me he does not have any pain, but he was really scared as he does not know what is going to happen and how it is going to happen. However, after the dental treatment was completed, he told me that he is fine now and would be happy to come back again for another treatment” D73.*

“Some children were worried about the treatment, as they do not know what was going to happen, however, after explaining the procedures more than once and answering their questions, they were fine and very cooperative. However, even though the treatment outcome was positive, some of them did not like the injection” D58 and 65

##### ***6.10.2.1.3.2 Storybook, made it easy***

The principle investigator of this study has developed a storybook, as part of the information given to the children to help understanding the treatment and thus the

child could give her/his assent to participation in the research (see Appendix 20). The main intention behind the development of this storybook was to explain the dental treatment procedure to the children, especially the younger ones, in an easy more child friendly way. The story was self-explanatory i.e. there was no text in it. It contained drawings only and the clinical area in the story was drawn to be very similar to the dental clinic at the LDI.

Telling the story to the child and asking her/him to show the similar things between the real clinical area and the one in the story would have made the child feel more comfortable, less anxious and more eager to engage in the discussion. All the children who were seen during the study, as well as the parents, had been interested in the story. Some parents commented on this:

*“Great idea to ease children into having dental treatment done, she looked forward to coming to the dentist” P13.*

*“I think the hardest thing was the idea of coming to the dentist....he was really scared” P44.*

*“He was very clever boy and with explaining the treatment using the storybook, he coped very well with the treatment” D44 (seven years old boy, first extraction experience).*

*“ I was very pleased with the way it was done especially the story... clearly experienced with children” P47.*

*“ the story was great, was well told and explained”P43.*

#### **6.10.2.1.3.3 Behaviour management procedures**

Majority of the parents had appreciated the dental team and the dentist; how they were informative and friendly throughout the dental treatment, parents also,

expressed their happiness about how much this made their child's dental treatment more comfortable and relaxed thus it was good experience.

*"I am really happy with how my daughter has been treated and very happy with the outcome ... thank you" P14.*

The child has commented:

*'it was ok...I was scared ...but not any more'*C39 (eight years old, boy).

An interesting comment from mother of one of the patients:

*"I though he is going to run away , that is why I asked my mum to come with me today for extra support, to be honest, I was not expecting him to sit on the chair and have dental treatment" P96.*

However, this patient was very cooperative and the treatment outcome was positive (five and half years old boy, this visit was his third dental visit and first dental treatment).

Even though most children coped extremely well with the dental treatment due to the use of behaviour management technique, some children reported feeling pain during treatment.

Patient's 47 mother mentioned that the experience was not so nice but her daughter was put at ease and thus went better than expected:

*"She was put at ease - not a nice experience but seemed to go along with it!"*

Child 56 (seven years old, girl, had dental extraction under local anaesthetic) had commented on the extraction of her tooth:

*'I think it was bad'*

Dentist comments: “patient number 56 did very well, and was very cooperative throughout the treatment and did not show any signs of pain or discomfort during injection and extraction procedures. However, patient gave a higher pain score and when I asked her about the pain experience she said ‘*Yes, I think it was bad*’, referring to the extraction. It is important to notice that, this was her first extraction experience” D56.

*“Even though the treatment went well for a six-year-old boy (extraction of lower primary molar), and mum was happy about the outcome; the child might not be cooperative to have any further dental treatment under local anaesthetics. Even with good behaviour management”* D4.

Children and parents appreciated behaviour management techniques that have been used during the children treatment. One mother was thinking of having her daughter’s dental treatment under general anaesthetic, however, after discussion the different treatment options; that included dental treatment under local anaesthetic , treatment under inhalation sedation and lastly, treatment under general anaesthetics, mother agreed to try with LA, even though she was not sure about the treatment and how her daughter will find it. She was happy about the treatment outcome and, how her daughter coped with the treatment! Mother was supportive to her child.

*“I am very pleased; my daughter coped very well...the way she had the treatment was fantastic.”* P12 (five years old, girl, first LA experience).

The dentist commented on the treatment of patient 36 (7years old, girl)

*“She was very anxious and scared, she would not let me do any treatment, even with all the behaviour management strategies that we did. I was not sure if it is because of pain or because of anxiety, therefore, I have to give her another injection (IDNB). The treatment session last about two hours,*

*this was first extraction experience but was not first dental treatment.” D  
36.*

Patient’s 63 mother had issues with the injection but the behaviour management was a great help:

*“She was initially needle phobia from past experience but from the staffs  
time and patience and the ‘magic wand’ the first time she was able to have  
a normal injection” P63.*

#### **6.10.2.1.3.4 Team work and dental staff**

One of the survey components was related to the strategies of the dental team in terms of patient’s care. The following statement was given to the parents: ‘The dental team were kind and helpful during My Child’s Treatment’. It had received the highest percentage of agreement in which the strongly agree statement received 51 % and strong statement received 45.9%. Several of parents had clearly identified this in their comments for example:

*‘ staff and dental nurse were very understanding and kept my child very  
calm’’ P39.*

Another parents had connected the staff management with the child been able to cope with having local anaesthetic and therefore resulted in successful treatment outcome:

*“My daughter cooped very well with the anaesthetic, the staff were gentle  
and caring when giving the anaesthetic” P20.*

*Staff were great, especially as my daughter was quit scared’’ P 68.*

*“ staff and dental nurse were very understanding and kept my child very  
calm.” P39.*

When children were asked “How friendly were we when you came to see us?”

Only two children gave negative answer. The same two children gave negative response as well to the following question: ‘How did we look after you when you had your treatment?’ comparing to more than two third of the children who gave positive answer.

These findings were supported by the parents’ and children’s responses and comments. For example,

*“She was treated very well by the staff and she felt comfortable which in turn she was relaxed with the treatment... ” P85.*

*“She was put at ease - not a nice experience but seemed to go along with it!” P47.*

Other positive comments from parents were:

*“the dental team have been excellent with my child, they have made him feel relaxed and calm which has made his experience very positive....the whole team are kind and very patient...been able to speak to the team , making him feel at ease’’ P84.*

*“she was treated very well by the staff and she felt comfortable which in turn she was relaxed with the treatment....I would be very happy to come back for another treatment, the staff are really good and thorough’’ P85.*

*“Love the way the staff were friendly with her” P24.*

*“I am really happy for him, I could not believe that my son had extraction and he did not cry... will done to the dentist” P48.*

## **6.11 DISCUSSION**

Dental treatment can be a stressful situation with a variety of unpleasant stimuli. Children in particular often show their distress in behaviour which leads to management problems in the clinics.

The aim of this part of the study was to explore children acceptance as well as parent satisfaction and experience of their child's dental treatment under local anaesthesia and their perception of the impact of this treatment on their child. In addition, to assess the experience associated with dental injection and compare both technique (IDNB and BI) to evaluate which one is associated with less pain or were more acceptable to the children.

The study also, aimed to view the efficacy of local anaesthetic from multiple perspectives, in order to enhance and enrich the meaning of a singular perspective. In addition, to develop a more complete understanding of a dental treatment under local anaesthetic, as well as to develop a complementary picture; to compare, and triangulate results as well as to examine experiences along with outcomes.

Considering the difficulty of evaluating pain objectively, as pain is a subjective experience in that while it is a sensory, felt experience, it is also affected by the meaning attached to it (e.g. anticipatory fear and distress) in this study we are evaluating the subjective dental injection acceptance and tolerance of children undergoing dental treatment.

Accordingly, we adopted a qualitative descriptive approach based on individual open-ended, semi-structured interviews.

### **6.11.1 Why mixed method?**

This part of the study implemented a mixed methods research strategy. It consisted of both quantitative and qualitative exploration elements. The quantitative data was derived from closed-ended structured questionnaire and the qualitative data was taken from answers to open questions along with the semi-structured interviews. The primary justification for using this type of research is that it is acknowledged that a comprehensive representation of the data could not be produced by any one method alone. Qualitative approach offered new understanding that would not have emerged only using quantitative methods. In addition, by adopting the mixed method research strategies, the objectives of the research study was covered and explored with more depth of understanding.

Each source of data represents an important material. The aim of the quantitative data was to provide an explanation of the relationship between the two local anaesthetics considering the participants experience, the data was presented in form of numbers that were analysed using mathematically based methods. The aim of the qualitative phase was to explain, clarify and enhance understanding the quantitative findings as well as to help to better understanding parent's experience of their child's dental treatment.

In this part of the study, the mixed method approach was used by combining data from the results gathered from structured closed ended questionnaire, and from the data gathered from open-ended questionnaire, as well as based on the researcher observations in the field (i.e. clinical setting). This could be considered as not being truly a qualitative approach because of the use of unstructured data collected from an open-ended questionnaire. This approach has been debated in the literature and the question has been raised as to whether such data can be regarded as indicative of a true qualitative approach (Bryman, 2006). However, in this research the

information was based on the responses collected from children and parents who attended for dental treatment. The questionnaire were answered in form of short interview with the parents and children. One important thing as well was that, the researcher gathered additional information from observation during the dental treatment and this was recorded immediately in each clinical session for each patient.

### **6.11.2 Evaluation of the study's treatment outcome**

In the present study, two research statements were considered;

- Evaluating the response and reaction of children when they receive the local anaesthetic injection.
- Assessing the acceptability of the provided dental treatment by the child as well as parent.

One of the most important aims for dentist is to carry out the dental procedures with as little pain or discomfort as possible. As a routine, pain control during dental treatment is achieved mainly by using local anaesthesia, which is a highly effective method. However, one of the main reasons for serious behaviour problems in children is painful experience in the dental situation (Wright, 1983). LA injection is the dental procedure that is most often associated with anxiety and negative responses especially when dealing with children (Nakai *et al.*, 2005).

Having LA injection is not pleasant experience and this was reported extensively in the dental literature. The findings of present study with this regard was not unexpected, this was expressed very clearly through the results and participants' responses.

As discussed earlier in chapter five, in the present study, the treatment success was based on the absence of pain during the providing of dental treatment as well as showing good behaviour and positive attitude, i.e. the child should demonstrate calm, relaxed and allow the safe completion of the procedures. According to Wright, Successful dental treatment provided to children is dependent on the proficiency of the dentist to guide them through their dental experiences. Therefore, the dentist should encourage a positive attitude in the child and carry out the treatment effectively and efficiently (Wright, 1983).

In the following sections, the main study findings will be integrated, and discussed in relation to the treatment outcomes. The dental treatment success, based on parents' and children's point of view, will be deliberated. Moreover, the relationship between the treatment success and the child behaviour will be explored based on the available data.

#### **6.11.2.1 Treatment success based on children's judgment**

In the current study, 84.7% of the children gave a positive response to the question asking about if they were glad to have the treatment, which can be reflected as treatment success. The second question in this category was if the treatment they had was acceptable. When looking at children responses to the statement 'Was it ok having your tooth fixed/extracted', only nine children had a negative experience comparing with 71 children who expressed a positive experience. This can be translated as a high success rate, if we consider the positive answer as treatment success.

Although six children in this study were not happy or did not like the LA anaesthetic process, when they were asked 'what do you think about numbing your tooth?'. Vast

majority of the children were positive about this statement and about third of them were neutral.

This high success rate reported by children could possibly explained by the fact the children were managed well in terms of behaviour management strategies and the way of delivering of the treatment (local anaesthetic injection and restoration/extraction procedures).

#### **6.11.2.2 Treatment success based on parents' judgment**

The findings from this study suggest different patterns of how parents defined treatment success.

##### **Comfortable to have treatment:**

A number of parents considered the treatment successful if the child was looking comfortable in the dental chair. One mother had linked the feeling of comfort with having local anaesthetic, as she had previous experience of having general anaesthetic for her another child. Another mother who was more worried about her son was happy to see him feeling comfortable which in her opinion indicated that the treatment was successful.

##### **Coping with the dental treatment:**

In psychology, coping is *'expending conscious effort to solve personal and interpersonal problems, and seeking to master, minimize or tolerate stress or conflict'* (Wiki, 2015).

The word **'coping'** has different meanings in different contexts. In this study, the parents' comments and responses reflected some of these differences.

For some parents coping means, 'not crying' and therefore showed good behaviour and acceptance of the treatment provided. Another mother correlated the coping with showing fearless, not as what she expected. Moreover, when parents were requested to respond to the statement 'how do they think their child coped with the dental treatment?' the majority of the parents (91%) gave a positive response compared to 4% who gave negative response. This indicates a high success rate.

### **Willingness to return to the dentist**

Some parents associated treatment success with showing good motivation for continuity of dental treatment in the future. Furthermore, a number of the children as well showed positive motivation to come back for further treatment. An example is an eight years old, boy, who had LA before and had attended for his first tooth extraction, even though he did not like to have his tooth out, he was willing to come back again:

*".....I am happy to come next time for the last extraction!" C37.*

### **Concerns about local anaesthetic**

The vast majority of the parents (94.9%) thought that LA was doing good job. This can be seen through the positive comments from the questionnaire. Most of the parents had expressed their understanding of '**good job**' based on the child reaction or coping with the treatment.

Likewise, the percentage of parents who agreed or strongly agreed regarding the statement 'I Have No Concerns about How the Local Anaesthetic Works', was very high (91%). Even though this can be considered as broad question with different possibilities in terms of concerns, the comments gathered from parents were very limited. This can be attributed to the way of asking the question. This was an

exploratory study and not an in-depth interview that could give other dimensions of the answers. However, the available data gave an insight to some of these possibilities.

### **6.11.2.3 Treatment success based on child's behaviour**

Based on the AAPD (2011), behaviour guidance as well as patient satisfaction are highly dependable on the dentist's communication skills (AAPD, 2011). Pinkham had indicated that behaviour management is equally important to the dexterity and knowledge and both are considered as fundamental pillar in clinical success in children dentistry (Pinkham, 1990).

The majority of treated children in this trial showed positive outcome and showed good behaviour, this may attributed to several factors:

- Good behaviour management techniques employed.
- The high clinician's skill level and experience with children.
- Well established relationship between the dentist and child/parents.
- Good case selection for the patients who fit very well with the trial inclusion criteria.

Based on the study findings and existing literature, the author proposed the following diagram (Figure 6-3) which correlate dental treatment outcome with dental treatment provided and behaviour management strategies (BMS).

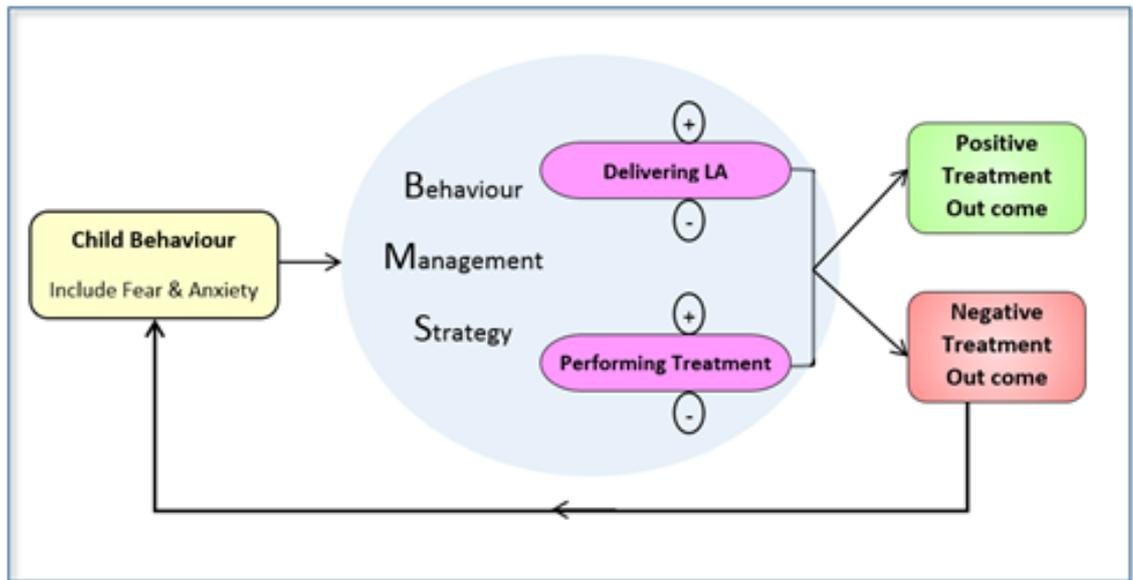


Figure 6-3: Relationship between the BMS and Treatment Outcome

In this study, most of the children attended for their dental treatment along with their different emotions, which included a fear of the unknown, anticipated anxiety based on previous treatment they had themselves or someone close to them (parents/siblings/friends). It is the dentist role here to guide the child through dental treatment and try to absorb the child negative emotions and build new positive ones.

This should be done through great understanding of the child feeling, engaging with the child in discussion about what makes him/her anxious, listen to the child and show that he/she will be looked after. Implementing good behaviour management strategies with good clinical skills, will improve the outcomes. The outcomes here can be related to objective outcome i.e. clinical treatment procedures and subjective outcome i.e. child satisfaction and ability to accept the future dental treatment.

Even though vast majority of the children in this study showed positive treatment outcomes (subjective as well as objective), three children did not complete the treatment and were referred to have their dental treatment under general anaesthetic.

This suggest a strong association between treatment outcome and good behaviour management strategies.

#### **6.11.2.4 Other factors which contribute to the treatment outcomes**

##### **6.11.2.4.1 Children feelings/emotions**

Dental anxiety is a common problem, which can affect people of all ages, but appears to develop mostly in childhood and adolescence (Locker, 2001; Porritt, 2012).

According to Klingberg, dental fear and dental anxiety are two different terms commonly used indistinguishable; however, each one has a different meaning. Dental fear *represents a reaction to a specific external threatening stimulus and is a normal emotional reaction to threatening stimuli in the dental situation*. While dental anxiety *represents a state, where a child is evoked and prepared for something to happen* (Klingberg, 2008). Dental anxiety and fear-related behaviours are considered to be one of the most challenging aspects of paediatric dentistry (Majstorovic and Veerkamp, 2004).

In present study, we have explored how the feeling “**scary**” might affect the dental treatment outcome and how this would that reflected on the child behaviour?

Different scenarios had emerged from the collected data, and ranged between very positive treatment’s outcomes to a negative outcome. The following Figure 6-4 will illustrate these findings. The percentage presented here were based on the treatment outcome success during the course of dental treatment as discussed in chapter four.

Which included only the children who participated in the qualitative analysis (75 children).

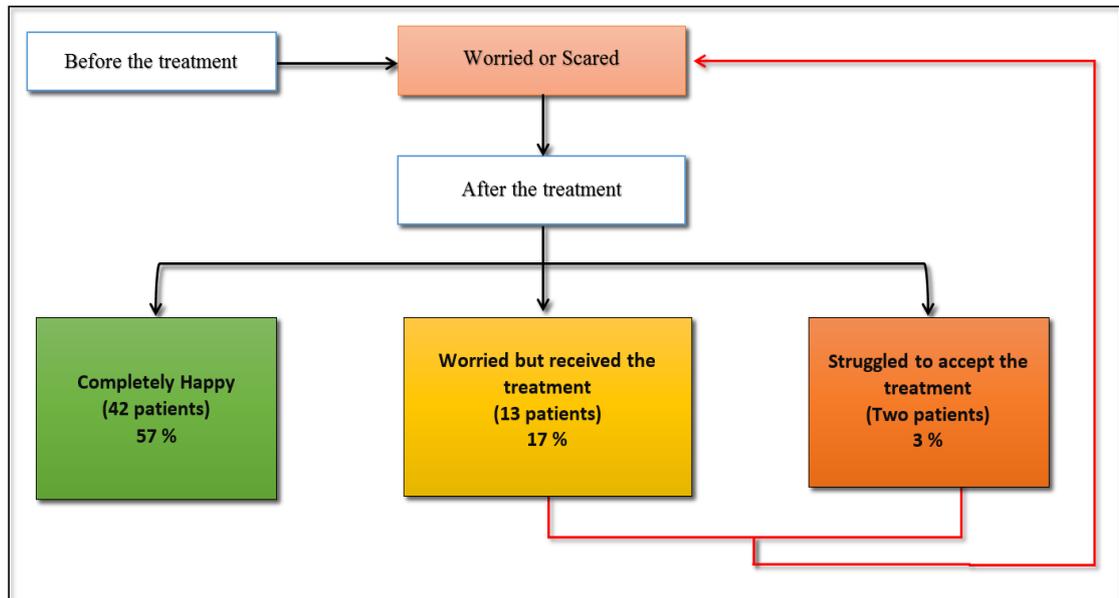


Figure 6-4: Treatment success based on children behaviour

In this study (RCT), the treatment success rate based on children's behaviour was very high, ranged from 87.8% to 95.9%. As discussed earlier, there were different factors, all worked together, which might have contributed to this high success rate. This finding highlighted the strong relationship between the dental staff approaches in reducing the children anxiety. A previous study that reviewed the effect of dental staff behaviour on child dental patient supported our finding (Zhou et al., 2011).

#### 6.11.2.4.2 Mother anxiety

The relationship between parental anxiety, especially the mother and children's anxiety and dental fear is well established in the dental literature. Exploring this in great details was beyond the scope of this study. However, the findings here suggest a strong relationship between mother anxiety and children dental anxiety.

Despite the fact that a number of children were cooperative and willing to follow the dentist's instructions, anxious mothers were interfering with some of these

instructions. Anxious mothers sometimes drew the child's attention and often alerted the child to things and/or procedures that he/she might have been willing to accept and then his/her awareness made it difficult to continue smoothly.

#### **6.11.2.4.3 Dental team**

Most of the children in this study gave positive answers and comments as well, this suggest that a good relationship between the dentist and children was established. The children, who gave negative answers here, may relate this to the pain associated with their treatment.

It might be argued that children give a positive answer because they want to please the person who was asking the questions; the dentist and they do not want to disappoint her. However, almost all the children who had the treatment in this study (94 out of 96 children) gave a positive answer, which might to some extent rule out this possibility.

Lastly, almost all of the parents had positive response and were happy that the dentist explained the procedures very well, including the need for dental treatment. This indicated the importance of good communication between the parents and dental team, as well as the importance of providing information regarding the planned dental treatment of their children under local anaesthesia.

## **6.12 SUMMARY**

The researcher conducted both a quantitative analysis and qualitative thematic analysis to discover and fulfill the purpose of the study.

Parent's responses to the questionnaire, reflected their opinion based on their observation of the dental treatment. Majority of the parents were happy about the treatment in general. More specifically, the administration of the LAs, delivery of the dental treatment and dentist managements including dental teamwork. It is interesting to note that 90.8% of the parents were happy about how their children coped with the dental treatment. In addition, almost all parents agreed that the dental team were kind and helpful during their children's treatment.

The children's responses were very positive as well. During the LA administration, 60.2% were happy comparing with 6.1% children who were not happy about numbing their teeth. During the dental treatment procedures (extraction/restorations), 72.4% were happy comparing with 9.2% children who did not like the treatment. Almost all the children (95.9%) thought that dentist/dental team were nice and friendly.

The questionnaire/interviews with the children, parents, along with the dentist's comments, allowed the development of three major themes addressing the aims and purposes of the study. The three major themes emerged were:

Firstly, "Experience of the anaesthetic procedures". Second major theme "Ease vs difficulty of the dental treatment" and the third major theme was "Perception of the dentist approach during the treatment".

Overall, 42 (56%) of the participants in the qualitative part of the study, were in articaine group while 31 (41%) were in lidocaine group. Only two of the participants (3%) had received both local anaesthetics.

