The Effects of Local Anaesthetic Infiltration via Wound Catheters versus Epidural Analgesia on Recovery Following Open Liver Resection

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Published Work From Thesis

A version of part of chapter 2 of this thesis has been published in a peer-reviewed journal as have the results of this thesis.

1. **Bell R**, Pandanaboyana S, Prasad KR. Epidural versus local anaesthetic infiltration via wound catheters in open liver resection: a meta-analysis. ANZ J Surg. 2015. 85(1-2):16-21

2. **Bell R**, Ward D, Jeffery J, Toogood GJ, Lodge JPA, Rao K, Lotia S, Hidalgo E. A Randomized Controlled Trial Comparing Epidural Analgesia vs. Continuous Local Anaesthetic Infiltration via Abdominal Wound Catheter in Open Liver Resection. Ann Surg. 2019 Mar;269(3):413-419

Presented Work From This Thesis

The results or part thereof of this thesis have been presented and published in abstract form at the following international conferences:

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Abstract

Introduction

Epidural analgesia provides satisfactory pain relief but is not without unwanted side effects or a significant failure rate. New multi-modal methods of delivering postoperative analgesia are being developed which aim to minimize side effects and enhance recovery. The aim of this thesis was to compare recovery following open liver resection (OLR) between patients receiving thoracic epidural (EP) or abdominal wound catheters plus patient-controlled analgesia (AWC-PCA).

Method

In order to address the aim of this thesis the following studies were developed:

1. A systematic review of current modalities used for post-operative analgesia and current evidence for ERAS protocols in liver surgery.
2. A systematic review and meta-analysis comparing outcomes between EP and AWC following open liver resection. This was performed according to PRISMA guidelines.
3. An open-label randomized controlled trial allocating participants 1:1 to receive either EP or AWC-PCA within an enhanced recovery protocol. Primary outcome was length of stay (LOS). Secondary outcomes included functional recovery, pain scores, peak flow, vasopressor, fluid requirements and postoperative complications.

4. An assessment of the impact the two methods of analgesia have on the systemic inflammatory response by analysing and comparing cytokine levels at baseline (Day 0), Day 1 and Day 3 post-surgery in patients enrolled in the randomized controlled trial.

Results

For parts 1 & 2, five studies were included in the analysis. Pain scores were significantly better in the EP group on postoperative day 1 but comparable thereafter. The complication rate was worse in the EP group. Length of stay was comparable as were the other secondary outcomes. The included studies were of generally poor quality with only 2 randomised controlled trials specific to liver resection published.

For part 3, between April 2015 and November 2017, 83 patients were randomized to EP (n=41) or AWC-PCA (n=42). Baseline demographics were comparable. No difference was noted in LOS (EP 6 days (3-27) vs. AWC-PCA 6 days (3-66), p=0.886). Treatment failure was 20% in the EP group vs. 7% in the AWC-PCA (p=0.09). Preoperative anaesthetic time was shorter in the AWC-PCA group, 49 min vs. 62 min (p=0.003). EP patients required more vasopressor support immediately postoperatively on day 0 (14% vs 54%, p=<0.001) and day 1 (5% v 23%, p=0.021). Pain scores were greater on day 0, afternoon of day 1 and morning of day 2 in the AWC-PCA group however were regarded as low at all time points. No other significant differences were noted in IV fluid requirements, nausea/sedation scores, days to open bowels, length of HDU and postoperative complications.

For part 4, thirty patients were recruited into the cytokine analysis section of this study, 17 in the AWC-PCA group and 13 in the EP group. Patients in the EP arm were

more likely to be ASA II and have a more extensive liver resection. Interleukin-9 and MIP-1β levels were significantly lower with time in the AWC-PCA arm. There were no other differences in cytokine levels between the two groups.

Conclusion

AWC-PCA was associated with reduced treatment failure and a reduced vasopressor requirement than EP up to two days post-operatively. Whilst the use of AWC-PCA did not translate into a shorter LOS in this study it simplified patient management after OLR. The inflammatory response was comparable. AWC-PCA was not inferior to EP when used in patients undergoing open liver resection. EP cannot be routinely recommended following open liver resections based on the evidence gathered throughout this study.