As observed and upon evaluation, the experiences of the participants from both the treatment procedures did not vary and in fact were found to be similar to each other.

Overall, it can be established that the quantitative and qualitative results of the analysis coincided and concurred one another.

### **6.13 CONCLUSION**

The findings of this study have important implications for both future practice and research. However, it should be acknowledge here that these results were based primarily on the quantative data form the main study with an embedded qualitative component.

- Considering the findings from the study, along with the results from the questionnaire/interview, it was establish that the reactions of the patients with both of the local anaesthetics were similar.
- The results with regard to comparison between the two local anaesthetics in terms of the efficacy of anesthesia as well as the reaction of the patients with anesthesia were very much similar. Mostly responses were positive from the questioned participants.
- Parents/children reported a high degree of satisfaction with the treatment outcomes. The satisfaction expressed by parents/children can have a positive impact on the children's future dental treatment.

#### **6.14 STRENGTH OF THE STUDY**

- 1- Using mixed method in the present study is one of the strength point of the study as both research designs can provide a general picture for the study aims and objectives.
- 2- In the current study, the limited qualitative data was used to explain to some extent the aspects of the quantitative data, was the main source of study data. Using descriptive and narrative style was helpful to facilitate the clarification of associations between variable as well as playing a significant role of suggesting potential relationships within the study findings.
- 3- Researcher's presence had profound reflective effect on the subjects of study. A good dentist-patient relationship was established and this allowed the researcher to find out more details by using systematic and more positivistic enquiries.

## 6.15 LIMITATIONS

There are some limitations within this exploratory investigation study that need to be acknowledged.

- The study was conducted in a tertiary care setting, involving patients from a range of socio-economic backgrounds. Most of the children who have had a negative past experience and /or negative behavioural problems in relation to dentistry had been excluded from this study. Therefore, the final sample might not be a fully representative of the general population.
  
- This was an explanatory investigatory study. There was no in-depth interview with parents/children. However, every effort was made to collect relevant data using different perspectives and using different techniques, which offer new understanding that, would not have emerged only using quantitative methods.
  
- The interviews with parents and children were not taped and transcribed. However, the presented data were collected and completed at the time of interview by the research participants and the investigator.
  
- The author had no previous experience of running a qualitative research. Hence, a more experienced researcher may have achieved different, more explanatory results. However, it should be noted that the data analysis have been enhanced by arranging an independent assessment of transcripts by an additional skilled qualitative researcher who had input in the final written report.

## **Chapter 7**

### **GLOBAL CONCLUSION**

#### **7.1 INTRODUCTION**

In this chapter, the global conclusions along with the significant research contributions and study implications will be presented. As with every research project we faced certain barriers, thus the main research limitations will be highlighted.

Finally, areas and fields for future research were highlighted during the course of these studies, and these will be presented in this chapter.

#### **7.2 CONCLUSION**

The quality of the included RCTs in the systematic review was generally inadequate. Common methodological inaccuracies, which increase the risk of bias of the trials in this review, included lack of proper randomisation and allocation concealment, lack of power calculation, lack of intention-to-treat analysis and lack of blinding. It is, however, promising that the recently included studies have improved reporting of some study details to enable quality assessment. Ultimately, all the included studies had several limitations in reporting which indicated a need for a randomised clinical trial with standardised methodology to address these limitations.

The findings of the systematic review indicated that, articaine and lidocaine presented the same efficacy when used as infiltration or blocks for routine dental treatments. The effect of numbness of soft tissues was longer using articaine than lidocaine, and few adverse events were reported following the use of both solutions. The results from this review indicate that articaine injections can cause slightly more

post injection pain in the area injected than lignocaine, the difference was not statistically significant.

Overall, the results of the present RCT pointed out that it would be acceptable to carry out invasive dental treatment for mandibular primary molars with the administration of buccal infiltration with buccal intrapapillary infiltration using 4% articaine instead of the traditional method of inferior dental block using lidocaine, which many children find difficult to cope with.

These results were based on W-BFRS and Behaviour scales, the difference in efficacy of success rates between articaine hydrochloride BI and lidocaine hydrochloride IDNB was well within the equivalence range and within the estimated 95% CI for intention-to treat analyses. Conversely, the difference in efficacy between the two local anaesthetics, during local anaesthetic injection, based on VAS results, was not within the equivalence range. However, during the treatment procedures and using the same scale (VAS), the equivalence was established. Therefore, equivalence between the two types of local anaesthetics/techniques can be established for the primary endpoint.

Considering the findings from the survey, along with the results from the questionnaire/interview, it was established that, the reactions of the patients with both of the local anaesthetics were very similar. The interview findings added meaning and depth to the survey findings, in terms of explaining and clarifying the children's responses and answers. Parents/children reported a high degree of satisfaction with the treatment outcomes. The satisfaction expressed by parents/children can have a positive impact on the children's future dental treatment.

### **7.3 IMPLICATION OF THE STUDY**

It is valuable and more manageable to divide the main research implications into the following points:

- From practitioners and professionals prospective: The findings of this study might assist dentists in terms of decision making and treatment planning; especially when dealing with young children regarding the best way of delivering the dental treatment. Moreover, dentist who might find the IDNB difficult to administer, can provide safe and effective local anaesthetic injection with administration of BI with buccal intrapillary infiltration using 4% Articaine hydrochloride.
- From research prospective: This study had established the association between dental treatment and behaviour management strategies and recognised the importance of behaviour managements during dental treatment and how can that affect the treatment outcome. However, further studies investigating the relationship between the dentist behaviour and the final treatment outcome would be of great value to this field.

### **7.4 RESEARCH CONTRIBUTION**

The main contributions of this study project were as below:

- Based on the findings from the systematic review, it is essential to point out the importance of improving the quality of RCTs, as well as adequacy of reporting the methodology in the RCT to permit future synthesis.
- The randomised clinical trial presented here has been developed based on a comprehensive literature review, and systematic review including the discussion of previous studies on the use of articaine in children's dentistry.

- This is the first study to adopt an equivalence randomised clinical trial in children dentistry. In addition, this is the first clinical trial that compare the local anaesthetic efficacy of 4% articaine as buccal infiltration vs 2% lidocaine as inferior dental nerve block and used three assessment scales for assessment of treatment efficacy in children.
- As far as the author is aware, this is the first study in children dentistry that used qualitative research method to evaluate the children's and their parents' acceptance of the dental treatment under local anaesthetics.
- The study findings might be consider as a guidance for the clinician on daily basis for routine dental treatment for children who require treatment (including pulpotomy and extraction) for mandibular primary molars; in term of using articaine as buccal infiltration with no need to use the dental nerve block.

## **7.5 RESEARCH LIMITATIONS**

It is very rare to find an ideal and integrated study or research project that covers all relevant aspects of the potential elements in the study area. Even though this study was carried out based on solid research methodology following the relevant guidelines; there were some limitations in this research as follow:

- The systematic review part of this study was conducted by a single reviewer. This may have resulted in an item receiving a score by one reviewer that may have not been selected by another. However, data abstraction was checked several times to avoid errors in data and decrease the likelihood of inaccuracy and bias. As there was no second reviewer this could not be qualified by inter-rater agreement.

- Additionally, the results of this systematic review may be indefinite because of the small sample sizes and because children's behaviours are more difficult to control.
- The RCT was very comprehensive study. It required time and effort, combined with the knowledge of all the clinical governance aspects and guidelines as well as the medico-legal subjects. It was a challenge to be carried out by one researcher; however, the support gained from the study's supervisors was of great advantage.
- The study was conducted in a tertiary care setting, involving patients from a range of socio-economic backgrounds. Most of the children who had a negative past experience and/or negative behavioural problems in relation to dentistry had been excluded from this study. Therefore, the final sample might not be fully representative of the general population.
- This was an exploratory investigatory study. Qualitative data drawn upon was limited to probed comments from the questionnaire as well as children's drawings. There was no in-depth interview with parents/children. However, every effort was made to collect relevant data using different perspectives and using different techniques, which offer new understanding that would not have emerged only using quantitative methods.
- The author had no previous experience of running a qualitative research project. Hence, a more experienced researcher may have achieved different, more explanatory results. However, it should be noted that the data analysis have been enhanced by arranging an independent assessment of transcripts by an additional skilled qualitative researcher who provided support in the analysis.

## **7.6 RECOMMENDATION FOR FURTHER RESEARCH**

Based on the research findings and conclusions, the following are the suggestions and recommendation for further studies and research:

- Well-designed and properly executed randomised controlled trials provide the best evidence on the efficacy of health care interventions. Extend research and further comparative RCT is necessary to look at articaine in the treatment of hypomineralised teeth (MIH) in children population.
- The present RCT was based in tertiary dental center, in which, most of the referrals were for difficult cases. This was an obstacle in term of patients' recruitment especially with very detailed inclusion criteria. Therefore, in future, if a study with the similar design will be carried out, it is advisable to take place in a primary care setting in which there will be more exposure to the patients with different background and differing levels of cooperation. This would aid in improving the generalisability of the results and findings.
- The qualitative part of this study was based on open-ended questionnaire and clinician observations would be more valuable if a focus group or an in-depth interview were conducted to give further insight and more depth to the understanding of the patient's experience during dental treatment under local anaesthetics.
- This study was carried out in the UK, it would benefit for further study to be carried out in different country in order to detect any variance, which might be related to different criteria such as social background, language, behaviour and other related factors.

## **7.7 INDEMNITY**

The University of Leeds provided indemnity for this research.

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# *Study Protocol*

Version 6 Date 10\02\2015

**COMPARATIVE STUDIES OF THE ANAESTHETIC EFFICACY OF 4% ARTICAIN  
USED AS MANDIBULAR INFILTRATION VERSUS 2% LIDOCAINE USED AS INFERIOR  
DENTAL NERVE BLOCK IN EXTRACTION AND PULPOTOMY OF MANDIBULAR  
PRIMARY MOLARS.**

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**Short study title:**

Use of Articaine in Children's Dentistry

**Study Full Title:**

Comparative studies of the anaesthetic efficacy of 4% Articaine used as mandibular infiltration versus 2% Lidocaine used as inferior dental nerve block, in extraction and pulpotomy of mandibular primary molars in children.

**Sponsor Name:**

University of Leeds, Leeds Dental Institute

**Sponsor Number:**

DT11/9936

**EudraCT Number:**

2011-004711-23

**ISRCTN Number:**

ISRCTN11415977

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**AMENDMENTS**

Document to be amended (inc. current version and date)	Details of amendment, inc. page number	Rationale for amendment	New document name, version number and date	Details of amendment, inc. page number
Protocol <b>V.4</b> Date: <b>17/12/2012</b>	Page 15 – <b>Ultra Care® topical Anaesthetic Gel</b> (Benzocaine 20% w/v)	This product is not available any more in the department	Protocol <b>V.4.1</b> Date : <b>11/11/2013</b>	Page 15: We are changing the topical anaesthetic ( <b>Ultra Care® topical Anaesthetic Gel</b> (Benzocaine 20% w/v), but not the technique of application. And we are going to use the available topical anaesthetic according to local practice.
Protocol <b>V.4.1</b> Date : <b>11/11/2013</b>	Page 9 and 21 <b>9.1.1.1 lidocaine</b>	This section has been removed	Protocol <b>V.5</b> Date : <b>07/02/2014</b>	Page 9 and 21: This was written in the protocol as an IMP and the MHRA this was not included, therefore, we have removed it from the protocol.
	Page 25 Maximum dosage of articaine and lidocaine	This has been changed, and corrected.	Protocol <b>V.5</b> Date : <b>07/02/2014</b>	Page 25: Typing error, the doses level has been mixed up, the information has been corrected.
Protocol <b>V.5</b> Date : <b>07/02/2014</b>	Page 24 Trial Schedule	This has been updated to include further information based on substantial amendments	Protocol <b>V.6</b> Date : <b>10/01/2015</b>	<b>EXCEPTION:</b> This part has been amended – and was added to the protocol following the Substantial Amendment 1.0, 9/4/14-NRES Committee: Some patients were seen in the screening visit and had received the dental treatment on the same day according to the randomisation table. This was done to facilitate the recruitment and for the best of patient's interests

## STUDY SUMMARY

<b>GENERAL INFORMATION</b>	
Short Title	Comparative studies of the anaesthetic efficacy of 4% Articaine versus 2% Lidocaine in children
Full Title	Comparative studies of the anaesthetic efficacy of 4% Articaine used as mandibular infiltration versus 2% Lidocaine used as inferior dental nerve block, in extraction and pulpotomy of mandibular primary molars in children.
Sponsor	University of Leeds
Sponsor ID	DT11/9936
EudraCT No.	2011-004711-23
ISRCTN Number	ISRCTN11415977
Chief Investigator	Monty S. Duggal
Principle Investigator	Fatma S. Alzahrani
Co-ordinating Centre	Leeds Dental Institute
National / International	National
<b>TRIAL INFORMATION</b>	
Phase	PhaseIV
Indication	1. Both drugs are licensed 2. Investigating how will the drugs work when it is used more widely.
Design	Aparallel prospective, randomised, controlled trial.
Primary Objectives	1. To test if the planned dental treatment has been accomplished 2. If the treatment has been completed, was there a complaint of pain, and 3. To evaluate the level of pain if any was experienced.
Secondary Objectives	To evaluate the acceptance of the provided dental treatment to the child by both the child who had the dental treatment and parents/guardian.
<b>TRIAL TIMELINES</b>	
Expected start date	01-01-2013
Subject enrolment phase	24 months
Follow-up duration	Not Required.
End of Trial Definition	Last visit for the last participant.

Expected completion date	01-01-2015
<b>TRIAL SUBJECT INFORMATION</b>	
Number of trial subjects	110children
Age group of trial subjects	5 to 9 Years old.
Inclusion criteria	<ul style="list-style-type: none"> <li>• Children aged 5 to 9 years.</li> <li>• Medically fit (ASA I,II).</li> <li>• Requiring extraction /pulpotomy of primary mandibular molars teeth under local anaesthetic.</li> <li>• Mentally capable of communication.</li> <li>• Understand English.</li> <li>• Tooth with no history of infection (abscess) or swelling and no evidence of periapical pathosis.</li> <li>• The roots resorption of the primary tooth must be less than two thirdof the root.</li> <li>• Parents/guardian must give informed written consent prior to participation.</li> <li>• Child must give assent prior to participation.</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Medically and mentally compromised children.</li> <li>• Allergic to amide local anaesthetic or any of the ingredients in the cartilages.</li> <li>• History of significant behaviour management problems.</li> <li>• Evidence of infection near the proposed injection site as this might affect the efficacy of local anaesthesia.</li> </ul>
<b>INVESTIGATIONAL MEDICINAL PRODUCT</b>	
IMP name(s)	<p>1- Articaine (Septanest 1:100,000) 4% articaine with 1:100,000 epinephrine injection solution</p> <p>2- Lidocaine (Lignospan Special) 2% lidocaine with 1:80,000 epinephrine injection solution.</p>
Duration of IMP Treatment	30- 60 minutes.
IMP Supplier(s)	Septodont.
Non IMP name(s)	<p>1- Topical anaesthesia.</p> <p>2- Adrenaline</p>

## **DATA EXTRACTION SHEET**

### **General information**

<b>Article number</b>	
<b>Date of data extraction</b>	
<b>Title</b>	
<b>Details of publication</b>	
<b>Year</b>	
• Volume	
• Pages	
<b>Country of origin</b>	
<b>Institutional affiliation</b>	
<b>When was the fieldwork conducted</b>	
<b>Language</b>	
<b>Author</b>	
<b>Source</b>	
<b>Publication type</b>	<input type="checkbox"/> Published
	<input type="checkbox"/> Unpublished
	<input type="checkbox"/> Thesis
	<input type="checkbox"/> Other

<b>Research question</b>	
<b>Aim</b>	
<b>Hypothesis</b>	
<b>Study design</b>	
<b>Randomisation</b>	<input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, describe it : _____
<b>Blinding</b>	Subject <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Operator <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Evaluator <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Statistician <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Standardization</b>	Number of operators <input type="checkbox"/> Not reported <input type="checkbox"/> Single <input type="checkbox"/> Multiple
	Attempt to standardize operators <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
	Number of evaluators <input type="checkbox"/> Not reported <input type="checkbox"/> Single <input type="checkbox"/> Multiple
	Attempt to standardize evaluators <input type="checkbox"/> Not reported <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Statistical analysis</b>	Appropriate for study design <input type="checkbox"/> Not Clear <input type="checkbox"/> Yes <input type="checkbox"/> No
Data Extraction Sheet	

<b>Treatment procedures</b>		
	<b>Treatment group</b>	<b>Control group</b>
<b>Arch anaesthetised</b>	<input type="checkbox"/> Maxilla <input type="checkbox"/> Mandible <input type="checkbox"/> Combine (max & mand)	<input type="checkbox"/> Maxilla <input type="checkbox"/> Mandible <input type="checkbox"/> Combine (max & mand)
<b>Technique used for application of LA</b>	<input type="checkbox"/> Not specified <input type="checkbox"/> Infiltration <input type="checkbox"/> Periodontal ligament <input type="checkbox"/> IANB <input type="checkbox"/> Buccal infiltration - mand <input type="checkbox"/> Palatal infiltration- max <input type="checkbox"/> Other	<input type="checkbox"/> Not specified <input type="checkbox"/> Infiltration <input type="checkbox"/> Periodontal ligament <input type="checkbox"/> IANB <input type="checkbox"/> Buccal infiltration - mand <input type="checkbox"/> Palatal infiltration- max <input type="checkbox"/> Other
<b>Type of LA used</b>	<input type="checkbox"/> Articaine <input type="checkbox"/> Lidocaine <input type="checkbox"/> Other	<input type="checkbox"/> Articaine <input type="checkbox"/> Lidocaine <input type="checkbox"/> Other
<b>Amount of LA used</b>		
<b>Treated tooth/teeth</b>	<input type="checkbox"/> Primary <input type="checkbox"/> Permanente	<input type="checkbox"/> Primary <input type="checkbox"/> Permanente
<b>Treated tooth/teeth</b>	<input type="checkbox"/> Not specified <input type="checkbox"/> Central incisors <input type="checkbox"/> Lateral incisors <input type="checkbox"/> Canine <input type="checkbox"/> 1 <sup>st</sup> premolar <input type="checkbox"/> 2 <sup>nd</sup> premolar <input type="checkbox"/> 1 <sup>st</sup> molar <input type="checkbox"/> 2 <sup>nd</sup> molar <input type="checkbox"/> 3 <sup>rd</sup> molar	<input type="checkbox"/> Not specified <input type="checkbox"/> Central incisors <input type="checkbox"/> Lateral incisors <input type="checkbox"/> Canine <input type="checkbox"/> 1 <sup>st</sup> premolar <input type="checkbox"/> 2 <sup>nd</sup> premolar <input type="checkbox"/> 1 <sup>st</sup> molar <input type="checkbox"/> 2 <sup>nd</sup> molar <input type="checkbox"/> 3 <sup>rd</sup> molar
<b>Type of dental treatment</b>	<input type="checkbox"/> Extraction <input type="checkbox"/> Pulp therapy <input type="checkbox"/> Simple restoration <input type="checkbox"/> Moderate restoration	<input type="checkbox"/> Extraction <input type="checkbox"/> Pulp therapy <input type="checkbox"/> Simple restoration <input type="checkbox"/> Moderate restoration

Data Extraction Sheet

<b>Outcome</b>		
<b>Initial Diagnosis of the Tooth</b>	<input type="checkbox"/> Not specified <input type="checkbox"/> Vital <input type="checkbox"/> Irreversible pulpitis	
<b>Definition of pulpal anaesthetic success</b>	<input type="checkbox"/> Not reported <input type="checkbox"/> Negative EPT responses at 80 ,of consecutive reading <input type="checkbox"/> Ability to perform treatment without pain using VAS scale <input type="checkbox"/> Ability to perform treatment without requiring re injection <input type="checkbox"/> No pain <input type="checkbox"/> Other _____	
<b>Pulpal anaesthetic success</b>	<input type="checkbox"/> VAS categorical <input type="checkbox"/> EPT <input type="checkbox"/> Others _____	
<b>Pulpal anaesthetic effect</b>	Onset	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported
	Duration	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported
	Success	<input type="checkbox"/> 30 minute <input type="checkbox"/> 60 minutes
<b>Soft tissue anaesthetic effect</b>	Onset	<input type="checkbox"/> Reported _____ <input type="checkbox"/> Not reported
Data Extraction Sheet		

	Duration	<input type="checkbox"/> Reported <hr/> <input type="checkbox"/> Not reported
	Success	<input type="checkbox"/> 30 minute <input type="checkbox"/> 60 minutes

<b>Participants</b>			
<b>Target population</b>	<input type="checkbox"/> Adult	<input type="checkbox"/> Children	
<b>Characteristic of population</b>			
<b>Number of participants</b>	Total :	Girls:	Boys:
<b>Age</b>	Mean age:	Girls:	Boys:
<b>Social class</b>			
<b>Geographic location</b>			
<b>Ethnicity</b>			
<b>Health status</b>			
<b>Other information</b>			

<b>Methodology of study</b>	
<b>Inclusion criteria</b>	
<b>Exclusion criteria</b>	
<b>Sample size calculation</b>	
<b>Randomisation</b>	
<b>Allocation</b>	

Data Extraction Sheet

<b>Data analysis</b>	
<b>Intend to treat analysis</b>	
<b>Statistical technique used</b>	
<b>Qualitative analysis</b>	
<b>Computer analysis tools used</b>	
<b>Ethics</b>	Was ethics committee approval obtained? <input type="checkbox"/> Yes <input type="checkbox"/> No
Data Extraction Sheet	