Contents

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Abbreviations

ALPPS – Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy

AWC – Abdominal Wound Catheter

ASA – American Society of Anaesthesiologists

BMI – Body Mass Index

CCA - Cholangiocarcinoma

CNS – Central Nervous System

CRLM – Colorectal Liver Metastases

CI – Confidence Interval

CONSORT – Consolidated Standardised Reporting of Trials

CT – Computed Tomography

CUSA – Cavitron Ultrasonic Surgical Aspirator

CVP – Central venous Pressure

ERAS – Enhanced Recovery After Surgery

EP – Epidural

GA – General Anaesthetic

GM-CSF – Granulocyte- macrophage colony stimulating factor

HCC – Hepatocellular carcinoma

HDU – High-Dependency Unit

ITU – Intensive Treatment Unit

IFN - Interferon

IL - Interleukin

ISRCTN – International Standard Randomised Controlled Trial Number

IV – Intravenous

LOS – Length of Stay

MELD – Model for End-Stage Liver Disease

MIP – Macrophage Inflammatory Protein

NET – Neuroendocrine Tumour

NICE – National Institute for Clinical Excellence

OLR – Open Liver Resection

PCA – Patient Controlled Analgesia

POD – Postoperative Day

RCT – Randomised Controlled Trial

RCoA – Royal College of Anaesthetists

SD – Standard Deviation

SIR – Systemic Inflammatory Response

TAP – Transversus Abdominis Plane

TIVA – Total Intravenous Anaesthesia

TNF – Tumour Necrosis Factor

VEGF – Vascular Endothelial Growth Factor

Chapter 1

Introduction

1.1 - The Scope of Liver Disease

From a surgical perspective the liver is a frequent site for both benign and malignant disease. Benign liver lesions are common and can be difficult to differentiate from either primary or secondary liver malignancies. Benign liver lesions can frequently be asymptomatic and are often identified incidentally on radiological imaging for an unrelated problem [1]. Although benign liver lesions tend to be asymptomatic, they can produce symptoms due to mass effect or present acutely with symptoms related to haemorrhage, necrosis or infection [1]. The management of benign liver lesions can vary hugely from simple observation to complex hepatic resection or even liver transplantation [2, 3].

The liver is also a common site for cancer to metastasize to, however, primary liver cancers, particularly hepatocellular carcinomas (HCCs), are becoming increasingly prevalent. Whilst multi-modal treatments for such cancers are increasing, surgery remains the mainstay of treatment when aiming to cure [4].

Hepatocellular Carcinoma

HCC accounts for approximately 90% of all primary liver malignancy and over 5% of all cancers and is currently the commonest cause of cancer related death [5, 6]. It is more frequent in male patients and liver cirrhosis precedes the vast majority of cases. The risk of HCC developing in

these patients during their lifetime is increasing in part due to better medical management leading to increased survival. Curative management of HCC may be achieved by surgical resection, ablation or by transplantation [7, 8]. Resection and ablation are readily available but are associated with a high tumour recurrence rate. In addition, *de novo* tumours are common as the diseased background liver parenchyma remains untreated. There is a consensus that liver transplantation offers the optimal long-term results for patients with HCC although this solution cannot be offered to all patients given the shortage of suitable organs and the restricted eligibility criteria [9, 10].

In patients with no, or very minimal, cirrhosis the treatment of choice is liver resection as the liver remnant has a high capacity to regenerate allowing major resection to be performed. Perioperative mortality in these patients should be less than 1% with a morbidity of approximately 15% and overall survival in these patients is over 50% at 5-years [11].

Liver resection in patients with a background of well-established liver cirrhosis is more challenging. Liver resection in these patients has several limitations. Recurrence rates remain high as background cirrhosis persists. Cirrhosis is a major risk factor for postoperative morbidity and the diseased liver requires a parenchymal sparing approach whereas oncologically, wider margins may be needed [12]. Liver resection is however a valid treatment option in well selected patients, mainly Child-Pugh A or those with a low Model for End Stage Liver Disease (MELD) score with a single tumour and low morbidity has been reported in these groups. However, in Child-Pugh B and C groups, patients are at risk of liver failure after laparotomy alone [13]. In some circumstances, resection is the only option when the tumour burden precludes transplantation. Additionally, with resection, there is no need for lifelong immunosuppression and donor grafts can be allocated to other patients on the waiting list

without other options. Offering liver resection as curative treatment is therefore reasonable and less complex than liver transplantation [14].

In recent years, there has been increasing interest in the management of the future liver remnant with CT volumetry studies and increased use of pre-operative portal vein embolization to stimulate hypertrophy in the future liver remnant. This has become standard practice in colorectal liver metastases (CRLM) after extensive chemotherapy and in liver resection in patients with cirrhosis has been shown to reduce post-operative complications, reduce intensive care and total hospital stay [15]. Modification of surgical technique has also been linked to improved long-term survival with anatomical resection and wide margins favoured over parenchymal sparing surgery and limited margins due to tumour spread through microvascular invasion. This is however linked to tumour size and differentiation. Overall, when liver resection for patients with background cirrhosis is adopted the annual recurrence rate is reported to be 20 % with an estimated 5-year disease-free survival close to 37 % and overall survival as high as 68% [16-18].

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after HCC. These tumours arise from the peripheral intrahepatic biliary radicles, thus differentiating them from hilar (Klatskin) and distal common bile duct cholangiocarcinomas. This tumour is associated with a very poor overall prognosis and its incidence is increasing in the Western world. This is likely to be explained by improved identification of this tumour as well as increasing obesity related, non-alcoholic fatty liver disease or chronic hepatitis C infection [19, 20]. Surgical resection is, at present, the only curative treatment with only a debatable role for liver transplantation in small cholangiocarcinomas. As this tumour usually presents at an

advanced stage and can extend to major portal or hepatic vein branches a major resection is often required in 75-80% of cases [21]. This includes resection of the common bile duct in over 20% of cases and is associated with significant postoperative mortality [22]. In addition, up to one-third of patients will have a contraindication to resection at laparotomy and of those resected 25% of patients will have an R1 or R2 resection [22, 23]. The overall survival for patients undergoing R0 resection for intrahepatic cholangiocarcinoma is reported between 15-40% at 5 years [24, 25].

Peri-Hilar Cholangiocarcinoma (formerly known as Klatskin Tumour)

Hilar cholangiocarcinoma is the most common type of cholangiocarcinoma, accounting for approximately 60% of all cases (intrahepatic, hilar and distal) [26, 27]. These tumours most commonly present with jaundice with a tendency to local spread rather than distant metastases. Complete surgical resection is essential for long-term survival in patients presenting with hilar cholangiocarcinoma. However, patients frequently present with advanced disease involving the hepatic artery, portal vein and caudate lobe. This has meant that historically only about 20% of patients were deemed 'resectable'. Consequently, major hepatic resections including bile duct and frequently vascular resection is required to achieve complete microscopic margin negative resection (R0) [28, 30]. Morbidity associated with such major resections is understandably significant with rates as high as 75% reported with mortality rates between 5-15% [26, 31, 32]. More recently, the use of preoperative portal vein embolization has been associated with a reduction in morbidity and mortality [33, 34]. With resection, 5-year survival rates approaching 40% have been reported although recurrence rates have disappointingly been between 50-75%. The most important factor for recurrence is complete surgical excision, although tumour differentiation and lymph node involvement

are important biological predictors [28, 29, 35 - 37]. For these reasons only a very few centres are advocating liver transplantation under strict criteria and as part of a multimodal therapeutic approach [38].

Colorectal Liver Metastases

Colorectal cancer is the most prevalent gastrointestinal malignancy and the second most frequent cause of cancer related death in the Western world [39]. The liver is the most common site for metastasis and may be the only site in 30-40% of cases [40]. At presentation, 20-25% of patients will have liver metastases and up to 50% will develop them following resection of the primary colonic tumour [41]. At present, surgery remains the only treatment aimed at curing patients with CRLM [7]. Originally only about 20% of patients were suitable for curative surgery at presentation, however, with improved preoperative staging, developments in systemic chemotherapy, new surgical strategies and multidisciplinary management of colorectal liver metastases (CRLM), increasing numbers of patients are being considered suitable. Resected CRLM are associated with a 5-year survival of 40-50% and a 10-year survival of 25%, although improved rates up to 67% at 5-years have been seen when combining surgery with chemotherapy [42]. Criteria for resection have been relaxed and are now based on whether a macroscopically complete resection can be completed with an adequate future liver remnant. Currently, apart from patient fitness issues, the following are considered to be the only contraindications to resection: an untreatable primary tumour, bone or CNS metastases, widespread pulmonary or uncontrolled pulmonary disease and extensive nodal disease [7, 43]. Typically, approximately 20% of patients are deemed to be resectable although a variety of strategies are now being employed to convert initially un-resectable patients to surgery. These include neo-adjuvant chemotherapy, portal vein embolization, two-stage

hepatectomy, redo hepatectomy, Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) and surgery for extrahepatic (usually oligometastatic) colorectal disease [44 – 50]. However, median survival without treatment for CRLM is approximately 8 months from presentation with only 3-5% of patients surviving 5 years, although this is dependent on disease burden [50, 52-54].

Neuroendocrine and Non-Colorectal Liver Metastases

Whilst colorectal cancer is the most common source of liver metastases, it is also possible for almost any solid tumour to metastasize there. These may be isolated liver metastases or associated with disseminated disease. Gastrointestinal tract cancers reach the liver via the porto-venous route whereas non-GI cancers spread via the systemic circulation and are thus usually indicative of disseminated disease. Non-colorectal liver metastases most commonly arise from the GI tract and can be broadly broken down into neuroendocrine and non-neuroendocrine groups. Neuroendocrine tumours (NETs) are usually indolent with survival following resection of liver metastases associated with 5- and 10-year survival of 77% and 50% respectively [54]. Resection for neuroendocrine metastases is an increasingly accepted treatment strategy although much of the evidence for resection of non-colorectal non-neuroendocrine liver metastases is based on retrospective studies.