Bias	

**ADDITIONAL COMMENTS:**

<b>FINAL STUDIES AFTER REMOVING THE DUPLICATE FOR 1<sup>ST</sup> REVIEW</b>			
<b>No</b>	<b>Study Information</b>	<b>Included</b>	<b>Excluded / why</b>
1.	ABDULWAHAB, M., BOYNES, S., MOORE, P., SEIFIKAR, S., AL-JAZZAF, A., ALSHURAI DAH, A., ZOVKO, J. & CLOSE, J. 2009. The efficacy of six local anesthetic formulations used for posterior mandibular buccal infiltration anesthesia. <i>Journal of the American Dental Association (JADA)</i> , 140, 1018-1024.	Yes	
2.	ABRAMS, R., MORRISON, J. E., VILLASENOR, A., HENCMANN, D., DA FONSECA, M. & MUELLER, W. Safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures. <i>Anesthesia Progress</i> , 40, 63-6.	No	Sedation
3.	AITKEN, J. C., WILSON, S., COURY, D. & MOURSI, A. M. The effect of music distraction on pain, anxiety and behavior in pediatric dental patients. <i>Pediatric Dentistry</i> , 24, 114-8.	No	effect of music distraction
4.	AL-BAHLANI, S., SHERRIFF, A. & CRAWFORD, P. J. Tooth extraction, bleeding and pain control. <i>Journal of the Royal College of Surgeons of Edinburgh</i> , 46, 261-4.	No	Tooth extraction, bleeding and pain control
5.	ALEMANY-MARTÍNEZ, A., VALMASEDA-CASTELLÓN, E., BERINI-AYTÉS, L. & GAY-ESCODA, C. 2008. Hemodynamic changes during the surgical removal of lower third molars. <i>Journal of Oral &amp; Maxillofacial Surgery (02782391)</i> , 66, 453-461.	No	Hemodynamic changes during
6.	ALLEN, K. D., KOTIL, D., LARZELERE, R. E., HUTFLESS, S. & BEIRAGHI, S. Comparison of a computerized anesthesia device with a traditional syringe in preschool children. <i>Pediatric Dentistry</i> , 24, 315-20.	No	computerized anaesthesia device
7.	AMINABADI, N. A. & FARAHANI, R. M. Z. The effect of pre-cooling the injection site on pediatric pain perception during the administration of local anesthesia. <i>Journal of Contemporary Dental Practice [Electronic Resource]</i> , 10, 43-50.	No	pre-cooling the injection site
8.	AMINABADI, N. A., FARAHANI, R. M. Z. & BALAYI GAJAN, E. The efficacy of distraction and counterstimulation in the reduction of pain reaction	No	The efficacy of distraction

	to intraoral injection by pediatric patients. <i>Journal of Contemporary Dental Practice [Electronic Resource]</i> , 9, 33-40.		
9.	ANDRZEJOWSKI, J. & LAMB, L. The effect of swabs soaked in bupivacaine and epinephrine for pain relief following simple dental extractions in children. <i>Anaesthesia</i> , 57, 281-3.	No	The effect of swabs soaked
10.	ANNEQUIN, D., CARBAJAL, R., CHAUVIN, P., GALL, O., TOURNIAIRE, B. & MURAT, I. Fixed 50% nitrous oxide oxygen mixture for painful procedures: A French survey. <i>Pediatrics</i> , 105, E47.	No	Sedation
11.	ARAPOSTATHIS, K. N., DABARAKIS, N. N., COOLIDGE, T., TSIRLIS, A. & KOTSANOS, N. Comparison of acceptance, preference, and efficacy between jet injection INJEX and local infiltration anesthesia in 6 to 11 year old dental patients. <i>Anesthesia Progress</i> , 57, 3-12.	No	Comparison between jet injection INJEX and local infiltration anaesthesia
12.	ARCH, L. M., HUMPHRIS, G. M. & LEE, G. T. Children choosing between general anaesthesia or inhalation sedation for dental extractions: the effect on dental anxiety. <i>International Journal of Paediatric Dentistry</i> , 11, 41-8.	No	choosing between general anaesthesia or inhalation sedation
13.	ARMSTRONG, P. J. The value of associating pentazocine with drugs used in accepted intravenous techniques. <i>Australian Dental Journal</i> , 20, 235-8.	No	Sedation
14.	ARROW, P. 2012. A comparison of articaine 4% and lignocaine 2% in block and infiltration analgesia in children. <i>Australian Dental Journal</i> , 57, 325-333.	Yes	
15.	ASARCH, T., ALLEN, K., PETERSEN, B. & BEIRAGHI, S. Efficacy of a computerized local anesthesia device in pediatric dentistry. <i>Pediatric Dentistry</i> , 21, 421-4.	No	a computerized local anaesthesia device
16.	AY, S., KÜÇÜK, D., GÜMÜS, C. & KARA, M. I. 2011. Distribution and absorption of local anesthetics in inferior alveolar nerve block: evaluation by magnetic resonance imaging. <i>Journal of Oral &amp; Maxillofacial Surgery (02782391)</i> , 69, 2722-2730.	No	Distribution and absorption of local anaesthetics
17.	BAGESUND, M. & TABRIZI, P. Lidocaine 20% patch vs lidocaine 5% gel for topical anaesthesia of oral mucosa. <i>International Journal of Paediatric Dentistry</i> , 18, 452-60.	No	Topical anaesthesia
18.	BAGHDADI, Z. D. A comparison of parenteral and electronic dental anesthesia during operative	No	A comparison of parenteral and

	procedures in children. <i>General Dentistry</i> , 48, 150-6.		electronic dental anaesthesia
19.	BAGHDADI, Z. D. Evaluation of electronic dental anesthesia in children. <i>Oral Surgery Oral Medicine Oral Pathology Oral Radiology &amp; Endodontics</i> , 88, 418-23.	No	Evaluation of electronic dental anaesthesia
20.	BALUGA, J. C. Allergy to local anesthetics in dentistry. Myth or reality? <i>Revista Alergia Mexico</i> , 50, 176-81.	No	Allergy
21.	BAYGIN, O., TUZUNER, T., ISIK, B., KUSGOZ, A. & TANRIVER, M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. <i>International Journal of Paediatric Dentistry</i> , 21, 306-13.	No	reducing post-operative pain
22.	BERLIN, J., NUSSTEIN, J., READER, A., BECK, M. & WEAVER, J. 2005. Efficacy of articaine and lidocaine in a primary intraligamentary injection administered with a computer-controlled local anesthetic delivery system. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 99, 361-366.	No	Adult - - Inter-ligamental - - computer-controlled local anaesthetic
23.	BHANANKER, S. M., AZAVEDO, L. F. & SPLINTER, W. M. Addition of morphine to local anesthetic infiltration does not improve analgesia after pediatric dental extractions. <i>Paediatric Anaesthesia</i> , 18, 140-4.	No	Addition of morphine to local anaesthetic
24.	BORIO, P. S., DEFABIANIS, E. & ROCCIA, G. M. [Clinical experimentation of a new local anesthetic, Citanest 3 O]. <i>Minerva Stomatologica</i> , 18, 291-8.	Yes	
25.	BRADLEY, D. J. & MARTIN, N. D. Clinical evaluation of mepivacaine and lidocaine. <i>Australian Dental Journal</i> , 14, 377-81.	Yes	
26.	CARREL, R., FRIEDMAN, L. & BINNS, W. H., JR. Laboratory and clinical evaluation of a new topical anesthetic. <i>Anesthesia Progress</i> , 21, 126-31.	No	Topical anaesthesia
27.	CHIARETTI, A., BARONE, G., RIGANTE, D., RUGGIERO, A., PIERRI, F., BARBI, E., BARONE, G. & RICCARDI, R. Intranasal lidocaine and midazolam for procedural sedation in children. <i>Archives of Disease in Childhood</i> , 96, 160-3.	No	Sedation
28.	CHIN, K. L., YAGIELA, J. A., QUINN, C. L., HENDERSON, K. R. & DUPERON, D. F. Serum mepivacaine concentrations after intraoral injection	No	Serum mepivacaine concentrations

	in young children. <i>Journal of the California Dental Association</i> , 31, 757-64.		
29.	CHO, S. Y., DRUMMOND, B. K., ANDERSON, M. H. & WILLIAMS, S. Effectiveness of electronic dental anesthesia for restorative care in children. <i>Pediatric Dentistry</i> , 20, 105-11.	No	Effectiveness of electronic dental anaesthesia
30.	COBAN, Y. K., SENOGLU, N. & OKSUZ, H. Effects of preoperative local ropivacaine infiltration on postoperative pain scores in infants and small children undergoing elective cleft palate repair. <i>Journal of Craniofacial Surgery</i> , 19, 1221-4.	No	cleft palate repair
31.	COLLEGE, C., FEIGAL, R., WANDERA, A. & STRANGE, M. Bilateral versus unilateral mandibular block anesthesia in a pediatric population. <i>Pediatric Dentistry</i> , 22, 453-7.	No	Bilateral versus unilateral mandibular block
32.	COLOMBINI, B. L., MODENA, K. C. S., CALVO, A. M., SAKAI, V. T., GIGLIO, F. P. M., DIONÍSIO, T. J., TRINDADE, A. S., JR., LAURIS, J. R. P. & SANTOS, C. F. 2006. Articaine and mepivacaine efficacy in postoperative analgesia for lower third molar removal: a double-blind, randomized, crossover study. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 102, 169-174.	No	postoperative analgesia Articaine and mepivacaine Adult
33.	COSTA, C. G., TORTAMANO, I. P., ROCHA, R. G., FRANCISCHONE, C. E. & TORTAMANO, N. 2005. Onset and duration periods of articaine and lidocaine on maxillary infiltration. <i>Quintessence International</i> , 36, 197-201.	Yes	
34.	COULTHARD, P., ROLFE, S., MACKIE, I. C., GAZAL, G., MORTON, M. & JACKSON-LEECH, D. Intraoperative local anaesthesia for paediatric postoperative oral surgery pain--a randomized controlled trial. <i>International Journal of Oral &amp; Maxillofacial Surgery</i> , 35, 1114-9.	No	postoperative oral surgery pain
35.	DE MENEZES ABREU, D. M., LEAL, S. C., MULDER, J. & FRENCKEN, J. E. postoperative oral surgery pain atraumatic, and ultraconservative restorative treatments in 6- to 7-yr-old children. <i>European Journal of Oral Sciences</i> , 119, 163-8.	No	postoperative oral surgery pain
36.	DEEPIKA, A., RAO, C. R., VINAY, C., ULOOPI, K. S. & RAO, V. V. Effectiveness of two flavored topical anesthetic agents in reducing injection pain in children: a comparative study. <i>Journal of Clinical Pediatric Dentistry</i> , 37, 15-8.	No	topical anaesthetic

37.	DONALDSON, D., JAMES-PERDOK, L., CRAIG, B. J., DERKSON, G. D. & RICHARDSON, A. S. A comparison of Ultracaine DS (articaine HCl) and Citanest forte (prilocaine HCl) in maxillary infiltration and mandibular nerve block. <i>Journal (Canadian Dental Association)</i> , 53, 38-42.	Yes	
38.	DUDKIEWICA A, SCHWARTZ S, LALIBEERTE R. Effectiveness of mandibular infiltration in children using the local anesthetic Ultracaine (articaine hydrochloride). <i>J Can Dent Assoc</i> 1987; 53:29-31.	Yes	
39.	EIFINGER, F. F. & STRATMANN, K. R. [New aspects of local anesthesia in conservative dentistry]. <i>SSO: Schweizerische Monatsschrift fur Zahnheilkunde</i> , 91, 1-7.	Yes	
40.	ELAD, S., ADMON, D., KEDMI, M., NAVEH, E., BENZKI, E., AYALON, S., TUCHBAND, A., LUTAN, H. & KAUFMAN, E. 2008. The cardiovascular effect of local anesthesia with articaine plus 1:200,000 adrenalin versus lidocaine plus 1:100,000 adrenalin in medically compromised cardiac patients: a prospective, randomized, double blinded study. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 105, 725-730.	No	cardiovascular effect
41.	ELHAKIM, M. Painless dental extraction in children. <i>Anaesthesiologie und Reanimation</i> , 18, 80-2.	No	Painless dental extraction
42.	EL-SEIFY, Z. A., KHATTAB, A. M., SHAABAN, A. A., METWALLI, O. S., HASSAN, H. E. & AJJOUB, L. F. Xylometazoline pretreatment reduces nasotracheal intubation-related epistaxis in paediatric dental surgery. <i>British Journal of Anaesthesia</i> , 105, 501-5.	No	Xylometazoline pre-treatment
43.	FAN, S., CHEN, W. L., PAN, C. B., HUANG, Z. Q., XIAN, M. Q., YANG, Z. H., DIAS-RIBEIRO, E., LIANG, Y. C., JIAO, J. Y., YE, Y. S. & WEN, T. Y. 2009. Anesthetic efficacy of inferior alveolar nerve block plus buccal infiltration or periodontal ligament injections with articaine in patients with irreversible pulpitis in the mandibular first molar. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 108, e89-93.	No	No comparison Adult
44.	FAN, S., CHEN, W. L., YANG, Z. H. & HUANG, Z. Q. 2009. Comparison of the efficiencies of permanent maxillary tooth removal performed with single buccal infiltration versus routine buccal and	No	No comparison Adult

	palatal injection. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 107, 359-363.		
45.	FAYTROUNY, M., OKTE, Z. & KUCUKYAVUZ, Z. Comparison of two different dosages of hydroxyzine for sedation in the paediatric dental patient.[Erratum appears in Int J Paediatr Dent. 2007 Nov-Dec;29(6):456]. <i>International Journal of Paediatric Dentistry</i> , 17, 378-82.	No	Sedation
46.	FEDA, M., AL AMOUDI, N., SHARAF, A., HANNO, A., FARSI, N., MASOUD, I. & ALMUSHYT, A. A comparative study of children's pain reactions and perceptions to AMSA injection using CCLAD versus traditional injections. <i>Journal of Clinical Pediatric Dentistry</i> , 34, 217-22.	No	Injection technique
47.	FLAITZ, C. M., NOWAK, A. J. & HICKS, M. J. Evaluation of the anterograde amnesic effect of rectally administered diazepam in the sedated pedodontic patient. <i>Journal of Dentistry for Children</i> , 53, 17-20.	No	Sedation
48.	GARISTO, G. A., GAFFEN, A. S., LAWRENCE, H. P., TENENBAUM, H. C. & HAAS, D. A. 2010. Occurrence of paresthesia after dental local anesthetic administration in the United States. <i>Journal of the American Dental Association (JADA)</i> , 141, 836-844.	No	Occurrence of paresthesia
49.	GAZAL, G., BOWMAN, R., WORTHINGTON, H. V. & MACKIE, I. C. A double-blind randomized controlled trial investigating the effectiveness of topical bupivacaine in reducing distress in children following extractions under general anaesthesia. <i>International Journal of Paediatric Dentistry</i> , 14, 425-31.	No	Treatment under GA
50.	GEENEN, L., MARKS, L. A. M. & MARTENS, L. C. [Clinical evaluation of the INJEX system, a local anesthesia system without needles: a comfort evaluation study]. <i>Revue Belge de Medecine Dentaire</i> , 59, 149-55.	No	evaluation of the INJEX system
51.	GIBSON, R. S., ALLEN, K., HUTFLESS, S. & BEIRAGHI, S. The Wand vs. traditional injection: a comparison of pain related behaviors. <i>Pediatric Dentistry</i> , 22, 458-62.	No	Wand vs. traditional injection
52.	GOKLI, M. A., WOOD, A. J., MOURINO, A. P., FARRINGTON, F. H. & BEST, A. M. Hypnosis as an adjunct to the administration of local anesthetic	No	Hypnosis

	in pediatric patients. <i>Journal of Dentistry for Children</i> , 61, 272-5.		
53.	GREENGRASS, S. R., ANDRZEJOWSKI, J. & RUIZ, K. Topical bupivacaine for pain control following simple dental extractions. <i>British Dental Journal</i> , 184, 354-5.	No	Topical anaesthesia
54.	GREGORIO, L. V., GIGLIO, F. P., SAKAI, V. T., MODENA, K. C., COLOMBINI, B. L., CALVO, A. M., SIPERT, C. R., DIONÍSIO, T. J., LAURIS, J. R., FARIA, F. A., TRINDADE JUNIOR, A. S. & SANTOS, C. F. 2008. A comparison of the clinical anesthetic efficacy of 4% articaine and 0.5% bupivacaine (both with 1:200,000 epinephrine) for lower third molar removal. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 106, 19-28.	No	Adult Comparing with bupivacaine
55.	GROSSMANN, M., SATTLER, G., PISTNER, H., OERTEL, R., RICHTER, K., SCHINZEL, S. & JACOBS, L. 2004. Pharmacokinetics of articaine hydrochloride in tumescent local anesthesia for liposuction. <i>Journal of Clinical Pharmacology</i> , 44, 1282-1289.	No	Pharmacokinetics of articaine
56.	GUELMANN, M., BRACKETT, R., BEAVERS, N. & PRIMOSCH, R. E. Effect of continuous versus interrupted administration of nitrous oxide-oxygen inhalation on behavior of anxious pediatric dental patients: a pilot study. <i>Journal of Clinical Pediatric Dentistry</i> , 37, 77-82.	No	Sedation
57.	HERSH, E. V., GIANNAKOPOULOS, H., LEVIN, L. M., SECRETO, S., MOORE, P. A., PETERSON, C., HUTCHESON, M., BOUHAJIB, M., MOSENKIS, A. & TOWNSEND, R. R. 2006. The pharmacokinetics and cardiovascular effects of high-dose articaine with 1:100,000 and 1:200,000 epinephrine. <i>Journal of the American Dental Association (JADA)</i> , 137, 1562-1571.	No	Pharmacokinetics of articaine
58.	HERSH, E. V., HERMANN, D. G., LAMP, C. J., JOHNSON, P. D. & MACAFEE, K. A. Assessing the duration of mandibular soft tissue anesthesia. <i>Journal of the American Dental Association</i> , 126, 1531-6.	No	Assessing the duration of mandibular soft tissue anaesthesia
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	<i>Journal of the American Dental Association (JADA)</i> , 139, 1080-1093.		
60.	HUNG, P.-C., CHANG, H.-H., YANG, P.-J., KUO, Y.-S., LAN, W.-H. & LIN, C.-P. Comparison of the Gow-Gates mandibular block and inferior alveolar nerve block using a standardized protocol. <i>Journal of the Formosan Medical Association</i> , 105, 139-46.	No	Comparing dental nerve block technique
61.	JAKOBS, W., LADWIG, B., CICHON, P., ORTEL, R. & KIRCH, W. Serum levels of articaine 2% and 4% in children. <i>Anesthesia Progress</i> , 42, 113-5.	No	Serum levels of articaine
62.	JAKOBS, W., LIPP, M. & DAUBLANDER, M. [Ambulatory dental surgery in high-risk patients using a combination of nitrous oxide analgesia and local anesthesia]. <i>Deutsche Zahnärztliche Zeitschrift</i> , 41, 347-9.	No	Sedation
63.	JANJUA, O. S., LUQMAN, U., IBRAHIM, M. W. & SHAH, I. Transpapillary versus palatal injection technique for maxillary tooth extractions. <i>Jcpsp, Journal of the College of Physicians &amp; Surgeons - Pakistan</i> , 22, 143-6.	No	Injection site
64.	KANTOVITZ, K. R., PUPPIN-RONTANI, R. M. & GAVIAO, M. B. D. Sedative effect of oral diazepam and chloral hydrate in the dental treatment of children. <i>Journal of the Indian Society of Pedodontics &amp; Preventive Dentistry</i> , 25, 69-75.	No	Sedation
65.	KAVVADIA, K., KARAGIANNI, V., POLYCHRONOPOULOU, A. & PAPAGIANNOULI, L. Primary teeth caries removal using the Carisolv chemomechanical method: a clinical trial. <i>Pediatric Dentistry</i> , 26, 23-8.	No	Caries removal
66.	KILPATRICK, N. M., MURRAY, J. J. & MCCABE, J. F. A clinical comparison of a light cured glass ionomer sealant restoration with a composite sealant restoration. <i>Journal of Dentistry</i> , 24, 399-405.	No	Light cure machine
67.	KLEEMANN, P. P., JACOBS, W., BRISSE, B. & TETSCH, P. [Effect of nitrogen oxide on hemodynamic parameters and catecholamine secretion of patients during oral-dental surgery under combined nitrogen oxide anesthesia and local anesthesia]. <i>Deutsche Zeitschrift für Mund-, Kiefer-, und Gesichts-Chirurgie</i> , 8, 223-31.	No	Sedation
68.	KLEIN, U., HUNZEKER, C., HUTFLESS, S. & GALLOWAY, A. Quality of anesthesia for the	No	Local anaesthetic technique

	maxillary primary anterior segment in pediatric patients: comparison of the P-ASA nerve block using CompuMed delivery system vs traditional supraperiosteal injections. <i>Journal of Dentistry for Children (Chicago, Ill.)</i> , 72, 119-25.		
69.	KOHLER, B. R., CASTELLON, L. & LAISSLE, G. Gow-Gates technique: a pilot study for extraction procedures with clinical evaluation and review. <i>Anesthesia Progress</i> , 55, 2-8.	No	Local anaesthetic technique
70.	KOIKE, S., AMANO, Y., YARITA, M., KAKINUMA, T., SUDA, M., SAGIYA, T., SAITO, Y., NIKURA, M., KOBAYASHI, K., YAMAGUCHI, N. & ET AL. [Clinical evaluation of new toothache drug "LTA"]. <i>Josai Shika Daigaku Kiyō - Bulletin of the Josai Dental University</i> , 15, 576-87.	No	Clinical evaluation of new toothache drug
71.	KOYUTURK, A. E., AVSAR, A. & SUMER, M. Efficacy of dental practitioners in injection techniques: computerized device and traditional syringe. <i>Quintessence International</i> , 40, 73-7.	No	Local anaesthetic technique
72.	KREIDER, K. A., STRATMANN, R. G., MILANO, M., AGOSTINI, F. G. & MUNSELL, M. Reducing children's injection pain: lidocaine patches versus topical benzocaine gel. <i>Pediatric Dentistry</i> , 23, 19-23.	No	lidocaine patches versus topical benzocaine gel.
73.	KUIVALAINEN, A. M., NIEMI-MUROLA, L., WIDENIUS, T., ELONEN, E. & ROSENBERG, P. H. 2010. Comparison of articaine and lidocaine for infiltration anaesthesia in patients undergoing bone marrow aspiration and biopsy. <i>European Journal of Pain</i> , 14, 160-163.	No	Not dental topic
74.	KUSCU, O. O. & AKYUZ, S. Is it the injection device or the anxiety experienced that causes pain during dental local anaesthesia? <i>International Journal of Paediatric Dentistry</i> , 18, 139-45.	No	Injection/anxiety
75.	LAI, T.-N., LIN, C.-P., KOK, S.-H., YANG, P.-J., KUO, Y.-S., LAN, W.-H. & CHANG, H.-H. Evaluation of mandibular block using a standardized method. <i>Oral Surgery Oral Medicine Oral Pathology Oral Radiology &amp; Endodontics</i> , 102, 462-8.	No	Evaluation of mandibular block
76.	LAM, C., UDIN, R. D., MALAMED, S. F., GOOD, D. L. & FORREST, J. L. Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. <i>Anesthesia Progress</i> , 52, 56-61.	No	Sedation
77.	LAVIOLA, M., MCGAVIN, S. K., FREER, G. A., PLANCICH, G., WOODBURY, S. C.,	No	reversal of local anaesthesia

	MARINKOVICH, S., MORRISON, R., READER, A., RUTHERFORD, R. B. & YAGIELA, J. A. Randomized study of phentolamine mesylate for reversal of local anesthesia. <i>Journal of Dental Research</i> , 87, 635-9.		
78.	LEEK, M. 2011. Sub-Tenon's drug combination and volume: a systematic review. <i>Technic: The Journal of Operating Department Practice</i> , 2, 10-13.	No	Not dental topic
79.	LEI, D., JUN, L., DEQIN, Y. & YUNJI, W. 2013. The effectiveness of an additional lingual infiltration in the pulpal anesthesia of mandibular teeth: A systematic review. <i>Quintessence International</i> , 44, 457-464.	No	The effectiveness of an additional lingual infiltration
80.	LEITH, R., LYNCH, K. & O'CONNELL, A. C. 2012. Articaine use in children: a review. <i>European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry</i> , 13, 293-6.	No	Review article
81.	LEONG, K. J., ROBERTS, G. J. & ASHLEY, P. F. Perioperative local anaesthetic in young paediatric patients undergoing extractions under outpatient 'short-case' general anaesthesia. A double-blind randomised controlled trial. <i>British Dental Journal</i> , 203, E11; discussion 334-5.	No	Treatment under GA
82.	LIKAR, R., KOPPERT, W., BLATNIG, H., CHIARI, F., SITTL, R., STEIN, C. & SCHÄFER, M. 2001. Efficacy of peripheral morphine analgesia in inflamed, non-inflamed and perineural tissue of dental surgery patients. <i>Journal of Pain &amp; Symptom Management</i> , 21, 330-337.	NO	Efficacy of peripheral morphine analgesia
83.	LIM, S. & JULLIARD, K. Evaluating the efficacy of EMLA topical anesthetic in sealant placement with rubber dam. <i>Pediatric Dentistry</i> , 26, 497-500.	NO	Topical anaesthesia
84.	LOKKEN, P., BAKSTAD, O. J., FONNELOP, E., SKOGEDAL, N., HELLSTEN, K., BJERKELUND, C. E., STORHAUG, K. & OYE, I. Conscious sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. <i>Scandinavian Journal of Dental Research</i> , 102, 274-80.	No	Sedation
85.	LOUW, A. J., SARVAN, I., CHIKTE, U. M. E. & HONKALA, E. One-year evaluation of atraumatic restorative treatment and minimum intervention techniques on primary teeth. <i>SADJ</i> , 57, 366-71.	No	evaluation of a traumatic restorative treatment