Resection for metastatic NETs leads to improved overall survival when compared with patients undergoing conservative treatment. Improved survival is also seen in patients having R1 and even R2 resections with 5-year survival as high as 70%. This is likely a result of reducing tumour burden which in addition has a benefit in symptom management [55-57].

Resection of liver metastases from a variety of primary tumours such as breast, renal, melanoma, ovary, lung and endometrium have all been reported. In general, surgical resection of these metastases is controversial with only poor-quality evidence supporting its role. In breast cancer, isolated liver metastases are uncommon and reported survival after liver resection is variable. It appears that survival in breast liver metastasis patients is closely linked to pre-operative chemotherapy response and surgery may be cyto-reductive rather than a curative procedure [58]. With regards to other liver metastases from other sites, it is generally impossible to draw strong conclusions or recommendations for surgery with the evidence available [7].

1.2 - Enhanced Recovery After Surgery (ERAS)

Approximately 2350 liver resections were performed in England in 2015, mainly for primary liver cancers and metastatic colorectal cancer with limited spread to the liver [59]. Liver resection is a major and complex operation with an in-hospital death rate of 1% and a short-term complication rate of roughly 20% although it remains the main treatment modality in such patients [60]. Perioperative care for patients who are undergoing liver resection varies widely from unit to unit and surgeon to surgeon, with a lack of evidence base for much of the care patients receive. In the 1990s, Kehlet et al developed an 'enhanced recovery pathway' to improve outcomes in patients undergoing colorectal surgery and demonstrated faster recovery, reduced morbidity and shorter length of stay [61]. Since then the concept of enhanced recovery after surgery (ERAS) has grown with these multi-modality pathways adopted by many surgical specialities led within the UK by pioneers such as the late Professor Kenneth Fearon from Edinburgh [62-64]. Current evidence suggests a benefit in colorectal, urological and gastric surgery with a growing body of evidence for hepato-biliary surgery [65-67].

ERAS pathways aim to streamline and standardise patient care by using varying methods to reduce surgical stress and ultimately reduce medical complications and improve patient recovery. These can be broken down into pre-, intra- and post-operative factors.

Pre-operatively, ERAS Society recommendations are that patients receive counselling and education prior to surgery which improves patient involvement in decision making and can also improve motivation post-operatively, thereby increasing compliance with the pathway [68, 69]. In addition, avoidance of prolonged fasting and carbohydrate loading the evening before surgery has been shown to reduce insulin resistance as well as nausea, thirst and malaise. At present, the role of carbohydrate loading is well established in colorectal pathways although

the ERAS Society recommendations for liver surgery were only able give a weak recommendation based on currently available evidence [70-72]. Nutrition is an eminently modifiable factor in patients scheduled for major surgery. Malnourished patients are at increased risk of complications postoperatively, and nutrition screening is an essential part of pre-operative workup. Patients with a low body mass index (BMI) or significant weight loss should receive nutritional supplementation in the week preceding surgery or, in severe cases, have surgery postponed whilst oral, enteral or even parenteral feeding is established. In addition, the use of antibiotic prophylaxis, venous thromboembolism prophylaxis and avoidance of long acting anxiolytics as a premedication are all recommended [67, 73, 74].

Intraoperative factors that can be modified include the type of surgical incision and the surgical approach. Minimally invasive (laparoscopic) approaches to 'minor' liver resection, particularly in the left-lateral and anterior segments, have become the standard practice and have been demonstrated to reduce length of stay [75]. However, the ORANGE-II study comparing open versus laparoscopic left-lateral sectionectomy had to be discontinued due to slow recruitment with no differences seen up to that point [76]. The use of patient warming systems is recommended as intraoperative hypothermia is associated with increased blood loss and the need for transfusion as well as cardiac and non-cardiac complications, although evidence specific to liver surgery is lacking [77-79].

Fluid management is another important aspect of perioperative care, with fluid overload being associated with increased peri-operative morbidity [80]. Poor fluid management can also lead to postoperative ileus, delayed gastric emptying and delayed discharge from hospital [81]. With regards to hepatic resection, fluid balance is particularly important with a variety of strategies used to minimise intraoperative blood loss and the ischaemia-reperfusion injury associated with hepatic transection. Such techniques include reverse Trendelenburg

positioning, restricted fluid intervention, maintenance of low CVP as well as surgical techniques such as Pringle's manoeuvre and total vascular exclusion [82].

Goal-directed fluid therapy refers to operative and immediate postoperative techniques aimed at modifying the haemodynamic status of patients undergoing major surgery. The ultimate goal of these techniques is to achieve optimal oxygen delivery while avoiding the deleterious complications associated with over- and under-resuscitation [83]. The response to fluid can be assessed by measuring a number of cardiovascular parameters which vary during the ventilatory cycle. These include stroke volume, pulse pressure and systolic pressure which are more sensitive than blood pressure or pulse rate. The size of these variations also corresponds to the degree of hypovolaemia [84]. The evidence regarding goal-directed fluid therapy shows that whilst it is a safe technique, the results have been mixed, although several meta-analyses showed a reduction in nausea, haemodynamic instability and a shorter hospital stay following major surgery [85]. However, the benefit of goal-directed fluid therapy in the context of enhanced recovery appears to be less certain. This is likely to be because the patient is not hypovolaemic at induction of anaesthesia [84]. Studies looking at goal-directed fluid therapy in patients who were hypovolaemic at induction found a reduction in length of stay compared to those not receiving fluid guided by oesophageal Doppler. The patients in this study also had fewer complications [86]. An RCT comparing goal-directed fluid therapy using stroke volume variation to standard perioperative resuscitation in patients undergoing liver resection found less intraoperative fluid was given with goal-directed fluid therapy although postoperative complications were comparable. However, lower intraoperative fluid volume was independently associated with decreased morbidity in the entire cohort [83]. However, other studies within colorectal surgery have found no such difference [87, 88]. Despite this, the

use of goal-directed fluid therapy has been endorsed by the Enhanced Recovery Partnership and NICE [89, 90].

Postoperatively, ERAS pathways focus on good post-operative analgesia, early mobilization, early reinstatement of diet and avoidance of nausea and vomiting. In one RCT, early reinstatement of food resulted in faster return of bowel function when compared with a more conservative 'nil by mouth' and enteral tube feeding regime [91]. Similarly, the use of routine nasogastric tube placement has been associated with increased pulmonary complications including post liver resection and thus recommendations have been against its routine use [92, 93]. Postoperative analgesia is a paramount part of ERAS with many different modalities described. Traditionally, thoracic epidural has been considered the gold-standard for post-operative analgesia. However, newer, multi-modality regimes are gaining popularity. Differing analgesic modalities are discussed in more detail later (Chapter 1.3).

In hepatobiliary surgery, ERAS pathways have only been introduced relatively recently when compared with other surgical specialities. Multiple studies have been published comparing ERAS protocols with a more traditional care in liver surgery. This includes a combination of retrospective and prospective studies as well as RCTs. Almost all studies demonstrated a shorter length of stay with the use of an ERAS protocol following liver surgery. In addition, some RCTs demonstrated a significant reduction in complications [94, 95] whereas some non-randomised studies have failed to show such a difference [96 - 103]. The reduction in overall complication rate is generally thought to relate to a reduction in medical complications, with surgical complication remaining relatively constant [94]. High compliance with ERAS protocols is associated with a reduction in length of stay and improved outcome and, conversely, poor

compliance is associated with increased readmission rates [104]. Improving compliance rates with the ERAS protocols is obviously an important area for improvement, although even in ERAS protocols with low compliance (<70%) its use has been shown to improve short-term outcomes [105].

The evidence regarding the use of ERAS pathways in liver surgery has largely been based on small studies which have lacked standardisation and therefore strong recommendations about their use have been difficult to make [67]. In addition, compliance with the protocols in these studies is variable. However, in recent years a number of meta-analyses of the RCTs that have been published have demonstrated that ERAS pathways for liver resection are feasible, efficient and associated with a reduced length of stay and fewer complications [95, 106-110]. In reality, ERAS is now here to stay, and studies are needed that are specific to hepatobiliary surgery and will help to develop the various components of future ERAS protocols. In fact, one might argue that nowadays not implementing ERAS would be a departure from best practice following liver surgery.

1.3 - Post-Operative Analgesia

Good post-operative pain control is essential after any major surgery and is a fundamental part of all ERAS protocols. It allows early mobilisation, helps to reduce post-operative complications, reduces patient distress, cost and length of stay [107, 111-115]. There are numerous different methods of delivering postoperative pain relief, ranging from simple oral analgesics to regional anaesthesia. Following major abdominal surgery, the recognised 'gold standard' has generally been considered to be epidural analgesia [114].