86.	LOZANO-CHOURIO, M. A., ZAMBRANO, O., GONZALEZ, H. & QUERO, M. Clinical randomized controlled trial of chemomechanical caries removal (Carisolv). <i>International Journal of Paediatric Dentistry</i> , 16, 161-7.	No	Chemo-mechanical caries removal
87.	MALAMED, S. F., GAGNON, S. & LEBLANC, D. A comparison between articaine HCl and lidocaine HCl in pediatric dental patients. <i>Pediatric Dentistry</i> , 22, 307-11.	Yes	
88.	MALAMED, S. F., GAGNON, S. & LEBLANC, D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. <i>Journal of the American Dental Association</i> , 132, 177-85.	Yes	
89.	MALAMED, S. F., GAGNON, S. & LEBLANC, D. Efficacy of articaine: a new amide local anesthetic. <i>Journal of the American Dental Association</i> , 131, 635-42.	Yes	
90.	MANN, P. E., HATT, S. D., DIXON, R. A., GRIFFIN, K. D., PERKS, E. R. & THORNTON, J. A. A minimal increment methohexitone technique in conservative dentistry. A comparison with treatment under local analgesia. <i>Anaesthesia</i> , 26, 3-21.	No	Sedation
91.	MCWILLIAMS, P. A. & RUTHERFORD, J. S. Assessment of early postoperative pain and haemorrhage in young children undergoing dental extractions under general anaesthesia. <i>International Journal of Paediatric Dentistry</i> , 17, 352-7.	No	Treatment under GA
92.	MEECHAN, J. G. & DONALDSON, D. The intraoral use of EMLA cream in children: a clinical investigation. <i>Journal of Dentistry for Children</i> , 61, 260-2.	No	Topical anaesthesia
93.	MEECHAN, J. G., COLE, B. & WELBURY, R. R. The influence of two different dental local anaesthetic solutions on the haemodynamic responses of children undergoing restorative dentistry: a randomised, single-blind, split-mouth study. <i>British Dental Journal</i> , 190, 502-4.	No	haemodynamic responses of children undergoing restorative dentistry
94.	MIKESELL P, NUSSTEIN J, READER A, BECK M, WEAVER J. A comparison of articaine and lidocaine for inferior alveolar nerve blocks. <i>J Endod</i> 2005; 31:265-270.	No	Adults
95.	MOORE, P. A., BOYNES, S. G., HERSH, E. V., DEROSI, S. S., SOLLECITO, T. P., GOODSON, J. M., LEONEL, J. S., FLOROS, C., PETERSON, C. & HUTCHESON, M. 2006. The anesthetic efficacy	Yes	

	of 4 percent articaine 1:200,000 epinephrine: two controlled clinical trials. <i>Journal of the American Dental Association (JADA)</i> , 137, 1572.		
96.	MOORE, P. A., MICKEY, E. A., HARGREAVES, J. A. & NEEDLEMAN, H. L. Sedation in pediatric dentistry: a practical assessment procedure. <i>Journal of the American Dental Association</i> , 109, 564-9.	No	Sedation
97.	NADANOVSKY, P., COHEN CARNEIRO, F. & SOUZA DE MELLO, F. Removal of caries using only hand instruments: a comparison of mechanical and chemo-mechanical methods. <i>Caries Research</i> , 35, 384-9.	No	comparison of mechanical and chemo-mechanical methods of caries removal
98.	NAIDU, S., LOUGHLIN, P., COLDWELL, S. E., NOONAN, C. J. & MILGROM, P. A randomized controlled trial comparing mandibular local anesthesia techniques in children receiving nitrous oxide-oxygen sedation. <i>Anesthesia Progress</i> , 51, 19-23.	No	sedation
99.	NAYAK, R. & SUDHA, P. Evaluation of three topical anaesthetic agents against pain: a clinical study. <i>Indian Journal of Dental Research</i> , 17, 155-60.	No	Topical anaesthesia
100.	ODABAS, M. E., CINAR, C., DEVECI, C. & ALACAM, A. Comparison of the anesthetic efficacy of articaine and mepivacaine in pediatric patients: a randomized, double-blind study. <i>Pediatric Dentistry</i> , 34, 42-5.	Yes	
101.	OULIS, C. J., VADIAKAS, G. P. & VASILOPOULOU, A. The effectiveness of mandibular infiltration compared to mandibular block anesthesia in treating primary molars in children. <i>Pediatric Dentistry</i> , 18, 301-5.	No	mandibular infiltration compared to mandibular block anaesthesia
102.	OZEÇ, I., TASDEMİR, U., GÜMÜS, C. & SOLAK, O. 2010. Is it possible to anesthetize palatal tissues with buccal 4% articaine injection? <i>Journal of Oral &amp; Maxillofacial Surgery (02782391)</i> , 68, 1032-1037.	No	anesthetize palatal tissues with buccal 4% articaine
103.	OZTAS, N., OLMEZ, A. & YEL, B. Clinical evaluation of transcutaneous electronic nerve stimulation for pain control during tooth preparation. <i>Quintessence International</i> , 28, 603-8.	No	Evaluation of transcutaneous electronic nerve stimulation
104.	OZTAS, N., ULUSU, T., BODUR, H. & DOGAN, C. The wand in pulp therapy: an alternative to inferior alveolar nerve block. <i>Quintessence International</i> , 36, 559-64.	No	The wand

105.	PALM, A. M., KIRKEGAARD, U. & POULSEN, S. The wand versus traditional injection for mandibular nerve block in children and adolescents: perceived pain and time of onset. <i>Pediatric Dentistry</i> , 26, 481-4.	No	The wand versus traditional injection
106.	PANDEY, R. K., PADMANABHAN, M. Y., SAKSENA, A. K. & CHANDRA, G. Midazolam-fentanyl analgo-sedation in pediatric dental patients-a pilot study. <i>Journal of Clinical Pediatric Dentistry</i> , 35, 105-10.	No	Sedation
107.	PASCHOS, E., HUTH, K. C., BENZ, C., REEKABARDSCHMIDT, A. & HICKEL, R. Efficacy of intraoral topical anesthetics in children. <i>Journal of Dentistry</i> , 34, 398-404.	No	topical anaesthetics
108.	PAXTON, K. & THOME, D. E. 2010. Efficacy of articaine formulations: quantitative reviews. <i>Dental Clinics of North America</i> , 54, 643-653.	No	quantitative reviews.
109.	PAXTON, K. 2008. <i>Anesthetic efficacy of articaine hydrochloride versus lidocaine hydrochloride: A meta-analysis</i> . MS (Master of Science)	No	meta-analysis
110.	PENARROCHA-OLTRA, D., ATA-ALI, J., OLTRAMOSCARDO, M. J., PENARROCHA-DIAGO, M. A. & PENARROCHA, M. Comparative study between manual injection intraosseous anesthesia and conventional oral anesthesia. <i>Medicina Oral, Patología Oral y Cirugía Bucal</i> , 17, e233-5.	No	Comparative between manual injection and conventional
111.	PERETZ, B. & GLUCK, G. M. Assessing an active distracting technique for local anesthetic injection in pediatric dental patients: repeated deep breathing and blowing out air. <i>Journal of Clinical Pediatric Dentistry</i> , 24, 5-8.	No	Assessing an active distracting technique
112.	PERIC, T., MARKOVIC, D. & PETROVIC, B. Clinical evaluation of a chemomechanical method for caries removal in children and adolescents. <i>Acta Odontologica Scandinavica</i> , 67, 277-83.	No	chemomechanical method for caries removal
113.	PIOT, B., SIGAUD-FIKS, M., HUET, P., FRESSINAUD, E., TROSSAERT, M. & MERCIER, J. [Dental extraction in patients with bleeding disorders. Proposal of a protocol based on the type of anesthesia used]. <i>Revue de Stomatologie et de Chirurgie Maxillo-Faciale</i> , 104, 73-6.	No	Patients with bleeding disorders.
114.	PRIMOSCH, R. E. & ROLLAND-ASENSI, G. Comparison of topical EMLA 5% oral adhesive to benzocaine 20% on the pain experienced during palatal anesthetic infiltration in children. <i>Pediatric Dentistry</i> , 23, 11-4.	No	Topical anaesthesia

115.	RAM, D. & AMIR, E. Comparison of articaine 4% and lidocaine 2% in paediatric dental patients. <i>International Journal of Paediatric Dentistry</i> , 16, 252-6.	Yes	
116.	RAM, D. & KASSIRER, J. Assessment of a palatal approach-anterior superior alveolar (P-ASA) nerve block with the Wand in paediatric dental patients. <i>International Journal of Paediatric Dentistry</i> , 16, 348-51.	No	Assessment of a palatal approach-anterior superior alveolar
117.	RAM, D. & PERETZ, B. Reactions of children to maxillary infiltration and mandibular block injections. <i>Pediatric Dentistry</i> , 23, 343-6.	No	Children reaction to LA
118.	RAM, D. & PERETZ, B. The assessment of pain sensation during local anesthesia using a computerized local anesthesia (Wand) and a conventional syringe. <i>Journal of Dentistry for Children (Chicago, Ill.)</i> , 70, 130-3.	No	Wand
119.	RAM, D., AMIR, E., KEREN, R., SHAPIRA, J. & DAVIDOVICH, E. Mandibular block or maxillary infiltration: does it influence children's opposition to a subsequent dental visit? <i>Journal of Clinical Pediatric Dentistry</i> , 36, 245-9.	No	Mandibular block or maxillary infiltration
120.	RAM, D., BERSON, T., MOSKOVITZ, M. & EFRAT, J. Unsweetened ice popsicles impart a positive feeling and reduce self-mutilation after paediatric dental treatment with local anaesthesia. <i>International Journal of Paediatric Dentistry</i> , 20, 382-8.	No	popsicles , Post-operative
121.	RAM, D., EFRAT, J., MICHOVITZ, N. & MOSKOVITZ, M. The use of popsicles after dental treatment with local anesthesia in pediatric patients. <i>Journal of Clinical Pediatric Dentistry</i> , 31, 41-3.	No	popsicles , Post-operative
122.	RAM, D., HERMIDA B, L. & AMIR, E. Reaction of children to dental injection with 27- or 30-gauge needles. <i>International Journal of Paediatric Dentistry</i> , 17, 383-7.	No	Reaction of children to dental injection
123.	RAM, D., HERMIDA, L. B. & PERETZ, B. A comparison of warmed and room-temperature anesthetic for local anesthesia in children. <i>Pediatric Dentistry</i> , 24, 333-6.	No	warmed and room-temperature anaesthetic
124.	RAN, D. & PERETZ, B. Assessing the pain reaction of children receiving periodontal ligament anesthesia using a computerized device (Wand). <i>Journal of Clinical Pediatric Dentistry</i> , 27, 247-50.	No	the pain reaction of children receiving periodontal

			ligament anaesthesia
125.	RASHAD, A. & EL-ATTAR, A. Cardiac dysrhythmias during oral surgery: effect of combined local and general anaesthesia. <i>British Journal of Oral &amp; Maxillofacial Surgery</i> , 28, 102-4.	No	Cardiac dysrhythmias during oral surgery
126.	RASHAD, A. & EL-ATTAR, A. Dysrhythmias during oral surgery--effect of combined local and general anesthesia. <i>Middle East Journal of Anesthesiology</i> , 10, 499-505.	No	Dysrhythmias during oral surgery
127.	RASPALL, G., SALAVERT, A., ESCARTIN, J. & GAY, C. [Clinical trial in maxillo-facial surgery with HOE 40 045/Articain]. <i>Revista Espanola de Estomatologia</i> , 29, 167-70.	No	maxillo-facial surgery with HOE 40 045/Articain
128.	REZNIK, D. S., JESKE, A. H., CHEN, J.-W. & ENGLISH, J. Comparative efficacy of 2 topical anesthetics for the placement of orthodontic temporary anchorage devices. <i>Anesthesia Progress</i> , 56, 81-5.	No	Topical anaesthesia
129.	ROBBINS, M. B. Chloral hydrate and promethazine as premedicants for the apprehensive child. <i>Journal of Dentistry for Children</i> , 34, 327-31.	No	Sedation
130.	ROBERTSON, D., NUSSTEIN, J., READER, A., BECK, M. & MCCARTNEY, M. 2007. The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth. <i>Journal of the American Dental Association (JADA)</i> , 138, 1104-1112.	Yes	
131.	ROEBER, B., WALLACE, D. P., ROTHE, V., SALAMA, F. & ALLEN, K. D. Evaluation of the effects of the VibraJect attachment on pain in children receiving local anesthesia. <i>Pediatric Dentistry</i> , 33, 46-50.	No	Evaluation of the effects of the VibraJect attachment
132.	ROELOFSE, J. A., JOUBERT, J. J. & ROELOFSE, P. G. A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of pediatric dental patients. <i>Journal of Oral &amp; Maxillofacial Surgery</i> , 54, 838-44; discussion 845-6.	No	Sedation
133.	ROELOFSE, J. A., JOUBERT, J. J., SWART, L. C., STANDER, I. & ROELOFSE, P. G. An evaluation of the effect of oral ketamine and standard oral premedication in the sedation of paediatric dental	No	Sedation

	patients. <i>Journal of the Dental Association of South Africa</i> , 51, 197-201.		
134.	ROELOFSE, J. A., LOUW, L. R. & ROELOFSE, P. G. A double blind randomized comparison of oral trimeprazine-methadone and ketamine-midazolam for sedation of pediatric dental patients for oral surgical procedures. <i>Anesthesia Progress</i> , 45, 3-11.	No	Sedation
135.	ROHLFING, G. K., DILLEY, D. C., LUCAS, W. J. & VANN, W. F., JR. The effect of supplemental oxygen on apnea and oxygen saturation during pediatric conscious sedation. <i>Pediatric Dentistry</i> , 20, 8-16.	No	Sedation
136.	SALOMON, E., MAZZOLENI, S., SIVOLELLA, S., COCILOVO, F., GREGORI, D., GIUCA, M. R. & FERRO, R. Age limit for infiltration anaesthesia for the conservative treatment of mandibular first molars. A clinical study on a paediatric population. <i>European Journal of Paediatric Dentistry</i> , 13, 259-62.	No	Age limit for infiltration anaesthesia
137.	SAMMONS, H. M., UNSWORTH, V., GRAY, C., CHOONARA, I., CHERRILL, J. & QUIRKE, W. Randomized controlled trial of the intraligamental use of a local anaesthetic (lignocaine 2%) versus controls in paediatric tooth extraction. <i>International Journal of Paediatric Dentistry</i> , 17, 297-303.	Yes	
138.	SAN MARTIN-LOPEZ, A. L., GARRIGOS-ESPARZA, L. D., TORRE-DELGADILLO, G., GORDILLO-MOSCOSO, A., HERNANDEZ-SIERRA, J. F. & DE POZOS-GUILLEN, A. J. Clinical comparison of pain perception rates between computerized local anesthesia and conventional syringe in pediatric patients. <i>Journal of Clinical Pediatric Dentistry</i> , 29, 239-43.	No	Pain perception in LA techniques
139.	SANTOS, C. F., MODENA, K. C., GIGLIO, F. P., SAKAI, V. T., CALVO, A. M., COLOMBINI, B. L., SIPERT, C. R., DIONÍSIO, T. J., FARIA, F. A., TRINDADE, A. S., JR. & LAURIS, J. R. 2007. Epinephrine concentration (1:100,000 or 1:200,000) does not affect the clinical efficacy of 4% articaine for lower third molar removal: a double-blind, randomized, crossover study. <i>Journal of Oral &amp; Maxillofacial Surgery (02782391)</i> , 65, 2445-2452.	No	articaine for lower third molar removal
140.	SCHOTTKE, C., MEHNERT, J. & DRAUSCHKE, M. [The use of Ornipressin in dental local anesthesia]. <i>Stomatologie der DDR</i> , 28, 644-8.	No	of Ornipressin in dental local anaesthesia

141.	SENER, M., PEKTAS, Z. O., YILMAZ, I., TURKOZ, A., UCKAN, S., DONMEZ, A. & ARSLAN, G. 2005. Comparison of preemptive analgesic effects of a single dose of nonopioid analgesics for pain management after ambulatory surgery: a prospective, randomized, single-blind study in Turkish patients. <i>Current Therapeutic Research</i> , 66, 541-551.	No	Comparison of pre-emptive analgesic effects
142.	SEWARD, M. H. The effectiveness of a teething solution in infants. A clinical study. <i>British Dental Journal</i> , 127, 457-61.	No	teething solution in infants
143.	SIXOU, J. L. & BARBOSA-ROGIER, M. E. 2008. Efficacy of intraosseous injections of anesthetic in children and adolescents. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 106, 173-178.	No	intraosseous injections of anaesthetic in children
144.	SIXOU, J.-L., MARIE-COUSIN, A., HUET, A., HINGANT, B. & ROBERT, J.-C. Pain assessment by children and adolescents during intraosseous anaesthesia using a computerized system (QuickSleeper). <i>International Journal of Paediatric Dentistry</i> , 19, 360-6.	No	intraosseous injections of anaesthetic in children
145.	SPIELMANN, T., WIESLANDER, L. & HEFTI, A. F. [Acceleration of orthodontically induced tooth movement through the local application of prostaglandin (PGE1)]. <i>Schweizer Monatsschrift fur Zahnmedizin</i> , 99, 162-5.	No	Orthodontics
146.	SRINIVASAN, N., KAVITHA, M., LOGANATHAN, C. S. & PADMINI, G. 2009. Comparison of anesthetic efficacy of 4% articaine and 2% lidocaine for maxillary buccal infiltration in patients with irreversible pulpitis. <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 107, 133-136.	No	Adult
147.	STECKER, S. S., SWIFT, J. Q., HODGES, J. S. & ERICKSON, P. R. Should a mucoadhesive patch (DentiPatch) be used for gingival anesthesia in children? <i>Anesthesia Progress</i> , 49, 3-8.	No	mucoadhesive patch (in children)
148.	SULLIVAN, D. C., WILSON, C. F. & WEBB, M. D. A comparison of two oral ketamine-diazepam regimens for the sedation of anxious pediatric dental patients. <i>Pediatric Dentistry</i> , 23, 223-31.	No	Sedation
149.	TAHMASSEBI, J. F., NIKOLAOU, M. & DUGGAL, M. S. A comparison of pain and anxiety associated with the administration of maxillary local analgesia with Wand and conventional technique. <i>European</i>	No	A comparison of pain and anxiety

	<i>Archives of Paediatric Dentistry: Official Journal of the European Academy of Paediatric Dentistry</i> , 10, 77-82.		
150.	TAVARES, M., GOODSON, J. M., STUDEN-PAVLOVICH, D., YAGIELA, J. A., NAVALTA, L. A., ROGY, S., RUTHERFORD, B., GORDON, S. & PAPAS, A. S. 2008. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. <i>Journal of the American Dental Association (JADA)</i> , 139, 1095-1104.	No	Reversal of soft-tissue local anaesthesia
151.	TEDUITS, E., GOEPFERD, S., DONLY, K., PINKHAM, J. & JAKOBSEN, J. The effectiveness of electronic dental anesthesia in children. <i>Pediatric Dentistry</i> , 15, 191-6.	No	The effectiveness of electronic dental anesthesia
152.	TEIXEIRA, L. S., DEMARCO, F. F., COPPOLA, M. C. & BONOW, M. L. Clinical and radiographic evaluation of pulpotomies performed under intrapulpal injection of anaesthetic solution. <i>International Endodontic Journal</i> , 34, 440-6.	No	Pulpotomy
153.	TOWNSEND, J. A., GANZBERG, S. & THIKKURISSY, S. The effect of local anesthetic on quality of recovery characteristics following dental rehabilitation under general anesthesia in children. <i>Anesthesia Progress</i> , 56, 115-22.	No	GA
154.	TYAGI, P., DIXIT, U., TYAGI, S. & JAIN, A. Sedative effects of oral midazolam, intravenous midazolam and oral diazepam. <i>Journal of Clinical Pediatric Dentistry</i> , 36, 383-8.	No	Sedation
155.	UCKAN, S., DAYANGAC, E. & ARAZ, K. 2006. Is permanent maxillary tooth removal without palatal injection possible? <i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology &amp; Endodontology</i> , 102, 733-735.	No	permanent maxillary tooth removal
156.	VAN BOCHOVE, J. A. & VAN AMERONGEN, W. E. The influence of restorative treatment approaches and the use of local analgesia, on the children's discomfort. <i>European Archives of Paediatric Dentistry: Official Journal of the European Academy of Paediatric Dentistry</i> , 7, 11-6.	No	influence of restorative treatment approaches and the use of local analgesia
157.	VAN DE HOEF, N. & VAN AMERONGEN, E. Influence of local anaesthesia on the quality of class II glass ionomer restorations. <i>International Journal of Paediatric Dentistry</i> , 17, 239-47.	No	Influence of local anaesthesia

158.	VASMANOVA, E. V. & AZREL'IAN, B. A. [Use of the Soviet BI-8 jet injector for local anesthesia in pediatric stomatology]. <i>Stomatologija</i> , 58, 29-33.	No	Use of the Soviet BI-8 jet
159.	VEERKAMP, J. S., VAN AMERONGEN, W. E., HOOGSTRATEN, J. & GROEN, H. J. Dental treatment of fearful children, using nitrous oxide. Part I: Treatment times. <i>Journal of Dentistry for Children</i> , 58, 453-7.	No	Dental treatment of fearful children
160.	VERSLOOT, J., VEERKAMP, J. S. J. & HOOGSTRATEN, J. Computerized anesthesia delivery system vs. traditional syringe: comparing pain and pain-related behavior in children. <i>European Journal of Oral Sciences</i> , 113, 488-93.	No	Computerized anesthesia delivery system vs. traditional syringe
161.	VERSLOOT, J., VEERKAMP, J. S. J. & HOOGSTRATEN, J. Pain behaviour and distress in children during two sequential dental visits: comparing a computerised anaesthesia delivery system and a traditional syringe. <i>British Dental Journal</i> , 205, E2; discussion 30-1.	No	Pain behaviour and distress
162.	WAHL, M. J., SCHMITT, M. M. & OVERTON, D. A. 2006. Injection pain of prilocaine plain, mepivacaine plain, articaine with epinephrine, and lidocaine with epinephrine. <i>General Dentistry</i> , 54, 168-171.	Yes ????	
163.	WAIKAKUL, A. & PUNWUTIKORN, J. A comparative study of the extra-intraoral landmark technique and the direct technique for inferior alveolar nerve block. <i>Journal of Oral &amp; Maxillofacial Surgery</i> , 49, 804-8; discussion 808-9.	No	IDNB
164.	WATTS, A. K., THIKKURISSY, S., SMILEY, M., MCTIGUE, D. J. & SMITH, T. Local anesthesia affects physiologic parameters and reduces anesthesiologist intervention in children undergoing general anesthesia for dental rehabilitation. <i>Pediatric Dentistry</i> , 31, 414-9.	NO	GA
165.	WILSON, K. E., GIRDLER, N. M. & WELBURY, R. R. A comparison of oral midazolam and nitrous oxide sedation for dental extractions in children. <i>Anaesthesia</i> , 61, 1138-44.	No	Sedation
166.	WILSON, S., MOLINA, L. D. L., PREISCH, J. & WEAVER, J. The effect of electronic dental anesthesia on behavior during local anesthetic injection in the young, sedated dental patient. <i>Pediatric Dentistry</i> , 21, 12-7.	No	The effect of electronic dental anaesthesia