1.3.1 Epidural Analgesia

Thoracic epidural analgesia (EP) is a major component of acute pain services and is primarily used to treat acute pain following major surgery. It is one of the most commonly utilised regional anaesthetic techniques with thoracic epidural consistently being shown to deliver good analgesia, improve post-operative pulmonary function, attenuate the stress response and allow early oral intake [114, 116, 117]. It has also been well established that thoracic epidural with local anaesthetic reduces the length of postoperative ileus when compared to systemic opioids following abdominal surgery [118, 119], and it can also reduce pulmonary morbidity [120]. The indication for thoracic epidural is generally considered to be moderate-to-large thoracic or upper abdominal incisions, and it is commonly used in combination with general anaesthesia in patients undergoing major abdominal surgery. Multiple studies have demonstrated the benefit of thoracic epidural, including the MASTER Anaesthesia trial. This was a large RCT which compared general anaesthesia and epidural plus postoperative epidural to IV opioid patient controlled analgesia (PCA) in high-risk patients with significant pre-operative comorbidity. It found a significant reduction in respiratory failure and improved

pain scores in the epidural group [121]. As such, it has been considered by many to be the gold standard for postoperative analgesia and has been incorporated into many ERAS protocols. There is also evidence that the use of EP is associated with significant reductions in postoperative morbidity and mortality, although subsequent RCTs have not confirmed this [114]. EP also has some potential advantages specific to liver surgery. This primarily relates to the sympathetic blockade associated with EP which can be used to maintain a low central venous pressure. This in turn can minimise blood loss and reduce transfusion requirements [94].

The choice of analgesia to be infiltrated with an epidural catheter can vary from local anaesthetic to opioids, or a combination of the two, with the decision usually dependent on patient factors. Use of local anaesthetic alone has shown comparable pain relief to a combined approach, but with a reduction in postoperative ileus [122]. However, the use of local anaesthetic alone is often limited by hypotension although it can be used in patients with obstructive sleep apnoea or significant side-effects to opioids [120]. There is no clear evidence that thoracic epidural with opioid alone is advantageous with the most common scenario being local anaesthetic and opioid used in combination. This method aims to use the two synergistically and reduce dose related side effects associated with larger doses of either drug alone [120].

Whilst epidural analgesia has been shown to provide superior pain control when compared to other modalities, such as PCA alone, it is not without risk or side effects. Placement of a thoracic epidural catheter is generally considered to be of higher risk than a lumbar epidural although the risks with both techniques are considered to be small [120]. One study analysing

4185 patients undergoing thoracic epidural found a complication rate of 3.1%, which included unsuccessful placement (1.1%), dural puncture (0.7%), radicular pain (0.2%) and peripheral nerve lesions (0.2%) [123]. Another prospective study of 5628 patients found an overall epidural failure rate of 22%, with almost 70% of these removed due to accidental dislodgement [124]. Whilst other publications have reported rates of epidural failure (inadequate analgesia or failed insertion) as high as 30% [112-115, 125]. Other side effects include blockade of the sympathetic nervous system leading to hypotension requiring increased volumes of intravenous fluid and even vasopressors to maintain an adequate blood pressure [112-115]. This is in addition to a growing body of evidence that increased volumes of intraoperative fluid can negatively impact on patient recovery [126]. The insertion and ongoing management of epidurals is also time consuming and requires specialist input from an acute pain or 'out of hours' service, and even an on-call anaesthetist. This can obviously have a huge impact on service provision. Whilst the complications associated with epidural analgesia are rare, they can be potentially devastating such as epidural haematoma and abscess, although these are exceedingly rare [127, 128]. This is particularly relevant in liver surgery where patients can develop a transient post-operative coagulopathy which potentially increases the risk of such complications.

1.3.2 Patient Controlled Analgesia

Patient controlled intravenous opiate analgesia is a simple method to implement that is already commonly used for postoperative and acute pain. The pain relief provided at rest is good but not without unwanted side effects due to opioid use [129]. Nausea and vomiting are frequently seen with intravenous opioid use, as are pruritus, constipation and confusion. However, less commonly, but more seriously, sedation and respiratory depression can also be seen. PCA has been shown to be more effective than the intermittent administration of intramuscular or subcutaneous morphine. However, when compared with epidural analgesia, both continuous and patient controlled, pain relief was inferior with PCA regardless of operation type, analgesic agent and method of pain assessment, although much of the literature is contradictory [130-133]. Interestingly, an RCT comparing intravenous morphine PCA with epidural analgesia following cardiac surgery showed no difference in length of stay, pain scores, quality of recovery or morbidity with higher nausea scores in the epidural group [134]. There are also RCTs published comparing the two techniques following gynaecological surgery showing no difference in pain relief [135]. Schenk et al published a double blinded RCT following major spinal surgery which concluded that epidural analgesia provided superior pain control with a greater patient satisfaction [136]. Similar studies in thoracic surgery, transplantation and general surgery have also showed epidural analgesia to be superior [137]. Poor postoperative pain control is also associated with impaired pulmonary function following major surgery. Panaretou et al demonstrated improved pulmonary function in patients receiving epidural analgesia compared to PCA in patients with chronic obstructive pulmonary disease undergoing open infra-renal abdominal aortic aneurysm repair [138]. A meta-analysis of RCTs has subsequently been performed demonstrating that pain relief with epidural analgesia is superior to that provided by opioid PCA regardless of operation [130].

Recently, several studies have been published comparing epidural with PCA following liver resection. One retrospective study found largely comparable outcomes between the two groups although the epidural group underwent more major resections and required less IV analgesia than the PCA group [139]. A randomised trial comparing epidural with PCA following major hepato-pancreato-biliary surgery found improved pain relief, better patient experience and less opiate use in the epidural group with comparable length of stay and complications [140].

1.3.3 Intrathecal Morphine

Intrathecal morphine has been used for postoperative analgesia since the 1970s, although its popularity was limited due to concerns regarding high rates of respiratory depression [141-143]. More recently, its popularity has increased again with the use of smaller doses in an attempt to limit such side effects. Within the field of hepatobiliary surgery, intrathecal morphine has been compared to numerous other methods of delivering postoperative analgesia with mixed results. Several studies have compared epidural to intrathecal morphine following hepatectomy and found no difference in resting or dynamic pain scores [144, 145], although improved pain scores were seen when epidural and intrathecal morphine were combined and compared to a group receiving only intrathecal morphine [146]. Length of stay was also found to be shorter in one RCT comparing epidural to intrathecal morphine [144]. Several RCTs have also compared intrathecal morphine to either placebo or PCA, with both finding improved pain scores albeit without differences in complication rate between PCA and intrathecal morphine [147 - 148]. Interestingly, Dichtwald et al compared preoperative intrathecal morphine to intraoperative intravenous remifentanil during hepato-pancreatic surgery and found that pain control was superior in the intrathecal morphine group up to 3 days postoperatively [149].

However, Kasivisvanathan et al found in their prospective study that intrathecal morphine plus a fentanyl PCA was associated with worse pain scores, shorter length of stay and less vasopressor support than epidural. However, they noted that intraoperative blood loss was higher than the thoracic epidural group [150]. Sakowska et al compared patients undergoing hepato-pancreato-biliary surgery who received either thoracic epidural, intrathecal morphine plus opiate PCA or PCA alone. This study demonstrated a reduced incidence of postoperative hypotension, reduced intravenous fluid requirement, shorter length of stay and fewer respiratory complications in favour of intrathecal morphine when compared to thoracic epidural [151].

A further RCT comparing local anaesthetic infiltration with 0.5% ropivacaine via a wound catheter with intrathecal morphine followed by continuous infusion of fentanyl found that pain scores were better in the intrathecal morphine group for the initial 12 hours postoperatively but comparable beyond this. However, the time to first pass flatus was earlier in the wound catheter group [152].

1.3.4 Transversus Abdominis Plane (TAP) and Rectus Sheath Blocks

Regional anaesthesia of the abdominal wall can provide excellent pain relief following a variety of abdominal operations. It has however been noted that these do not provide analgesia to the abdominal viscera and therefore must be used as part of a multimodal technique. Historically, these blocks were performed using anatomical landmarks and clinically feeling 'pops' as the needle crossed the fascial planes. More recently, ultrasound has been increasingly used to visualise correct needle placement and the spread of local anaesthetic [153]. Specific nerve blocks that have been described include the rectus sheath block. This aims to block the terminal branches of the 9-11th intercostal nerves, which run

between the internal oblique and transversus abdominis muscle before piercing the posterior wall of the rectus abdominis muscle. They terminate in an anterior cutaneous branch supplying the skin of the umbilicus.

The TAP block aims to block the sensory nerves of the abdominal wall before they enter the musculature to innervate the abdomen by infiltrating with a large volume of local anaesthetic into the plane between the transversus abdominis muscle and the internal oblique. This plane contains the nerves from T7 to L1. This was initially described using the lumbar 'triangle of Petit' which is bound by the external oblique anteriorly, the latissimus dorsi posteriorly and the iliac crest inferiorly. Good postoperative analgesia and reduced opioid requirements for up to 48-hours post-operatively have been demonstrated for multiple surgical specialities including colorectal surgery, prostatectomy, hysterectomy and other gynaecological surgery [154]. Complications following such blocks include failure, intravascular injection or entry into the peritoneal cavity risking bowel or visceral injury, although this risk is minimised with ultrasound guidance [153]. Literature comparing epidural analgesia to TAP blocks is also conflicting. Several studies have shown that TAP blocks are inferior to epidural [155], with other showing comparable outcomes [156]. Notably, some of these studies were underpowered to detect small outcomes.