167.	WILSON, T. G., PRIMOSCH, R. E., MELAMED, B. & COURTS, F. J. Clinical effectiveness of 1 and 2% lidocaine in young pediatric dental patients. <i>Pediatric Dentistry</i> , 12, 353-9.	No	Clinical effectiveness of 1 and 2% lidocaine
168.	WOLF, A. R., STODDART, P. A., MURPHY, P. J. & SASADA, M. Rapid skin anaesthesia using high velocity lignocaine particles: a prospective placebo controlled trial. <i>Archives of Disease in Childhood</i> , 86, 309-12.	No	Rapid skin anaesthesia
169.	WOOD, M. The safety and efficacy of using a concentrated intranasal midazolam formulation for paediatric dental sedation. <i>SAAD Digest</i> , 27, 16-23.	No	Sedation
170.	WRIGHT GZ, WEINBERGER SJ, FRIEDMAN CS, PLOTZKE OB. The use of articaine local anesthesia in children under 4 years of age: a retrospective report. <i>Anaesth Prog</i> 1989; 36:268-271.	No	Report
171.	WU, S. J. & JULLIARD, K. Children's preference of benzocaine gel versus the lidocaine patch. <i>Pediatric Dentistry</i> , 25, 401-5.	No	Topical
172.	WU, Y., SHI, Z. & SHI, J. Randomized controlled trial study for preventing dental fear during caries treatments. <i>Chung-Hua Kou Chiang i Hsueh Tsa Chih Chinese Journal of Stomatology</i> , 37, 343-5.	No	dental fear during caries treatments
173.	YASSEN, G. H. Evaluation of mandibular infiltration versus mandibular block anaesthesia in treating primary canines in children. <i>International Journal of Paediatric Dentistry</i> , 20, 43-9.	Yes	
174.	YILMAZ, Y., EYUBOGLU, O. & KELES, S. Comparison of the efficacy of articaine and prilocaine local anaesthesia for pulpotomy of maxillary and mandibular primary molars. <i>European Journal of Paediatric Dentistry</i> , 12, 117-22.	Yes	
175.	YOON, R. K. & CHUSSID, S. Topical anesthesia for rubber dam clamp placement in sealant placement: comparison of lidocaine/prilocaine gel and benzocaine. <i>Pediatric Dentistry</i> , 31, 377-81	No	Topical anaesthesia

NHS REC Form

Reference:  
13/YH/0049

IRAS Version 3.4

**Integrated Research Application System**  
**Application Form for Clinical trial of an investigational medicinal product**

  
**National Patient Safety Agency**  
National Research Ethics Service

**Application to NHS/HSC Research Ethics Committee**

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

**Short title and version number:** (maximum 70 characters - this will be inserted as header on all forms)  
Use of Articane in Children's Dentistry

*Please complete these details after you have booked the REC application for review.*

**REC Name:**  
NRES Committee Yorkshire & The Humber - Leeds East

**REC Reference Number:**  
13/YH/0049

**Submission date:**  
29/01/2013

**PART A: Core study information****1. ADMINISTRATIVE DETAILS****A1. Full title of the research:**

Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars.

**A2-1. Educational projects**

Name and contact details of student(s):

**Student 1**

	Title	Forename/Initials	Surname
	DR	FATMA SA	ALZAHIRANI
Address	LEEDS DENTAL INSTITUTE UNIVERSITY OF LEEDS		
Post Code	LS2 9LU		
E-mail	ML09FSA@LEEDS.AC.UK		
Telephone	07760841101		

NHS REC Form

Reference:  
13/YH/0049

IRAS Version 3.4

Fax 01133436165

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:  
INTEGRATED PhD - CHILD DENTAL HEALTHName of educational establishment:  
LEEDS DENTAL INSTITUTE

Name and contact details of academic supervisor(s):

**Academic supervisor 1**

	Title	Forename/Initials	Surname
	PROF.	MONTY S	DUGGAL
Address	LEEDS DENTAL INSTITUTE UNIVERSITY OF LEEDS		
Post Code	LS2 9LU		
E-mail	M.S.DUGGAL@LEEDS.AC.UK		
Telephone	01133436177		
Fax	01133436140		

**Academic supervisor 2**

	Title	Forename/Initials	Surname
	DR	JINOUS	TAHAMASSEBI
Address	LEEDS DENTAL INSTITUTE UNIVERSITY OF LEEDS		
Post Code	LS2 9LU		
E-mail	J.TAHMASSEBI@LEEDS.AC.UK		
Telephone			
Fax	01133436140		

Please state which academic supervisor(s) has responsibility for which student(s):

*Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.***Student(s)****Student 1** DR FATMA SA  
ALZHRANI**Academic supervisor(s)**

- 
- PROF. MONTY S DUGGAL
- 
- 
- DR JINOUS TAHAMASSEBI

*A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.***A2-2. Who will act as Chief Investigator for this study?**

- Student
- Academic supervisor
- Other

NHS REC Form

Reference:  
13/YH/0049

IRAS Version 3.4

**A3-2. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)**

- National coordinating investigator  
 Principal investigator

Given name                    FATMA S A  
 Family name                 ALZHRANI  
 Qualification  
 (MD...)                      BDS Dental surgery, king Saud University, KSA.  
 Institution name  
 Institution department name  
 Street address               LEEDS DENTAL INSTITUTE  
 Town/city                    UNIVERSITY OF LEEDS  
 Post Code                    LS2 9LU  
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 \* Personal E-mail         ML09FSA@LEEDS.AC.UK  
 Work Telephone             07760841101  
 \* Personal  
 Telephone/Mobile  
 Fax                            01133436165

*\* This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.  
 A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.*

**A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?**

*This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.*

	Title	Forename/Initials	Surname
	MRS	CLARE E.	SKINNER
Address	Worsly bulding Level 10 university of leeds		
Post Code	LS2 9LU		
E-mail	neville.young@leedsth.nhs.uk		
Telephone	0113-343-4897		
Fax	0113 392 6397		

**A5-1. Research reference numbers. Please give any relevant references for your study:**

Applicant's/organisation's own reference number, e.g. R & D (if available):  
 Sponsor's/protocol number: DT11/9936  
 Protocol Version: 04  
 Protocol Date: 17/12/2012  
 Funder's reference number:  
 Project website:



**Health Research Authority**  
**NRES Committee Yorkshire & The Humber - Leeds East**

Yorkshire and Humber REC Office  
 First Floor, Millside  
 Mill Pond Lane  
 Meanwood  
 Leeds  
 LS6 4RA

Telephone: 0191 428 3564  
 Facsimile: 0191 428 3432

12 March 2013

Professor Monty Duggal  
 Leeds Dental Institute  
 Paediatric Dentistry, Worsley Building  
 Level 6, Clarendon Way  
 Leeds  
 LS2 6LU

Dear Professor Duggal

**Study Title:** Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars

**REC reference:** 13/YH/0049  
**Protocol number:** DT11/9936  
**EudraCT number:** 2011-004711-23  
**IRAS project ID:** 82161

The Research Ethics Committee reviewed the above application at the meeting held on 05 March 2013. Thank you for attending to discuss the application.

**Documents reviewed**

The documents reviewed at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/Consultant Information Sheets	4.0	17 December 2012
Investigator CV	M Duggal	27 November 2012
Letter from Sponsor		14 January 2013
Letter from Statistician		
Other: Letter of invitation to parent	4.0	17 December 2012
Other: Case Record form	02	10 October 2012
Other: Story book		
Other: CV: JF Tahmassebi		29 November 2012

Other: CV: F Alzahrani		
Other: Summary of Product Characteristics: Lignospan Special		01 July 2007
Other: Summary of Product Characteristics: Septanest etc		07 June 2012
Participant Consent Form: Parent	4.0	17 December 2012
Participant Consent Form: 7-9 years	4.0	17 December 2012
Participant Information Sheet: for parents	4.0	17 December 2012
Participant Information Sheet: Child information letter	4.0	17 December 2012
Protocol	4.0	17 December 2012
REC application		29 January 2013
Referees or other scientific critique report		

### Provisional opinion

In discussion, the Committee noted the following ethical issues:

The Committee felt that the questionnaire, which aimed to assess attitudes and experiences, would provide more information about behaviour only, rather than the child or parents' attitudes and/or feelings.

The Committee questioned why non-English speakers were not being recruited into the study, as it was felt that these patients would have translation services provided, either by the NHS or through friends or family.

It was noted that the Participant Information Sheet for Children referred to children aged 'four and over' but the document for Parents to 'ages 5-9' – clarification of this was therefore requested.

Members felt that the 'storyboard' for Children was inappropriate and should not be used, as the drawings were slightly 'scary' at times. It was felt that the Participant Information Sheet for Parents implied that the new technique was a better method, and it was felt that this should be re-written with more equipoise.

Members felt that section 11 of the Participant Information Sheet for Parents ('What are the side effects of any treatment received when taking part?') had not been answered appropriately, and should contain more information about the potential side effects.

Ethical issues raised by the Committee in private discussion, together with responses given by the researcher when invited into the meeting.

The Chair, Dr Carol Chu, welcomed you, Dr Jinous Tahamassebi and Dr Fatma Alzahrani to the meeting and thanked them for attending.

The Committee expressed concern that if the newer treatment was attempted with the child and was unsuccessful, it would 'put the child off' and prevent any form of treatment taking place under any method of anaesthetic.

*Dr Alzahrani replied that the infiltration technique was used routinely, and that this randomised controlled trial had been developed simply to prove that it is effective, in order to provide some evidence-based results. You added that there was currently no evidence in the literature on the use of this technique in children although in practice it appeared to be effective. Dr Tahamassebi added that they would be able to give the child extra local anaesthetic. Members*

questioned whether there was evidence available in the literature regarding this technique in adults.

*You replied that the evidence is available but it is not clear-cut, and that there was no data available from randomised controlled trials, although you have the impression that it is effective.*

Clarification was requested that the child could receive extra local anaesthetic if the intended method did not work and the alternative method had to be considered.

*You confirmed that this would be the case, although the particular patient would be removed from the study.*

*Dr Alzahrani added that you would be contacting the parents by telephone after 24 hours to assess for any potential adverse events; although this information is in the Protocol, they had forgotten to add it to the Participant Information Sheet.*

*The researchers left the room.*

The Committee discussed the responses.

It was noted that the study required children aged 7 years and over would be asked to give assent, however it was felt that this could be extended to all children in the study, and so these forms would need to be amended.

Members noted that the Participant Information Sheets required proof reading to remove typographical and grammatical errors.

### **Decision**

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair and Mr Tom Wilson

### **Further information or clarification required**

1. Clarification of why non-English speakers are not being recruited into the study, as it was felt that these patients will have translation services provided
2. Changes to the Participant Information Sheet(s):
  - a) Proof-reading to remove typographical and grammatical errors
  - b) Amendment of the Participant Information Sheet for Children to be appropriate for this age group, potentially seeking advice from a similar group of patients
  - c) Amendment of the Participant Information Sheet for Children to refer to children aged '5 to 9'
  - d) Amendment of the Participant Information Sheet for Parents to be re-written with more equipoise

- e) Section 11 of the Participant Information Sheet for Parents amendment to contain more information about the potential side effects
  - f) Information added regarding the contact by telephone after 24 hours to assess for any potential adverse events
3. Changes to the Consent/Assent Form(s):
- a) The Assent Form amended to relate to all children in the study (5 years and above)

**The Committee delegated any queries once the decision letter has been received to the Coordinator, or to the Chair, if the Coordinator was unable to help**

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 11 April 2013.

#### **Membership of the Committee**

The members of the Committee who were present at the meeting are listed on the attached sheet.

#### **Statement of compliance**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**13/YH/0049**

**Please quote this number on all correspondence**

Yours sincerely



(pp)

**Dr C E Chu**  
**Chair**

Email: [nrescommittee.yorkandhumber-leedseast@nhs.net](mailto:nrescommittee.yorkandhumber-leedseast@nhs.net)

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.*

*Copy to: R&D Office, Leeds Teaching Hospitals NHS Trust*

*Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust*

**NRES Committee Yorkshire & The Humber - Leeds East**  
**Attendance at Committee meeting on 05 March 2013**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>
Mrs Victoria Ajayi	Assistant Contracts Manager	Yes
Mrs Alison Barraclough	Clinical Studies Officer	Yes
Professor Kenneth Brodlie	Retired Professor of Visualization	No
Dr C E Chu	Chair	Yes
Professor Alan Ebbutt	Statistician	Yes
Dr Deborah Jane Fox	Senior Lecturer in Nursing	Yes
Ms Emily Griffiths	Performance & Development Manager	Yes
Dr Stuart Jamieson	Consultant Neurologist	No
Professor Rob Newell	Professor of Nursing Research and Director of Postgraduate Research	Yes
Mr Roly Squire	Consultant Paediatric Surgeon	Yes
Mr Tom Wilson	Consultant ENT Surgeon	Yes
Miss Kate Woodrow	Pharmacist	No

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Laura Kirkbride	Committee Coordinator



**Health Research Authority**  
**NRES Committee Yorkshire & The Humber - Leeds East**

North East REC Centre  
 Room 002  
 TEDCO Business Centre  
 Viking Industrial Park  
 Rolling Mill Road  
 Jarrow  
 NE32 3DT

Telephone: 0191 4283545

18 April 2013

Professor Monty Duggal  
 Leeds Dental Institute  
 Paediatric Dentistry, Worsley Building,  
 Level 6, Clarendon Way  
 Leeds  
 LS2 6LU

Dear Professor Duggal

**Study title:** Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars.

**REC reference:** 13/YH/0049  
**Protocol number:** DT11/9936  
**EudraCT number:** 2011-004711-23  
**IRAS project ID:** 82161

Thank you for your letter which was received 16<sup>th</sup> April 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and an additional REC member.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Hayley Jeffries, hayley.jeffries@nhs.net.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

1. Please can you remove the initial boxes from the Assent form for children and replace this with tick boxes.

### **Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

The assent form should contain tick boxes rather than initial boxes.

**You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is

available.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

### Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		
GP/Consultant Information Sheets	GP Letter - 5.0	15 March 2013
Investigator CV	M Duggal	27 November 2012
Letter from Sponsor		14 January 2013
Letter from Statistician		
Other: Letter of invitation to parent	4.0	17 December 2012
Other: Case Record form	02	10 October 2012
Other: CV: JF Tahmassebi		29 November 2012
Other: CV: F Alzahrani		
Other: Summary of Product Characteristics: Lignospan Special		01 July 2007
Other: Summary of Product Characteristics: Septanest etc		07 June 2012
Other: Assent form for children (5-9 years)	5.0	15 March 2013
Other: Story Book	2.0	
Participant Consent Form: Parent	4.0	17 December 2012
Participant Consent Form: 7-9 years	4.0	17 December 2012
Participant Information Sheet: Child information letter	5.0	15 March 2013
Participant Information Sheet: Parent Information Sheet	5.0	15 March 2013
Protocol	4.0	17 December 2012
REC application		29 January 2013
Referees or other scientific critique report		
Response to Request for Further Information		

### Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### **After ethical review**

#### Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

#### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

<b>13/YH/0049</b>	<b>Please quote this number on all correspondence</b>
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely

pp



**Dr C E Chu**  
**Chair**

Email: [hayley.jeffries@nhs.net](mailto:hayley.jeffries@nhs.net)

*Enclosures:* "After ethical review – guidance for researchers" [\[SL-AR1\]](#)

Leeds Dental Institute  
 Department of Paediatric Dentistry  
 A Centre for Children with Special Needs

Level 6, Worsley Building  
 Clarendon Way, Leeds LS2 9LU

T (Direct Line) +44 (0)113 343 6177  
 T (Enquiries) +44 (0)113 343 6138  
 F +44 (0) 113 343 6140  
 E m.s.duggal@leeds.ac.uk



**UNIVERSITY OF LEEDS**

**NRES Committee Yorkshire & The Humber - Leeds East**

Yorkshire and Humber REC Office  
 First Floor, Millside  
 Mill Pond Lane  
 Meanwood  
 Leeds  
 LS6 4RA  
 Telephone: 0191 428 3564  
 Facsimile: 0191 428 3432

Dear Dr C E Chu

<b>Study Title:</b>	<b>Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars</b>
<b>REC reference:</b>	<b>13/YH/0049</b>
<b>Protocol number:</b>	<b>DT11/9936</b>
<b>EudraCT number:</b>	<b>2011-004711-23</b>
<b>IRAS project ID:</b>	<b>82161</b>

Thank you for your provisional opinion on our study.

You have requested further information and clarification about our study.

**1- Clarification of why non-English speakers are not being recruited into the study, as it was felt that these patients will have translation services provided.**

- In the Leeds Dental Institute we do value and respect the cultural and ethnic diversity of our local and national community. However, in our study it is necessary to limit subjects to English-speaking participants only as it is highly dependent on communication and reaction between the investigator and the child patient and we need to get immediate directly feedback from the child and not through an interpreter as it would affect the result of the study.

REC Reference: **13/YH/0049**

Page 1 of 3

Monty S Duggal  
 BDS MDSc FDS(Paed) RCS(Eng) PhD  
 Professor of Child Dental Health  
 Head of Department of Paediatric Dentistry

## 2- Changes to the Participant Information Sheet(s):

### a) Proof- reading.

The corrections were highlighted.

### b) Amendment of the Participant Information Sheet for Children to be appropriate for this age group, potentially seeking advice from a similar group of patients

We have asked advice from Dr Stella Kwan, Senior Lecturer Dental Public Health at university of Leeds and hence the PIS has been changed accordingly.

Regarding the story book, we had presented the booklet to a group of 25 children at school (reception class). All the comments from the children regarding the pictures were very positive and they found it interesting. However, we checked it again and we think there is one picture might look bit scary and we have modified it.

### c) Amendment of the Participant Information Sheet for Children to refer to children aged '5 to 9'

We have made the changes on the story book: "IT IS DESIGNED BY THE PRINCIPLE INVESTIGATOR FOR CHILDREN AGED FROM **FIVE** YEARS OLD.

### d) Amendment of the Participant Information Sheet for Parents to be re-written with more equipoise

Please see the corrected PIS. We have made every effort to make sure that the PIS for the parents is equipoised and not biased in any way.

### e) Section 11 of the Participant Information Sheet for Parents amendment to contain more information about the potential side effects

We have considered your comment and this part was added to the PIS page 3 section 11:

**"Serious side effects are rare; it may include haematoma, paraesthesia, and toxicity. However, it should not occur if we administer the correct amount of local anaesthetic agent, which is specified and approved in the study protocol. The side effects of local anaesthetics may occur if the drugs have inadvertently or accidentally been injected straight into the bloodstream".**

- f) Information added regarding the contact by telephone after 24 hours to assess for any potential adverse events

This part was added to section 9 page 3 on PIS:

**“We will be contacting you by telephone within 24 hours following your child’s dental treatment to assess whether there has been any potential adverse events associated to the local anaesthetic procedure”.**

- g) Modifying information in PIS pages 3-4 section 13:

” If there is a difference it will then affect what we use in the future”.

Changed to **“The finding of the study will have an effect on deciding which local anaesthetic agent to be used for the dental treatment of the lower baby molars”**

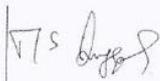
### 3- Changes to the Consent/Assent Form(s):

- a) The Assent Form amended to relate to all children in the study (5-9 years old).

The amended documents:

Document	version	Date
Participant Consent/Assent form	5.0	15/03/2013
Parent Information Sheet	5.0	15/03/2013
Children Information Sheet	5.0	15/03/2013
GP letter	5.0	15/03/2013
Story Book		

Yours sincerely




**Monty S Duggal and Fatma Alzahrani**



## Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds East

North East REC Centre  
Room 002  
TEDCO Business Centre  
Viking Industrial Park  
Rolling Mill Road  
Jarrow  
NE32 3DT

Telephone: 0191 4283545

23 April 2013

Professor Monty Duggal  
Leeds Dental Institute  
Paediatric Dentistry, Worsley Building,  
Level 6, Clarendon Way  
Leeds  
LS2 6LU

Dear Professor Duggal

**Study title:** Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars.

**REC reference:** 13/YH/0049  
**Protocol number:** DT11/9936  
**EudraCT number:** 2011-004711-23  
**IRAS project ID:** 82161

Thank you for your e-mail correspondence of 23<sup>rd</sup> April. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 18 April 2013

### Documents received

The documents received were as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Other: Assent form for children (5-9 years old)	6.0	22 April 2013

### Approved documents

The final list of approved documentation for the study is therefore as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		
GP/Consultant Information Sheets	GP Letter - 5.0	15 March 2013

Investigator CV	M Duggal	27 November 2012
Letter from Sponsor		14 January 2013
Letter from Statistician		
Other: Letter of invitation to parent	4.0	17 December 2012
Other: Case Record form	02	10 October 2012
Other: CV: JF Tahmassebi		29 November 2012
Other: CV: F Alzahrani		
Other: Summary of Product Characteristics: Lignospan Special		01 July 2007
Other: Summary of Product Characteristics: Septanest etc		07 June 2012
Other: Story Book	2.0	
Other: Assent form for children (5-9 years old)	6.0	22 April 2013
Participant Consent Form: Parent	4.0	17 December 2012
Participant Consent Form: 7-9 years	4.0	17 December 2012
Participant Information Sheet: Child information letter	5.0	15 March 2013
Participant Information Sheet: Parent Information Sheet	5.0	15 March 2013
Protocol	4.0	17 December 2012
REC application		29 January 2013
Referees or other scientific critique report		
Response to Request for Further Information		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

<b>13/YH/0049</b>	<b>Please quote this number on all correspondence</b>
-------------------	---

Yours sincerely



**Hayley Jeffries**  
**Committee Co-ordinator**

E-mail: hayley.jeffries@nhs.net

Copy to: Neville Young, Leeds Teaching Hospitals R and D department  
Mrs Anne Gowing, Leeds Teaching Hospitals NHS Trust

**Faculty of Medicine and Health  
Research Office**

Room 10.110, Level 10  
Worsley Building  
Clarendon Way  
Leeds LS2 9NL

T (General Enquiries) +44 (0) 113 343 4361  
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**UNIVERSITY OF LEEDS**

Prof Monty Duggal  
c/o Dr Fatma Alzahrani  
Child Dental Health  
Leeds Dental Institute  
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Leeds  
LS2 9LU  
United Kingdom

**Leeds Sponsor Quality Assurance Office**  
c/o Research & Development Directorate  
34 Hyde Terrace  
Leeds  
West Yorkshire  
LS9 6LN

Tel: 0113 392 6473  
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Fax: 0113 392 6397

[www.leedsteachinghospitals.com](http://www.leedsteachinghospitals.com)

16 October 2013

Dear Monty

**Confirmation of Sponsorship and Clinical Trial Approval**

**Short Project Title: The Use of Articaine in Children's Dentistry**

**Sponsor ID: DT11/9936**

**Chief Investigator: Professor Montgomery Duggal**

**Title:** Comparative studies of the anaesthetic efficacy of 4% Articaine used as mandibular infiltration versus 2% Lidocaine used as inferior dental nerve block, in extraction and pulpotomy of mandibular primary molars in children

I confirm that the University of Leeds has taken on the duties of Sponsor as defined under The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006\* for the above CTIMP.

The University of Leeds does provide insurance cover against claims arising from non-negligent harm under certain circumstances. However I can confirm that under normal circumstances clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

To monitor GCP compliance the sponsor Quality Assurance (QA) Department will be performing audits.

**You must contact QA if you require any advice on compliance with regulatory or sponsor process issues, or have any doubts about trial subject safety or Pharmacovigilance reporting requirements.**

Yours sincerely

**Ms Clare Skinner**  
Faculty Head of Research  
Faculty of Medicine and Health  
University of Leeds

cc: Caroline Bedford, Clinical Trials Manager, Pharmacy Department

\* These amend the principal Regulations [Medicines for Human Use (Clinical Trials) Regulations 2004, S.I. 2004/1031] which implemented the Council of the European Union Directive 2001/20/EC and the Commission of the European Communities Directive 2005/28/EC.

NHS SSI

IRAS Version 3.4

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

**Please enter a short title for this project** (maximum 70 characters)

Use of Articane in Children's Dentistry

**1. Is your project research?**

Yes  No

**2. Select one category from the list below:**

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

**If your work does not fit any of these categories, select the option below:**

Other study

**2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial?**

Yes  No

**2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?**

Yes  No

**2c. Please answer the following question:**

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?

Yes  No

**2d. Please answer the following question:**

NHS SSI

IRAS Version 3.4

Is this a trial of a gene therapy medicinal product?

 Yes  No**2e. Please answer the following question(s):**

- a) Does the study involve the use of any ionising radiation?  Yes  No
- b) Will you be taking new human tissue samples (or other human biological samples)?  Yes  No
- c) Will you be using existing human tissue samples (or other human biological samples)?  Yes  No

**3. In which countries of the UK will the research sites be located?(Tick all that apply)**

- England
- Scotland
- Wales
- Northern Ireland

**3a. In which country of the UK will the lead NHS R&D office be located:**

- England
- Scotland
- Wales
- Northern Ireland
- This study does not involve the NHS

**4. Which review bodies are you applying to?**

- NHS/HSC Research and Development offices
- Social Care Research Ethics Committee
- Research Ethics Committee
- Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- Gene Therapy Advisory Committee (GTAC)
- National Information Governance Board for Health and Social Care (NIGB)
- Ministry of Justice (MoJ)
- National Offender Management Service (NOMS) (Prisons & Probation)

*For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.*

**5. Will any research sites in this study be NHS organisations?** Yes  No**5a. Do you want your NHS R&D application(s) to be processed through the NIHR Coordinated System for gaining NHS Permission?** Yes  No

*If yes, you must complete and submit the NIHR CSP Application Form immediately after completing this project filter, before proceeding with completing and submitting other applications.*

**6. Do you plan to include any participants who are children?** Yes  No

NHS SSI

IRAS Version 3.4

**7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?**

Yes  No

*Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.*

**8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?**

Yes  No

**9. Is the study or any part of it being undertaken as an educational project?**

Yes  No

Please describe briefly the involvement of the student(s):  
This project is part of PhD degree.  
The student is the Principle Investigator.

**9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?**

Yes  No

**10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?**

Yes  No

**11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?**

Yes  No

NHS SSI

IRAS Version 3.4

## Site-Specific Information Form (NHS sites)

Is the site hosting this research a NHS site or a non-NHS site? NHS sites include Health and Social Care organisations in Northern Ireland. The sites hosting the research are the sites in which or through which research procedures are conducted. For NHS sites this includes sites where NHS staff are participants.

- NHS site  
 Non NHS site

*This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.*

*One Site-Specific Information Form should be completed for each research site and submitted to the relevant RSO office with the documents in the checklist. See guidance notes.*

The data in this box is populated from Part A:

Title of research:

Evaluation and comparing the analgesic efficacy of mandibular infiltration using 4% articaine with 1:100,000 epinephrine to mandibular block using 2% lidocaine with 1:200,000 epinephrine in extraction and pulpotomy of mandibular primary molars.

Short title: Use of Articaine in Children's Dentistry

Chief Investigator:	Title	Forename/Initials	Surname
	Dr.	FATMA S A	ALZAH RANI

Name of NHS Research Ethics Committee to which application for ethical review is being made:  
 NRES Committee Yorkshire & The Humber - Leeds - East

Protocol reference number from about REC: 13YH0048

1-1. Give the name of the NHS organisation responsible for this research site

The Leeds Teaching Hospitals NHS Trust

*If this site has not been included in the list of sites submitted to the main REC in Part C, please submit a Notice of Assent to the main REC, copied to MRA for information.*

1-2. In which country is the research site located?

- England  
 Wales  
 Scotland  
 Northern Ireland

1-3. Is the research site a GP practice or other Primary Care Organisation?

- Yes  No

NHS SSI

IRAS Version 3.4

## 2. Who is the Principal Investigator or Local Collaborator for this research at this site?

Select the appropriate title:  Principal Investigator  
 Local Collaborator

	Title	Forename/Initials	Surname
	Dr	Fatma SA	Alzahrani
Post	postgraduate student		
Qualifications	BDS (Bachelolar degree of dental sciences)		
Organisation	Leeds Dental Institute, University of Leeds		
Work Address	Clarendon way Leeds Dental Institute Leeds		
PostCode	LS1 9LU		
Work E-mail	m109fsa@leeds.ac.uk		
Work Telephone			
Mobile	07760841101		
Fax			

a) Approximately how much time will this person allocate to conducting this research? Please provide your response in terms of Whole Time Equivalents (WTE).

0.1 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?

 Yes  No

A copy of a current CV for the Principal Investigator (maximum 2 pages of A4) must be submitted with this form.

## 3. Please give details of all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

Please list all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Give details of any research procedures to be carried out off site, for example in participants' homes.

Location	Activity/facilities
1 Leeds Dental Institute- Department of Child Dental Health	First visit: New Patient Clinic - For consultation and screening Second Visit: Dental treatment.

## 5. Please give details of all other members of the research team at this site.

1

	Title	Forename/Initials	Surname
	PROF.	MONTY S	DUGGAL
Work E-mail	M.S.DUGGAL@LEEDS.AC.UK		
Employing organisation	University of leeds		

NHS SSI

IRAS Version 3.4

Post	Head of Paediatric Dentistry Department		
Qualifications	BDS, MDS, FDS(Eng)RCS(Paed), PhD Consultant and Head of Paediatric Dentistry		
Role in research team:	other (please specify)	- Chief Investigator, Supervisor.	
a) Approximately how much time (approximately) will this person allocate to conducting this research? <i>Please provide your response in terms of Whole Time Equivalents (WTE).</i>			
0.1 WTE			
b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?			
			<input checked="" type="radio"/> Yes <input type="radio"/> No
2			
	Title	Forename/Initials	Surname
	DR	JINOUS	TAHAMASSEBI
Work E-mail	J.TAHMASSEBI@LEEDS.AC.UK		
Employing organisation	University of leeds		
Post	Spicalist and Senior Lecturer in Paediatric Dentistry		
Qualifications	BDS	University of Newcastle Upon Tyne MDentSci, MRCD, FRCD ,Ph.D	
Role in research team:	other (please specify)	Supervisor	
a) Approximately how much time (approximately) will this person allocate to conducting this research? <i>Please provide your response in terms of Whole Time Equivalents (WTE).</i>			
0.1 WTE			
b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?			
			<input checked="" type="radio"/> Yes <input type="radio"/> No

**6. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share-holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?**

Yes  No

**7. What is the proposed local start and end date for the research at this site?**

Start date: 01/04/2013  
 End date (clinical interventions): 01/01/2015  
 End date (all local involvement): 01/01/2015  
 Total duration (Months): 21

**8-1. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. (These include seeking consent, interviews, non-clinical observations and use of questionnaires.)**

*Columns 1-4 have been completed with information from A18 as below:*

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.

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2. If this intervention would have been routinely given to participants as part of their care, how many of the total would have been routine?

3. Average time taken per intervention (in minutes, hours or days)

4. Details of who will conduct the procedure, and where it will take place

Please complete Column 5 with details of the names of individuals or names of staff groups who will conduct the procedure at this site.

Intervention or procedure	1	2	3	4	5
Informed Consent	1	1	15-30 minutes	- Researcher and designated supervisors - Place: Leeds Dental Institute.	
Get the feedback of the treatment (how was it) from children and parents/guardian.	1	1	10-15 minutes	- Researcher and designated supervisors - Place: Leeds Dental Institute.	

8-2. Will any aspects of the research at this site be conducted in a different way to that described in Part A or the protocol?

Yes  No

If Yes, please note any relevant changes to the information in the above table.

Are there any changes other than those noted in the table?

9-1. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. (These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.)

Columns 1-4 have been completed with information from A19 as below:

1. Total number of interventions to be received by each participant as part of the research protocol

2. If this intervention would have been routinely given to participants as part of their care, how many of the total would have been routine?

3. Average time taken per intervention (in minutes, hours or days)

4. Details of who will conduct the procedure, and where it will take place

Please complete Column 5 with details of the names of individuals or names of staff groups who will conduct the procedure at this site.

Intervention or procedure	1	2	3	4	5
Routine Dental Examination- to fill the screening sheet	1	1	10-20 minutes	- Researcher and designated supervisors  - Place: Paediatric clinic at Leeds Dental Institute	
Dental treatment/procedures.	1	1	30-90 minutes	- Principle investigator	

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- Place: Paediatric  
clinic at Leeds  
Dental Institute

**9-2. Will any aspects of the research at this site be conducted in a different way to that described in Part A or the protocol?**

Yes  No

*If Yes, please note any relevant changes to the information in the above table.*

*Are there any changes other than those noted in the table?*

**10. How many research participants/samples is it expected will be recruited/obtained from this site?**

110 PARTICIPANTS

**11. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study.**

All participants will be selected from patients attending for treatment at Leeds Dental Institute (consultant clinic - that is a new patient clinic)

Those who meet the inclusion criteria will be invited in to our study.

The participants will be offered the option joining the study and they will be told that their participation in this clinical trial is entirely voluntary and that refusal will not affect their clinical management in any way.

Patient's dental records (notes) will be reviewed to determine whether they meet the inclusion criteria of the study.

**12. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?**

Name	Expertise/training
Principle Investigator- Fatma S A Alzahrani	Had attended the following courses: <ul style="list-style-type: none"> <li>- course in research methodology and Ethics which covered the process of obtaining consent.</li> <li>- course in obtaining consent, at Leeds General Infirmary Hospital.</li> <li>- workshop (09/03/2012) at university of Leeds, about Research governance, ethics &amp; societal</li> <li>- workshop on Children and Research which covered the process of obtaining consent.</li> </ul>

**15-1. Is there an independent contact point where potential participants can seek general advice about taking part in research?**

In the participant's information sheet, parents were advised to visit NIHR CRN CC web site (Understanding clinical trials - [www.crncc.nihr.ac.uk](http://www.crncc.nihr.ac.uk)) to provide them with an independent advice about taking part in research.

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15-2. Is there a contact point where potential participants can seek further details about this specific research project?

There is a contact point and the person is part of the research team.

16. Are there any changes that should be made to the generic content of the information sheet to reflect site-specific issues in the conduct of the study? *A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.*

No.

*Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. Unless indicated above, this must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).*

17. What local arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

N/A

18. What local arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

A letter will be send to the participant's GP.

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19. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

The arrangement will follow the study protocol.

If the child shows uncooperative behaviour or becomes distressed we will consider the treatment failed and try by another different method to complete/end the dental treatment.  
We will discuss the different treatment options (with parents/guardian) in order to complete the child's dental treatment in the future (including treatment under sedation/general anaesthesia).

In case of emergency situation:

In the dental department, all emergency equipments and drugs are readily available and up-to-date, following NHS regulations.

there are adequately trained professional staff and dental nurses who can deal with emergency situations.

Emergency department at the Leeds general Infirmary Hospital is easily accessible.

20. What are the arrangements for the supervision of the conduct of the research at this site? Please give the name and contact details of any supervisor not already listed in the application.

Academic and Clinical supervisor based at the Leeds Dental Institute.

21. What external funding will be provided for the research at this site?

- Funded by commercial sponsor  
 Other funding  
 No external funding

How will the costs of the research be covered?  
 By University of Leeds- Leeds Dental Institute.

23. Authorisations required prior to R&D approval

This section deals with authorisations by managers within the NHS organisation. It should be signed in accordance with the guidance provided by the NHS organisation. This may include authorisation by clinical supervisors, line managers, service managers, support department managers, pharmacy, data protection officers or finance managers, depending on the nature of the research. Managers completing this section should confirm in the text what the authorisation means, in accordance with the guidance provided by the NHS organisation.

This section may also be used by university employers or research support staff to provide authorisation to NHS organisations, in accordance with guidance from the university.

1. Type of authorisation:

Academic Supervisor and Chief Investigator.

Title	Forename/Initials	Surname
	PROF. MONTY S	DUGGAL
Post	Head of paediatric department.	
Qualifications	BDS, MDS, FDS(Eng)RCS(Paed), PhD	
Organisation	University of Leeds	
Work Address	LEEDS DENTAL INSTITUTE UNIVERSITY OF LEEDS	
PostCode	LS2 9LU	
Work E-mail	M.S.DUGGAL@LEEDS.AC.UK	

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Work Telephone	01133436177
Mobile	
Fax	01133436140
Signature:	.....
Date:	.....

**Declaration by Principal Investigator or Local Collaborator**

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.
4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.
5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.
6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.
7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.
8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.
9. I undertake to complete any progress and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.
10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.
11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.
12. I understand that information relating to this research, including the contact details on this application, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
13. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

This section was signed electronically by Monty Duggal on 05/02/2013 13:29.

Job Title/Post: Prof/HOD

NHS SSI

IRAS Version 3.4

Organisation:	Leeds Dental institute
Email:	m.s.duggal@leeds.ac.uk

**Safeguarding public health**The MHRA logo consists of the letters 'MHRA' in a bold, white, sans-serif font, centered within a dark blue oval shape.

Prof M S Duggal  
LEEDS DENTAL INSTITUTE  
CLARENDON WAY  
LEEDS  
WEST YORKSHIRE  
LS2 9LU  
UNITED KINGDOM

22/05/2013

Dear Prof M S Duggal

**THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031**

Our reference: 22868/0001/001-0001  
Eudract Number: 2011-004711-23  
Product: SEPTANEST 1:100,000 INJECTION  
Protocol number: DT11/9936

**NOTICE OF ACCEPTANCE**

I am writing to inform you that the Licensing Authority accepts your request for a clinical trial authorisation (CTA), received on 30/04/2013.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

**Clinical Trials Unit  
MHRA**

**Medicines Management and Pharmacy Services  
Clinical Trial Review Process**

**Final Sign Off**

<b>Trial Title</b>	Comparative studies of the anaesthetic efficacy of 4% articaine used as mandibular infiltration versus 2% lidocaine used as inferior dental nerve block in extraction and pulpotomy of mandibular primary molars in children.
<b>Protocol Number</b>	DT11/9936
<b>EudraCT Number</b>	2011-004711-23
<b>Trial Sponsor</b>	University of Leeds
<b>netTRAMS Number</b>	1924
<b>R&amp;D Number</b>	DT11/9936
<b>Principal Investigator</b>	Dr Fatma Alzahrani
<b>Research Nurse</b>	Kendal Stead
<b>Clinical Area</b>	Dental

The following documents have been reviewed:

<b>Document</b>	<b>Version</b>	<b>Date</b>
Protocol	4	17 Dec 2012
MHRA CTA application form		
SmPC Septanest		07 Jun 2012
SmPC Lignospan special		Jul 2007
Parent information sheet	5	15 Mar 2013
Case record form	0.3	01 Oct 2013

I can confirm that, in principle, the Medicines Management and Pharmacy Services directorate is **able to support** the trial.

Please note: This support is conditional on an acceptable assessment of the proposed IMP storage area in the Dental Institute.

Any amendments to the protocol or new information that could significantly affect the conduct of the study will require reassessment of the pharmacy support to the trial.



Signed by  
Caroline Bedford, Lead Pharmacist for Clinical Trials

Date 8 October 2013

**Faculty of Medicine and Health  
Research Office**

Room 10.110, Level 10  
Worsley Building  
Clarendon Way  
Leeds LS2 9NL

T (General Enquiries) +44 (0) 113 343 4361  
F +44 (0) 113 343 4373



**UNIVERSITY OF LEEDS**

Prof Monty Duggal  
c/o Dr Fatma Alzahrani  
Child Dental Health  
Leeds Dental Institute  
Clarendon Way  
Leeds  
LS2 9LU  
United Kingdom

**Leeds Sponsor Quality Assurance Office**  
c/o Research & Development Directorate  
34 Hyde Terrace  
Leeds  
West Yorkshire  
LS9 6LN

Tel: 0113 392 6473  
Tel: 0113 392 2878  
Fax: 0113 392 6397

[www.leedsteachinghospitals.com](http://www.leedsteachinghospitals.com)

16 October 2013

Dear Monty

**Confirmation of Sponsorship and Clinical Trial Approval**

**Short Project Title:** The Use of Articaine in Children's Dentistry

**Sponsor ID:** DT11/9936

**Chief Investigator:** Professor Montgomery Duggal

**Title:** Comparative studies of the anaesthetic efficacy of 4% Articaine used as mandibular infiltration versus 2% Lidocaine used as inferior dental nerve block, in extraction and pulpotomy of mandibular primary molars in children

I confirm that the **University of Leeds** has taken on the duties of Sponsor as defined under **The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006\*** for the above CTIMP.

The University of Leeds does provide insurance cover against claims arising from non-negligent harm under certain circumstances. However I can confirm that under normal circumstances clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

To monitor GCP compliance the sponsor Quality Assurance (QA) Department will be performing audits.

**You must contact QA if you require any advice on compliance with regulatory or sponsor process issues, or have any doubts about trial subject safety or Pharmacovigilance reporting requirements.**

Yours sincerely

**Ms Clare Skinner**  
Faculty Head of Research  
Faculty of Medicine and Health  
University of Leeds

cc: Caroline Bedford, Clinical Trials Manager, Pharmacy Department

\* These amend the principal Regulations [Medicines for Human Use (Clinical Trials) Regulations 2004, S.I. 2004/1031] which implemented the Council of the European Union Directive 2001/20/EC and the Commission of the European Communities Directive 2005/28/EC.

# The Leeds Teaching Hospitals

NHS Trust

Prof Monty Duggal

Leeds Dental Institute  
University of Leeds  
Clarendon Way  
Leeds  
LS2 9LU

16 October 2013

Research & Development

**Leeds Teaching Hospitals NHS Trust**

34 Hyde Terrace  
Leeds  
LS2 9LN

Tel: 0113 392 2878  
Fax: 0113 392 6397

r&d@leedsth.nhs.uk  
www.leedsth.nhs.uk

Dear Prof Monty Duggal

**Re: NHS Permission at LTHT for: Comparative studies of the anaesthetic efficacy of 4% articaine used as mandibular infiltration versus 2% lidocaine used as inferior dental nerve block in extraction and pulpotomy of mandibular primary molars. [Articaine in children]**  
**LTHT R&D Number: DT11/9936**  
**EuDRACt: 2011-004711-23**  
**REC: 13/YH/0049**

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at <http://www.leedsth.nhs.uk/academic/research-development/>

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

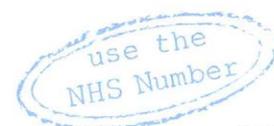
### Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust

Chairman Mike Collier CBE Chief Executive Maggie Boyle

The Leeds Teaching Hospitals incorporating:

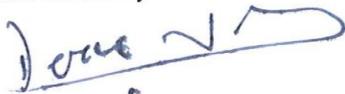
Chapel Allerton Hospital Leeds Dental Institute Seacroft Hospital  
St James's University Hospital The General Infirmary at Leeds Wharfedale Hospital



only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

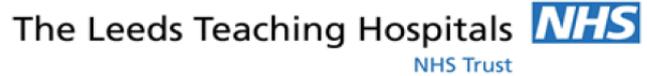


**Dr D R Norfolk**  
Associate Director of R&D

#### Approved documents

The documents reviewed and approved are listed as follows

<i>Document</i>	<i>Version</i>	<i>Date of document</i>
Directorate Approval	email	08/10/2013
Pharmacy Approval		08/10/2013
Clinical Trials Agreement with Indemnity		15/10/2013
REC Letter confirming favourable opinion		23/04/2013
MHRA Clinical Trial Authorisation Letter		22/05/2013
Protocol	V4	17/12/2012
Patient information sheet child	5.0	15/03/2013
Patient information sheet parent	5.0	15/03/2013
Participant Consent Form: Parent	4.0	17/12/2012
Participant Consent Form: 7-9 years	4.0	17/12/2012
Other: Letter of invitation to parent	4.0	17/12/2012
GP / Consultant Information sheets	GP letter – 5.0	15/03/2013
Assent Form for Children (5-9 years old)	V6.0	22/04/2013
Letter of Invitation to Parent	4.0	17/12/2012
Statistical Review		
Peer review		
SPC - Lignospan - Special		01/07/2007
SPC - Septanset		07/06/2012



Prof Monty Duggal  
Leeds Dental Institute  
University of Leeds  
Clarendon Way  
Leeds

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Fax: 0113 392 6397

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10<sup>th</sup> December 2013

**Ref: 9936/MON/0001**  
**Sponsor number – DT11/9936**  
**MREC ref no – 13/YH/0049**  
**EudraCT Number - 2011-004711-23**

Study Title: Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars. (Articaine in children)

Dear Professor Duggal,

I am writing on behalf of the sponsor, The University of Leeds, to inform you that I will be visiting the aforementioned site to monitor the Clinical Trial DT11/9936, study short name – Articaine in Children, for which you are the Chief Investigator.

This monitoring visit is in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments.

I plan to visit the week commencing the 20th January 2014 for the duration of a day in the first instance and spending a second day with your pharmacy department. Throughout the course of our visit you may wish to allocate some time (preferably half an hour) to gain feedback on any important issues or outcomes from the visit. Your time would be greatly appreciated.

If you are unable to attend on the dates provided, please could you suggest a date after this time which would be more suitable and if you wish us to liaise with another member of your staff over the planning of our visit please let us know.

Could you be kind enough to ensure the following is available:

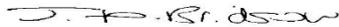
1. The site file

2. The pharmacy file (this will be seen in the visit to pharmacy)
3. Training files for yourself, any sub-investigators listed on the site delegation / authorisation log and for the pharmacy member of staff with the most input into the trial.
4. Case Report Forms for the 1st, 4th, 7th and last patient enrolled in the study along with their medical notes.

I will send you a more in depth monitoring plan nearer the time.

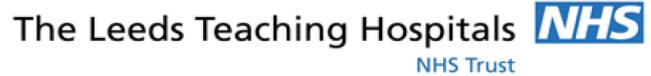
Please do not hesitate to contact me if you wish to discuss anything in more detail.

Yours sincerely,



Jessie Bridson  
Clinical Trials Quality Monitor  
Research and Development  
Leeds Teaching Hospitals and NHS Trust  
34 Hyde Terrace  
Leeds  
LS2 9LN  
Tel: 0113 39 26473  
E-mail: [j.bridson@leeds.ac.uk](mailto:j.bridson@leeds.ac.uk)

cc: Clare Skinner    Caroline Bedford



Professor Monty Duggal  
 Leeds Dental Institute  
 University of Leeds  
 Clarendon Way  
 Leeds  
 LS2 9LU

**Leeds Sponsor Quality Assurance Office**  
 c/o Research & Development Directorate  
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[www.leedsteachinghospitals.com](http://www.leedsteachinghospitals.com)

Wednesday 7<sup>th</sup> January 2015

**Ref:** 9936/MON/002  
**Sponsor number:** DT11/9936  
**MREC ref no:** 13/YH/0049  
**EudraCT Number:** 2011-004711-23

**Study Title:**

Evaluation and comparing the anaesthetic efficacy of mandibular infiltration using 4% articaine with 1:100:000 epinephrine to mandibular block using 2% lidocaine with 1:80:000 epinephrine in extraction and pulpotomy of mandibular primary molars (Articaine in children)

Dear Professor Duggal,

I am writing to inform you that I will be visiting your site to monitor the CTIMP DT11/9936, study short name – Articaine in children, sponsored by The University of Leeds and for which you are the Chief Investigator.

This monitoring visit is in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments.

We plan to visit the week commencing either the 2<sup>nd</sup> February 2015, 9<sup>th</sup> February 2015 or 23<sup>rd</sup> February 2015, for one day in the first instance, spending a second day with your pharmacy department. Please can you advise us of you and your research teams' availability for the weeks specified. Throughout the course of our visit you may wish to allocate some time (preferably half an hour) to gain feedback on any important issues or outcomes from the visit. Your time would be greatly appreciated.

If you are unable to attend on the dates provided, please could you suggest a date after this time which would be more suitable. If you wish us to liaise with another member of your staff over the planning of our visit, please let us know.

Could you be kind enough to ensure the following is available:

1. The site file.
2. The pharmacy file (this will reviewed in a separate visit to pharmacy).
3. Training files for yourself, the PI, sub-investigators listed on the site delegation / authorisation log and for the pharmacy member of staff with the most input into the trial.
4. Trial specific SOPs.
5. Case Report Forms for the 1st, 4th, 7th and last patient enrolled in the study along with their medical notes.

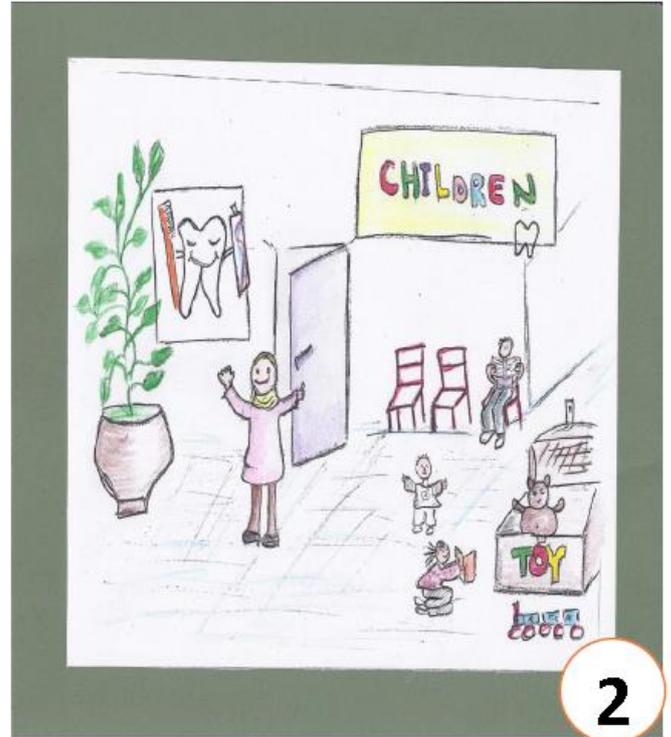
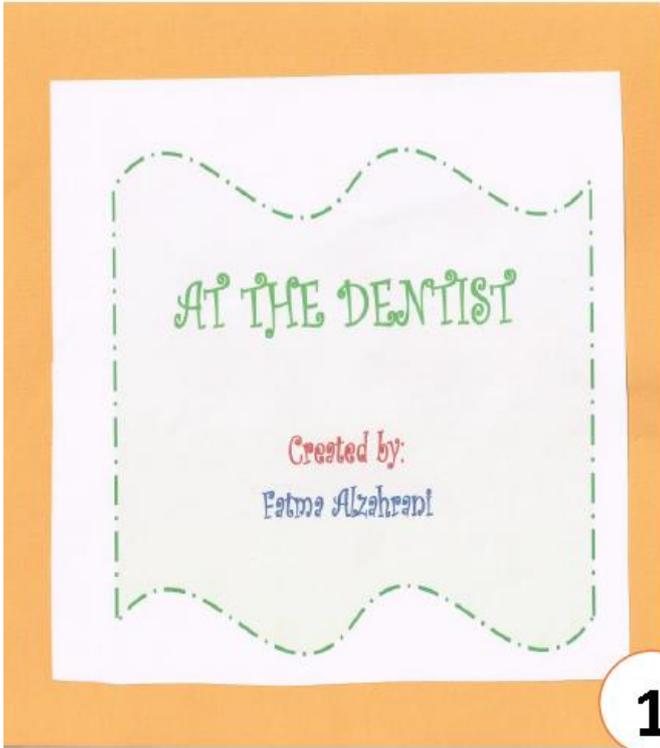
I will send you a more in depth monitoring plan nearer the time.

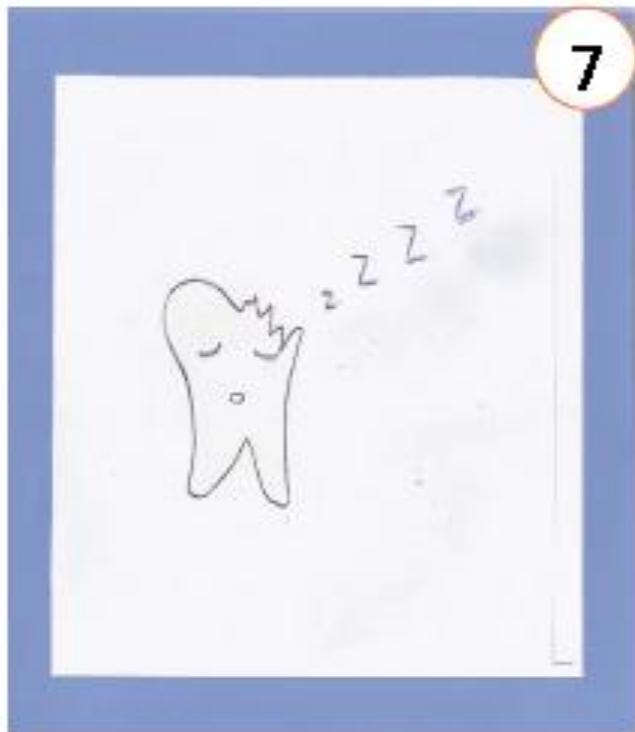
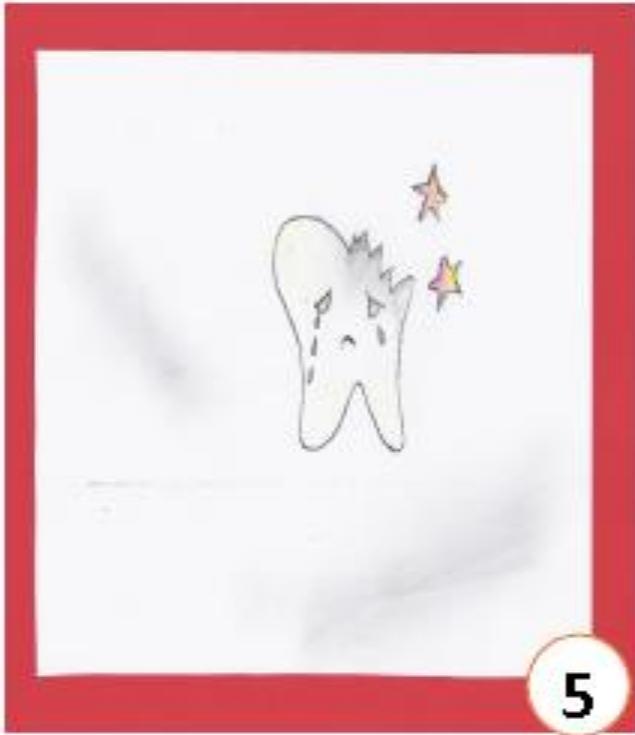
Please do not hesitate to contact me if you wish to discuss anything in more detail.

Yours sincerely,



Dr Sam Keating  
Clinical Trials Monitor  
Research and Innovation  
Leeds Teaching Hospitals NHS Trust  
34 Hyde Terrace  
Leeds  
LS2 9LN  
Tel: 0113 39 26473  
Email: [sam.keating@nhs.net](mailto:sam.keating@nhs.net)









**Leeds Dental Institute**  
 Department of Paediatric Dentistry  
 A Centre for Children with Special Needs

Level 6, Worsley Building  
 Clarendon Way, Leeds LS2 9LU

T (Direct Line) +44 (0)113 343 6177  
 T (Enquiries) +44 (0)113 343 6138  
 F +44 (0) 113 343 6140  
 E m.s.duggal@leeds.ac.uk

**Patient identification number for the trial:**



**UNIVERSITY OF LEEDS**

## Parent Information Sheet

Version 5.0 Date 15/03/2013

**Title of Project:** Comparative studies of the anaesthetic efficacy of 4% Articaine versus 2% Lidocaine in children

**Name of Researcher:** Fatma S. Alzahrani

### PART 1

#### 1- Invitation

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully, and discuss it with others if you wish.

PART 1 tells you the purpose of this study and what will happen to you if you take part.

PART 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

#### 2- Study Title

In this study, we aim to carry out a randomised control study to evaluate and compare the anaesthetic efficacy of mandibular infiltration with 4% Articaine with 1: 1 00:000 epinephrine to mandibular block with 2% Lidocaine with 1: 1 00:000 epinephrine in extraction and restoration of primary mandibular molars.

#### 3- Introduction

We are about to undertake research into looking at the effects of Local Anaesthetic for your child. Local Anaesthetic has been used for many years but it is clearly seems to be the most difficult part of being able to carry out dental treatment. In this study, we hope to look at your child's experience of two types of Local Anaesthetic agents given at two different sites of the mouth (your child will receive only one type of local anaesthetic) and both types of local anaesthetic has been used widely in dentistry and in particular in Children Dentistry.

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Protocol ID: DT11/9936 EudraCT Number:2011-004711-23 ISRCTN Number: ISRCTN11415977

**Monty S Duggal**  
 BDS MSc FDS (Paeds) RCS (Eng) PhD  
 Professor of Child Dental Health  
 Head of Department of Paediatric Dentistry

**UNIVERSITY OF LEEDS****4- The purpose of the study**

Often the main reason for failure to treat a child is the failure of being able to administer effective local anaesthetics. The main complaint appears to be pain associated with having the 'needle'. In this study we will look at which type of local anaesthetic drugs and site of the mouth is better and less painful. Our focus will be on which one your child finds more comfortable but we will also look at which agent/site is better for delivery of the dental treatment.

**5- Why has your child been chosen?**

We are interested in looking at the response to the two types of local anaesthetic agents in healthy children aged between 5-9 years old.

**6- Does my child have to take part?**

No. It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part you are free to leave the study at any time and without giving a reason. If you withdraw, unless you object, we will still keep records relating to the treatment given to you, as this is valuable to the study. A decision to withdraw at any time, or a decision not to take part, will not affect the quality of care you receive.

**7- What will happen to my child if he/she takes part?**

Your child will be seen first by one of the consultants at Leeds Dental Institute, and you will have a full dental treatment plan for your child at that visit, at that stage if your child fulfill the study criteria we will ask you/your child to take part in our study, If your child take part, he/she will receive dental treatment for one tooth and that should count for one dental visit, after that your child will continue his/her dental treatment according to the initial treatment plan made at the first dental visit.

**8- What do I have to do or does my child need to do?**

Usually at the assessment stage, the involvement to this study will be discussed and the information sheet will be handed to you and your child. If you are happy to be a part of the study, we will need you to sign a consent form. Having signed the consent form you can still withdraw consent at any time. On the day of the appointment, you will bring your child as normal and we will explain everything to your child before starting, during and afterwards.



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**9- What are the drug / treatment / procedure that are being tested?**

The two Local Anaesthetic agents that will be used in the study are already being used in the dentistry. One of the agents is the traditional local anaesthetic, lidocaine and the second is called Articaine. In both cases, your child will have topical or bubble gum gel placed prior to the injection. We only plan to carry out the study on one tooth over one visit.

As part of our study, **we will be contacting you by telephone within 24 hours following your child's dental treatment to assess whether there has been any potential adverse events associated to the local anaesthetic procedure.**

**10- What are the alternatives for treatment?**

In this study we are providing routine dental treatment to your child under local anaesthetic, the other alternatives would be having dental treatment under inhalation sedation or under general anaesthetic.

**11- What are the side effects of any treatment received when taking part?**

If you do decide to take part in the study, you must report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

Serious side effects are rare; it may include haematoma, paraesthesia, and toxicity. However, it should not occur if we administer the correct amount of local anaesthetic agent, which is specified and approved in the study protocol. The side effects of local anaesthetics may occur if the drugs have inadvertently or accidentally been injected straight into the bloodstream.

**12- What are other possible disadvantages and risks of taking part?**

There will be no risks or burdens for your child as part of his/her participation in the research itself. The study delivers dental treatment, and so the potential risks or hazards are the same as for any dental treatment provided to children, which may include pain, discomfort, strange feeling of numbness, and lip- and/or cheek-biting. Such procedures in this study reflect those carried out in current clinical practice. The potential for pain, discomfort or distress for participants will be no different to those experienced in routine dental treatment.

**13- What are the possible benefits of taking part in this study?**

We hope to use what we learn from the study to make changes to the children dental treatment.

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This study will help us find out which of the two local anaesthetic drugs is better for your child.

The finding of the study will have an effect on deciding which local anaesthetic agent to be used for the dental treatment of the lower baby molars.

**14- What happens when the research study stops?**

Your child will continue his/her dental treatment according to the initial treatment plan made at the first dental visit.

**15- What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

**In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.**

**16- Will my taking part in this study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

**17- Contact Details**

**Dentist:**

Name: Fatma Alzahrani                      Tel. Number: 0113-3436229

**Research/Specialist Nurse:**

Name: Janet Blackburn                      Tel. Number: 0113-3436228

**This completes Part 1 of the Information Sheet.**

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**If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.**

## **PART 2**

### **1- What if new information becomes available?**

Sometimes during the course of a clinical trial, new information becomes available on the drugs that are being studied. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

**If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.**

### **2- What will happen if I don't want to carry on with the study?**

You will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

### **3- Will my part in this study be kept confidential?**

If you consent for your child to take part in this study, the records obtained while your child is in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital (Leeds Dental Hospital) under the provisions of the 1998 Data Protection Act. Your child's name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. Your child will be allocated a trial number, which will be used as a code to identify him/her on all trial forms.

Your child's records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. A copy of your consent/your child

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assent form may be sent to the Research Sponsor during the course of the study. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you\your child withdraw from the current study.

*The information collected about your child may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.*

If you/ your child withdraw consent from further study treatment, unless you object, your child's data and samples will remain on file and will be included in the final study analysis. In line with Good Clinical Practice guidelines, at the end of the study, your child's data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

#### **4- Informing your General Practitioner (GP)**

With your permission, your child's GP, and other doctors who may be treating your child, will be notified that he\she is taking part in this study.

#### **5- Will any Genetic testing be done?**

No, there will be no genetic testing in this study.

#### **6- What will happen to the results of this clinical trial?**

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor.

#### **7- Who is organising and funding this clinical trial?**

The Research is funded by the Leeds Dental Institute.  
I am doing this research as part of my Integrated PhD Degree.

#### **8- Who reviewed this study?**

All research in the NHS is looked at by independent group of people, called research ethics committee to protect your safety, rights, wellbeing and dignity.



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### 9- Contact for further information

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact one of the following people:

**Dr. Fatma Alzahrani**  
Principal Investigator  
Child Dental Health  
Leeds Dental Institute  
Clarendon Way  
Leeds  
LS29LU  
United Kingdom  
[m109fsa@leeds.ac.uk](mailto:m109fsa@leeds.ac.uk)

**Prof. Monty Duggal**  
Consultant and Head of paediatric dentistry  
Child Dental Health  
Leeds Dental Institute  
Clarendon Way  
Leeds  
LS2 9LU  
United Kingdom  
[m.s.duggal@leeds.ac.uk](mailto:m.s.duggal@leeds.ac.uk)

**Dr. Jinous Tahmassebi**  
Associate Professor in Paediatric dentistry  
Child Dental Health  
Leeds Dental Institute  
Clarendon Way  
Leeds  
LS2 9LU  
United Kingdom  
[j.tahmassebi@leeds.ac.uk](mailto:j.tahmassebi@leeds.ac.uk)

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

### Looking for further information about randomised control trial?

You can find more information about clinical trials and research on:

[www.crncc.nihr.ac.uk/.../PPI/./uct\\_oct06\\_final.pdf](http://www.crncc.nihr.ac.uk/.../PPI/./uct_oct06_final.pdf)

At the end of this booklet you will find a list of further web sites and links.

**Leeds Dental Institute**  
Department of Paediatric Dentistry  
A Centre for Children with Special Needs

Level 6, Worsley Building  
Clarendon Way, Leeds LS2 9LU

T (Direct Line) +44 (0)113 343 6177  
T (Enquiries) +44 (0)113 343 6138  
F +44 (0) 113 343 6140  
E m.s.duggal@leeds.ac.uk



**UNIVERSITY OF LEEDS**

Patient identification number for the trial:

**CONSENT FORM**  
Version 4.0    Date 17/12/2012

Title of Project: Comparative studies of the anaesthetic efficacy of 4 %Articaine versus 2 %Lidocaine in children.

Name of Researcher: Fatma S. Alzahrani

Initial each point

1. I confirm that I have read and understand the information sheet dated 17/12/2012 (Version 4.0) for the above study, have had the opportunities to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw at any time without my child's medical care or legal rights being affected. I agree to take part in the study.

\_\_\_\_\_

2. I understand that my child's medical records may be looked at by authorised individuals from the Sponsor for the study, the UK Regulatory Authority or the Independent Ethics Committee in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my child's medical records for the above study and any further research that may be conducted in relation to it. I also give permission for a copy of my consent form to be sent to the Sponsor for the study.

\_\_\_\_\_

3. I understand that even if I withdraw from the above study, the data collected from me and my child will be used in and lysing the results of the trial, unless I specifically withdraw consent for this. I understand that my child's identity will remain anonymous.

\_\_\_\_\_

4. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify my child will be kept strictly confidential and that no personal information will be included in the study report or other publication.

\_\_\_\_\_

5. I agree that my child's GP, or any other doctor treating my child, will be notified of his/her participation in this study.

\_\_\_\_\_

Name of parent/guardian: \_\_\_\_\_ date: \_\_\_\_\_ signature: \_\_\_\_\_

Name of person taking consent: \_\_\_\_\_ date: \_\_\_\_\_ signature: \_\_\_\_\_

Investigator: \_\_\_\_\_ date: \_\_\_\_\_ signature: \_\_\_\_\_

Protocol ID: DT11/9936    EudraCT Number: 2011-004711-23    ISRCTN Number: ISRCTN11415977

**Monty S Duggal**  
BDS MSc FDS (Paeds) RCS (Eng) PhD  
Professor of Child Dental Health  
Head of Department of Paediatric Dentistry

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**THE USE OF ARTICAININE IN CHILDREN DENTISTRY**  
**Sponsor ID DT11/9936**

**PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL**

1

Patient's sticker

0

Lidocaine

**Date of randomisation:**

**Date of treatment:**

**THE USE OF ARTICAININE IN CHILDREN DENTISTRY**  
**Sponsor ID DT11/9936**

**PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL**

2

Patient's sticker

1

Articaine

**Date of randomisation:**

**Date of treatment:**

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



## **Case Record Form**

### **THE USE OF ARTICAININE IN CHILDREN DENTISTRY**

#### **STUDY NUMBERS:**

**Sponsor ID:** DT11/9936  
**EudraCT No:** 2011-004711-23  
**ISRCTN Number:** ISRCTN11415977

**PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:**

#### **PRINCIPLE INVESTIGATOR**

**DR. FATMA ALZHRANI**  
**PHD RESEARCH STUDENT**  
**CHILD DENTAL HEALTH**  
**LEEDS DENTAL INSTITUTE**

#### **SUPERVISOR 1**

**PROF. MONTY DUGGAL**  
**CONSULTANT AND HEAD OF PAEDIATRIC DENTISTRY**  
**CHILD DENTAL HEALTH**  
**LEEDS DENTAL INSTITUTE**

#### **SUPERVISOR 2**

**DR. JINOUS TAHMASSEBI**  
**ASSOCIATE PROFESSOR IN PAEDIATRIC DENTISTRY**  
**CHILD DENTAL HEALTH**  
**LEEDS DENTAL INSTITUTE**

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



# Screening visit

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



Screening Visit Check List

Personnel sheet completed	Yes	<input type="text"/>	No	<input type="text"/>
Medical history checked	Yes	<input type="text"/>	No	<input type="text"/>
Dental Examination completed	Yes	<input type="text"/>	No	<input type="text"/>
Inclusion criteria sheet completed	Yes	<input type="text"/>	No	<input type="text"/>
Exclusion criteria sheet completed	Yes	<input type="text"/>	No	<input type="text"/>
Information sheet given (Date: .....) (Version No :.....)	Yes	<input type="text"/>	No	<input type="text"/>
Patient is eligible after screening	Yes	<input type="text"/>	No	<input type="text"/>
<b>Dental appointment arranged for 2-3 weeks times</b>	<b>Yes</b>	<input type="text"/>	<b>No</b>	<input type="text"/>

**Date of appointment and Time** \_\_\_\_\_

**Other information to record**

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_





PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Dental Examination**

**CHARTING:**

<b>18</b>	<b>17</b>	<b>16</b>	<b>55</b>	<b>54</b>	<b>53</b>	<b>52</b>	<b>51</b>	<b>61</b>	<b>62</b>	<b>63</b>	<b>64</b>	<b>65</b>	<b>26</b>	<b>27</b>	<b>28</b>
<b>48</b>	<b>47</b>	<b>46</b>	<b>85</b>	<b>84</b>	<b>83</b>	<b>82</b>	<b>81</b>	<b>71</b>	<b>72</b>	<b>73</b>	<b>74</b>	<b>75</b>	<b>36</b>	<b>37</b>	<b>38</b>

**SOFT TISSUE EXAMINATION:**

**RADIOGRAPHIC EXAMINATION:**

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Inclusion Criteria**

<i>Inclusion Criteria</i>	<i>Yes</i>	<i>No</i>
Children aged 5to 9 years.		
Medically fit. (ASA I,II)		
Requiring extraction /restoration of primary mandibular molars teeth under local anaesthetic.		
Understand English.		
Mentally capable of communication.		
Tooth has no history of infection (abscess) or swelling and no evidence of periapical pathosis.		
The roots resorption of the primary tooth must be less than two third of the root.		
Parents /guardian must give informed written consent prior to participation.		
Child must give assent form prior to participation, as well as parental consent.		
Child body weight is 20 KG or more.		

**\*Note:** If any of the above questions are answered “No”, the subject should be discontinued from the study as a “Screen failure” on the study conclusion page.

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Exclusion Criteria**

<i>Exclusion Criteria</i>	<i>Yes</i>	<i>No</i>
Medically and mentally compromised children.		
History of significant behaviour management problems		
Evidence of infection near the proposed injection site as this might affect the efficacy of local anaesthesia.		
Child does not speak English.		
Allergic to amide local anaesthetic or any of the ingredients		

**\*Note:** If any of the above questions are answered “Yes”, the subject should be discontinued from the study as a “Screen failure” on the study conclusion page.

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



***Fitness and Eligibility to Participate in the Study***

In the investigator's opinion, on the basis of the screening assessments and Inclusion and Exclusion criteria, is the subject eligible to participate in the next part of the study?

Yes

No

Investigator's signature:..... Date \_\_/\_\_/\_\_\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



# Treatment visit

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Health Check**

Is there any change in medical history since screening visit?      YES      NO

*\*If yes, please specify in the comments' space below*

**Comments**

**Consent**

Patient consented      YES      NO  
Date of consent

Parent consented      YES      NO  
Date of consent

**Randomisation**

Patient randomized      YES      NO  
Date of randomization

**Subject eligibility**

Have there been any deviations from the protocol since the screening visit?      YES      NO

Is the subject still eligible to continue the study?      YES      NO

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



Assessment date: .....

**ASSESSMENT OF EFFICACY**

**1) AMOUNT OF LOCAL ANAESTHETIC USED**

Type of local anaesthetic:

Technique used:

Amount of local anaesthetic used:

**2) PAIN ASSESSMENT**

Pain will be assessed after each stage during dental treatment (according to the tables below)

**3) THE NEED OF RE-ANAESTHESIA.**

- Is there a need for re anaesthesia?

YES

NO

- Why re- anaesthesia?

- Technique for re- anaesthesia

- Amount of local anaesthetic used

Comments

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



4) SIGN OF DISCOMFORT

Comments

5) CHILD'S BEHAVIOUR

Comments

ASSESSMENT OF ADVERSE EVENTS

**If the subject experienced any adverse events, please complete the Adverse Events page.**

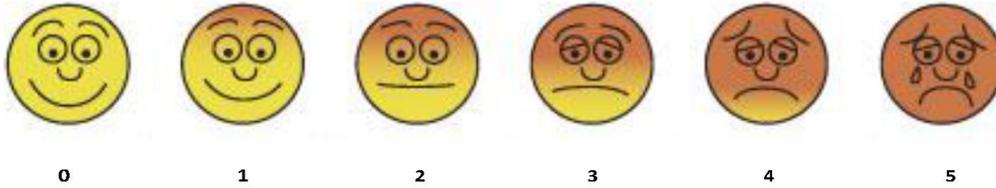
Comments

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Pain assessment**

- A) *Wong-Baker Faces Pain Rating Scale*

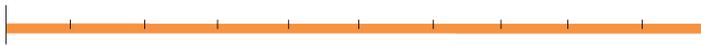


Pain during pulpotomy procedures		Pain during extraction procedures	
Injection		Injection	
Cavity Preparation		Extraction	
Pulp Removal			
Plasement of crown			

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



- B) *Visual analogue scale*



No pain

Pain as bad as it could possibly be

It is a 10 cm line with "no pain" at one end and "pain as bad as it could possibly be" at the other end. The children are asked to rate the level of pain that they are currently experiencing

Pain during pulpotomy procedures		Pain during extraction procedures	
Injection		Injection	
Cavity Preparation		Extraction	
Pulp Removal			
Plasement of crown			

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**Parents' questions about their child's dental treatment**

Statements	Response				
	Agree	Strongly agree	No opinion	Disagree	Disagree Strongly
1. The dentist explained very well why my child needed dental treatment.					
2. I have no concerns about how the local anaesthetic works.					
3. I think the local anaesthetic is doing a good job at helping my child to cope with the treatment					
4. My child coped well with having the local anaesthetic.					
5. The dental team were kind and helpful during my child's treatment.					

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PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



QUESTIONS	Response		
	POSITIVE 	NUTRAL 	Negative 
1. What do you think about numbing your tooth?			
2. Are you glad to have your tooth fixed /extracted?			
3. How did we look after you when you had your treatment?			
4. How friendly were we when you came to see us?			
5. How well did the dentist explain everything about treating your tooth?			
6. Was it ok having your tooth fixed / extracted?			

**Patient questions about attitudes and experiences of dental treatment**

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PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



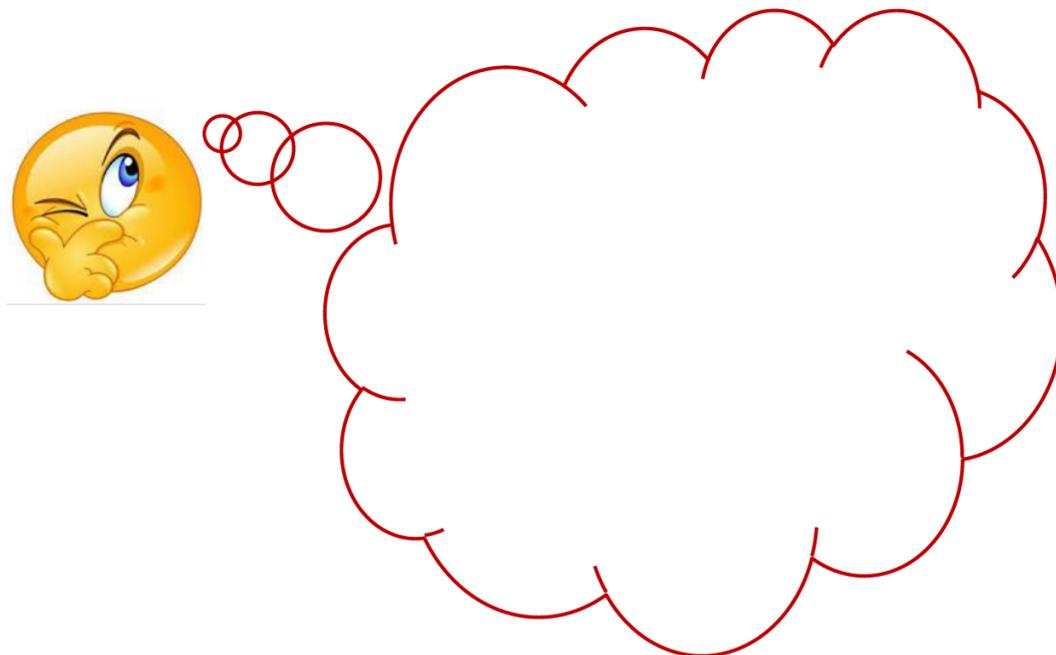
**Child's Behaviour during dental treatment**

Rating	Categories of behaviour	Level of acceptance	Influence on treatment	Child's Behaviour	
				Injection	Treatment
1	Active physical resistance, protests, screaming. Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism.	Definitely negative No acceptance	Treatment cannot be carried out without physical control.		
2	Crying, no cooperation, some evidence of negative attitude but not pronounced (i.e., sullen, withdrawn)	Negative acceptance	Treatment cannot be carried out without undue delay. Raised hands interfering with the treatment.		
3	Signs of resistance such as strained muscles. Reserved attitude. No answers but following directions with cooperation.	positive Reluctant acceptance.	Treatment can be carried out without undue delay. raised hands but no interference with the treatment		
4	Relaxed, calm eyes, talking and showing interest in the procedure. Good cooperation	Definitely Positive acceptance	Treatment can be carried out immediately (after proper information).		

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**What do you think about your dental treatment?**



PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



## Parents Comments;

What do you think about your child experience during the dental treatment?

Is there anything you would like to say about your child having local anaesthetic?

Is there anything you would like to say about your child treatment in general?

What do you think your child found easiest

What do you think your child found hardest

Would you be happy for your child to have dental treatment again?

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



# Follow up

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



Follow up

**Follow up phone call within 24 hours of dental treatment**

Who made the phone call?

Name:

Time:

Who did receive the phone call?

Name (initials):

Or

Relation to the patient:

Was there any adverse event recorded by parents/guardian?\* yes / no

\*Note: If the subject experienced any adverse events, please complete the Adverse Events page

Adverse events	Yes	No
Does your child have any pain?		
Has your child bitten his /her lip or tongue?		
Is your child still numb?		
For how long your child was numb?		
Other		

**Prolonged paraesthesia** was defined as numbness  $\geq$  3 hours post administration of LA injection.  
**Soft tissue injury** was defined as injury to the lips, tongue, or cheek since the dental appointment.  
**Post procedural pain** was defined as non-injection site pain occurring  $\geq$  3 hours after dental treatment.

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



Adverse events record

Adverse Event		Onset Date	End Date	Duration	Outcome	Pattern	Intensity	Relation to study	Action taken	Serious*
		__/__/__	__/__/__							
		__/__/__	__/__/__							
		__/__/__	__/__/__							
		__/__/__	__/__/__							
		__/__/__	__/__/__							
		__/__/__	__/__/__							
<b>Duration(Units)</b> 1. S-Seconds 2. M-Minutes 3. H-Hours 4. D-Days	<b>Outcome</b> 1. Resolved 2. Ongoing	<b>Pattern</b> 1. Continuous 2. Intermittent	<b>Intensity</b> 1. Mild 2. Moderate 3. Severe	<b>Relationship to study</b> 1. Not relate 2. Unlikely 3. Possible 4. Highly possible	<b>Action Taken (regarding the study)</b> 1. None 2. Interrupted 3. Discontinued		<b>Serious</b> 1. No 2. Yes*			
* All serious adverse events must be reported to the study monitor within 24 hours and require special action										

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_

PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



# Study conclusion



PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL:



**INVESTIGATOR DECLARATION**

I confirm that I have reviewed all the data collected in this Log and take responsibility that the information provided by the subject complete.

**Signed by (Investigator)**.....

**Print Name (Investigator)**.....

**Dated (DD/MM/YY)**

--	--	--	--	--	--	--	--



PATIENT IDENTIFICATION NUMBER FOR THIS TRIAL



Dental history		
<b>Treatment</b>		
Treated tooth		
Local anaesthetic used		Amount of LA
Bach number		exp. Date
Technique	IDNB	BI
Procedures		
Patient's behaviour		
<b>Next visit</b>		
<b>Follow up phone call</b>		
Date		
Who make the phone call		
Response *		

\* In case of any adverse event the 'adverse events record' should be filled and attached to this form.

Signed by (Investigator).....

Signed by (clinical supervisor).....

DT11/9936 Trial Master File



# ***Trial Master File***

**Sponsor ID:** DT11/9936  
**EudraCT No:** 2011-004711-23  
**ISRCTN Number:** ISRCTN11415977

DT11/9936 Trial Master File



## ‘Use of Articaine in Children Dentistry’

COMPARATIVE STUDIES OF THE ANAESTHETIC EFFICACY OF 4% ARTICAINES WITH 1:100,000 EPINEPHRINE USED AS MANDIBULAR INFILTRATION VERSUS 2% LIDOCAINE WITH 1:80,000 EPINEPHRINE USED AS INFERIOR DENTAL NERVE BLOCK IN EXTRACTION AND RESTORATION OF MANDIBULAR PRIMARY MOLARS.

### Study numbers:

**Sponsor ID:** DT11/9936

**EudraCT No:** 2011-004711-23

**ISRCTN Number:** ISRCTN11415977

### Principle Investigator

DR. FATMA ALZHRANI  
PHD RESEARCH STUDENT  
CHILD DENTAL HEALTH  
LEEDS DENTAL INSTITUTE

### Chief Investigator and Supervisor 1

PROF. MONTY DUGGAL  
CONSULTANT AND HEAD OF PAEDIATRIC DENTISTRY  
CHILD DENTAL HEALTH  
LEEDS DENTAL INSTITUTE

### Supervisor 2

DR. JINOUS TAHMASSEBI  
ASSOCIATED PROFESSOR IN PAEDIATRIC DENTISTRY  
CHILD DENTAL HEALTH  
LEEDS DENTAL INSTITUTE

DT11/9936 Trial Master File



## Use of Articaine in Children Dentistry

### TRIAL MASTER FILE INDEX

SECTION	TITLE	CONTENTS
1	<b>Study Personnel</b>	Contact details CV's Investigator & Co-investigators
2	<b>Trial Meetings / Visits</b>	Meeting minutes Monitoring/audit visit log/reports
3	<b>Randomisation / Registration</b>	Randomisation/Registration Log Randomisation/registration form
4	<b>Ethics Committees (EC) / Independent review boards (IRB)</b>	Ethics applications/amendments Ethics committee composition Ethics Approval letter/s (all sites) Interim/Annual Report/s Final report to document end of trial All other correspondence with EC/IRB
5	<b>Competent Authorities (CA)</b>	CTA applications CTA approval letter Amendment notification/s Notification of Safety reports/updates Notification of study closure Interim/Annual Report/s Inspection/audit documentation All other correspondence with CA
6	<b>CRF</b>	Copy of blank CRF Signed, dated & completed CRF's
7	<b>Investigational Medicinal Product</b>	Instructions for IMP handling Drug accountability records

DT11/9936 Trial Master File



8	Protocol	Final approved protocol
		All previously approved versions
		Protocol amendments
		Protocol peer review documentation
9	Patients information & consent	Related correspondence
		Patient/Donor Information sheets
		Patient/Donor Consent forms
		Story Book
10	Agreements/ Contracts	Sample GP letter
		All Study contracts/agreements
		Financial agreements
11	Reports	Insurance certificates/statements
		Interim analysis reports
12	SAE's	Final Study Report
		Blank SAE form
		SAE reporting procedure
		Annual safety report
13	Trail Amendments	SUSAR reports – notification to PI's, EC & CA
		All trial amendments
14	General Correspondence	All trial correspondence (fax, phone log, letters, emails, newsletters) not site/patient specific or specific to any other MF section
15	File Notes	General trial file notes to document all deviations or omissions from protocol/GCP etc.

Trial master randomisation log

**Use of Articaine in Children Dentistry**

<b>Study Title</b>	<b>Use of Articaine in Children Dentistry</b>			
<b>Chief Investigator</b>	Monty S Duggal		<b>EudraCT Number (if applicable)</b>	2011-004711-23
<b>Principle Investigator (if different)</b>	Fatma Alzahrani		<b>Rec Number</b>	13/YH/0049
<b>Sponsor</b>	University of Leeds		<b>R&amp;D number</b>	DT 11/9936

Study ID#	Randomisation #	Subject Name (initial)	Treatment Assignment	Date Randomised	Initial
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					

DT11/9936 Trial screening log



## Use of Articaine in Children Dentistry

### Screening Log

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**Study:** Use of Articaine in Children Dentistry

**Site:** LDI, Child Dental Health Department

**PI:** Fatma S Alzaharani

Patent's name	Attended with	1 <sup>st</sup> approached	Clinic	PIS given (Yes/No)	Contact No.

IMP Log

## Use of Articaine in Children Dentistry



<b>Study Title</b>	<b>Use of Articaine in Children Dentistry</b>		
<b>Chief Investigator</b>	Monty S Duggal	<b>EudraCT Number (if applicable)</b>	2011-004711-23
<b>Principle Investigator (if different)</b>	Fatma Alzahrani	<b>Rec Number</b>	13/YH/0049
<b>Sponsor</b>	University of Leeds	<b>R&amp;D number</b>	DT 11/9936

Subject's Study ID#	IMP Used	Batch number	Expiration date
1	Lignocaine	B06 870aa	March 2015
2	Articaine	B07814aa	Nov 2014
3	Articaine	B07814aa	Nov 2014
4	lignocaine	B06 870AA	March 2015
5	Articaine	B07814aa	Nov 2014
6	Articaine	B07814aa	Nov 2014
7	Lignocaine	B06 870 AA	March 2015
8	Articaine	B07814aa	Nov 2014
9	Lignocaine	B06 870 AA	March 2015
10	Articaine	B07814aa	Nov 2014
11	Articaine	B07814aa	Nov 2014
12	Lignocaine	B06 870AA	March 2015

## Delegation of Duties Log

## Use of Articaine in Children Dentistry



<b>Study Title</b>	Use of Articaine in Children Dentistry		
<b>Chief Investigator</b>	Monty S Duggal	<b>EudraCT Number (if applicable)</b>	2011-004711-23
<b>Principle Investigator (if different)</b>	Fatma Alzahrani	<b>Rec Number</b>	13/YH/0049
<b>Sponsor</b>	University of Leeds	<b>R&amp;D number</b>	DT 11/9936

## DELEGATED DUTIES

1. Eligibility Screening	11. Take blood or tissue samples
2. Confirming eligibility (inclusion/exclusion) criteria met	12. Maintain Investigator File
3. Obtain informed consent	13. Maintain Trial Master Site File
4. Trial related medical decisions	14. Maintain regulatory documents
5. Physical exam/Clinical evaluation	15. CRF Completion
6. Documenting in medical notes	16. CRF Corrections / Data Queries
7. Drug accountability	17. Other .....
8. Dispensing study drug	18. Other .....
9. Medical Prescriptions	19. Other .....
10:Reviewing and reporting adverse events, SAEs and SUSARS	20. Other .....

DT11/9936

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## Delegation of Duties Log

## Use of Articaine in Children Dentistry



All those involved in the above study must read the protocol (and amendments if applicable) and complete any necessary training.

Staff must only perform tasks for which they have delegated responsibilities as documented on this log and initialled by the PI.

Name (print)	Trial Role	Delegated Duties	Researcher Signature	Researcher Initials	Involved From	Involved To	PI Signature	Date of PI Signature
Fatma Alzahrani Monty Duggal Jinous Tahmassebi	Principle investigator Chief investigator Supervisor	Eligibility Screening						
Fatma Alzahrani Monty Duggal Jinous Tahmassebi	Principle investigator Chief investigator Supervisor	Confirming eligibility (inclusion/exclusion) criteria met						
Fatma Alzahrani Monty Duggal	Principle investigator Chief investigator	Obtain informed consent Trial related medical decisions						
Fatma Alzahrani Monty Duggal Jinous Tahmassebi	Principle investigator Chief investigator Supervisor	Physical exam/Clinical evaluation						
Fatma Alzahrani	Principle investigator	Documenting in medical notes						
Fatma Alzahrani	Principle investigator	Drug accountability						

DT11/9936

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Delegation of Duties Log

**Use of Articaine in Children Dentistry**



Fatma Alzahrani	Principle investigator	Dispensing study drug						
Fatma Alzahrani Monty Duggal Jinous Tahmassebi	Principle investigator Chief investigator Supervisor	Reviewing and reporting adverse events, SAEs and SUSARS						
Fatma Alzahrani	Principle investigator	Maintain Investigator File						
Fatma Alzahrani	Principle investigator	Maintain Trial Master Site File						
Fatma Alzahrani	Principle investigator	Maintain regulatory documents						
Fatma Alzahrani	Principle investigator	CRF Completion						
Fatma Alzahrani	Principle investigator	CRF Corrections / Data Queries						

DT11/9936 Investigator Log



## Use of Articaine in Children Dentistry

### Investigator Log

---

**Study:** Use of Articaine in Children Dentistry

**Site:** LDI, Child Dental Health Department

**PI:** Fatma S Alzahrani

Study ID #	Enrolment				Randomisation		Treatment
	Subject Name (last, first, initial)	D.O.B	ID	Date Enrolled	Randomisation #	Randomised Date	
1							
2							
3							
4							
5							

DT11/9936 Adverse events log

**Use of Articaine in Children Dentistry**



Adverse events record (log)

Adverse Event	Onset Date	End Date	Duration	Outcome	Pattern	Intensity	Relation to study	Action taken	Serious*
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
	__/__/__	__/__/__							
<b>Duration(Units)</b> 1. S-Seconds 2. M-Minutes 3. H-Hours 4. D-Days	<b>Outcome</b> 1. Resolved 2. Ongoing	<b>Pattern</b> 1. Continuous 2. Intermittent	<b>Intensity</b> 1. Mild 2. Moderate 3. Severe	<b>Relationship to study</b> 1. Not relate 2. Unlikely 3. Possible 4. Highly possible	<b>Action Taken (regarding the study)</b> 1. None 2. Interrupted 3. Discontinued			<b>Serious</b> 1. No 2. Yes*	
* All serious adverse events must be reported to the study monitor within 24 hours and require special action									

THIS FORM COMPLETED BY:

Name:..... signature:..... Date \_\_/\_\_/\_\_

**DT11/9936 Trial Meeting**



## **Use of Articaine in Children Dentistry**

**Date:**

**Time:**

**Meeting:**

---

**Attendees**

**Agenda**

**Update on on-going trial**

**Next Meeting**

## ROOM TEMPERATURE MONITORING FORM

Hospital Site: LDI – Children Department

Department /Room location: paediatric clinic -

Thermometer location: Drugs Cupboard

Date	Temperatures			Signature	Action Taken If Required
	Min	Current	Max		
26-09-14					
29-09-14					
01-10-14					
03-10-14					
06-10-14					
08-10-14					
10-10-14					
13-10-14					
15-10-14					
17-10-14					
20-10-14					
22-10-14					
24-10-14					
27-10-14					
29-10-14					
31-10-14					
03-11-14					
05-11-14					
07-11-14					
10-11-14					
12-11-14					

Temperatures should be monitored at least three times a week. Action should be taken if the temperature deviates from the accepted range 05.00 °C to 25.00 °C .

**We are recruiting patients for the following study:**

Sponsor ID: DT11/9936  
EudraCT No: 2011-004711-23  
ISRCTN Number: ISRCTN11415977

**COMPARATIVE STUDIES OF THE ANAESTHETIC  
EFFICACY OF 4% ARTICAIN VS 2%  
LIDOCAINE IN EXTRACTION AND RESTORATION  
OF MANDIBULAR PRIMARY MOLARS**

I would be grateful if you could refer to me any patient you come across on consultant clinic.

**The patients should meet the following****Inclusion criteria:**

- + Children aged 5 to 9 years
- + Requiring extraction /restoration of primary mandibular molars teeth under local anaesthetic
- + Tooth has no history of infection

There will be a NOTE BOOK with trial name on it at the nurses' desk in the clinic

It will be highly appreciated if you could put the patient's sticker in the designated box in the note book

**Contact: Fatma Alzahrani**

**email: [ml09fsa@leeds.ac.uk](mailto:ml09fsa@leeds.ac.uk)**

**We are recruiting patients for the following study:**

**COMPARATIVE STUDIES OF THE ANAESTHETIC EFFICACY OF 4% ARTICHAINE VERSUS 2% LIDOCAINE IN EXTRACTION AND RESTORATION OF MANDIBULAR PRIMARY MOLARS**

**The patients should meet the following criteria**

- Children aged 5 to 9 years**
- Requiring extraction of lower molar (lower E or D) – NOT REMAINING ROOTS**
- Requiring pulpotomy of lower molar (lower E or D)**

**If you have any patient meeting these criteria please inform one of the senior nurses or inform the clinical supervisors**

Sponsor ID: DT11/9936  
EudraCT No: 2011-004711-23  
ISRCTN Number: ISRCTN11415977