1.3.5 Wound Catheters in Abdominal Surgery

The main limitation of rectus sheath and transversus abdominis plane blocks was the duration of action with even the longest acting local anaesthetics being effective for 24 hours. To prolong the duration of action, catheters allowing the continual infusion of local anaesthetics have been developed. The use of wound catheters as a method of providing post-operative pain relief has been described in many different surgical specialities including colorectal surgery, gynaecology and urology. An initial meta-analysis showed that the use of these wound catheters to infuse local anaesthetic was associated with improved pain scores, improved satisfaction, reduced opioid consumption and earlier discharge when compared to saline/water infusion [157]. A further meta-analysis combining data from RCTs in multiple specialities performing abdominal surgery showed no difference in pain scores at rest after 48 hours, although there was a non-significant trend towards improved pain scores on movement in the epidural group [158]. However, this was a heterogeneous group of studies and the authors recommended further procedure-specific RCTs, including broader measures of recovery, in order to compare the overall efficacy of wound catheters. In hepato-pancreato-biliary surgery, the evidence surrounding their use is extremely limited with only three RCTs published, with two from the same institution (Edinburgh Royal Infirmary, Scotland, UK), and a small number of retrospective studies.

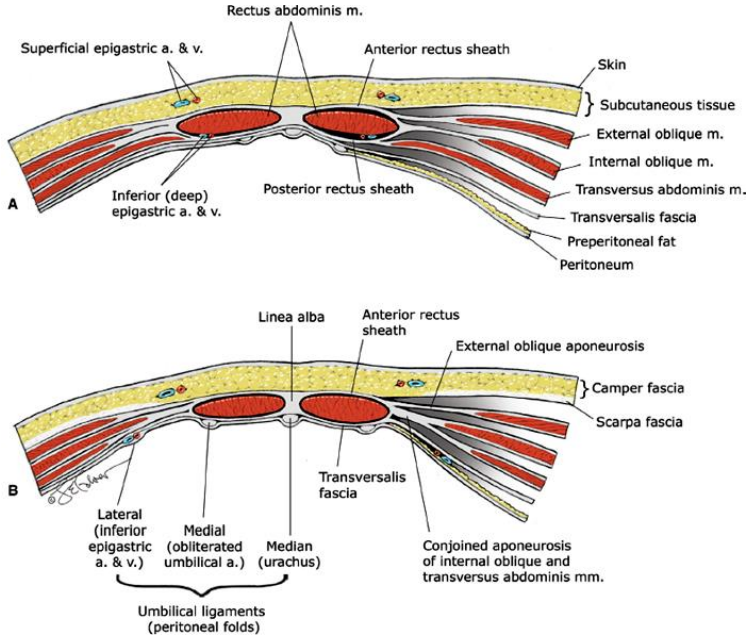
Specifically, in the context of liver surgery, there are three randomised studies comparing epidural with wound catheters [114, 159, 160]. Two of these studies demonstrated a shorter length of stay/functional recovery with wound catheters although one study demonstrated inferior pain scores with wound catheters and the other comparable pain relief. Neither study showed any difference in co-morbidity [114, 159]. A randomised, open label, non-inferiority trial (POP-UP trial) demonstrated that continuous wound infiltration is not inferior to epidural analgesia

within the enhanced recovery setting in hepato-pancreato-biliary surgery although this study included pancreatic surgery [160]. A further multicentre, blinded RCT compared wound catheters and PCA to PCA alone following open liver resection and found that the use of wound catheters reduced opioid requirements, pain and length of stay [161]. The current evidence comparing wound catheters and epidural in hepato-pancreato-biliary surgery is covered in chapter 2.

1.4 - Anatomy of the Anterior Abdominal Wall

An understanding of the anatomy of the anterior abdominal wall is essential for the correct placement of wound catheters. The anterior abdominal wall is the area between the costal margins and xiphoid process of the sternum superiorly, the inguinal ligaments and pelvic bones inferiorly and the mid-axillary lines laterally. The anterior abdominal wall is made up of three layers of muscle each surrounded by a fascial sheath or aponeurosis. These muscles are the external oblique, internal oblique and the transversus abdominis [162]. The paired rectus abdominis muscles are located either side of the midline and are enclosed by the rectus sheath, made up of aponeuroses of the other three muscles. The anterior layer of the rectus sheath is formed by the aponeuroses of the external oblique and half of the internal oblique with the posterior layer formed by the aponeuroses of the other half of the internal oblique and the transversus abdominis. One third of the way between the umbilicus and pubic symphysis all the aponeuroses condense and form an anterior layer only leaving just the transversalis fascia and peritoneum posteriorly. This transition is known as the arcuate line. In the midline all layers of the rectus sheath join to form the linea alba [163]. The transversus abdominis plane exists between the internal oblique and transversus abdominis muscles and carries the neurovasculature of the anterior abdominal wall [164]. Correct placement of wound catheters within this layer of the abdominal wall is essential if effective blockade of the nerves is to be achieved, thereby providing good analgesia. See Figure 1.

Figure 1 – Anatomy of the Anterior Abdominal Wall



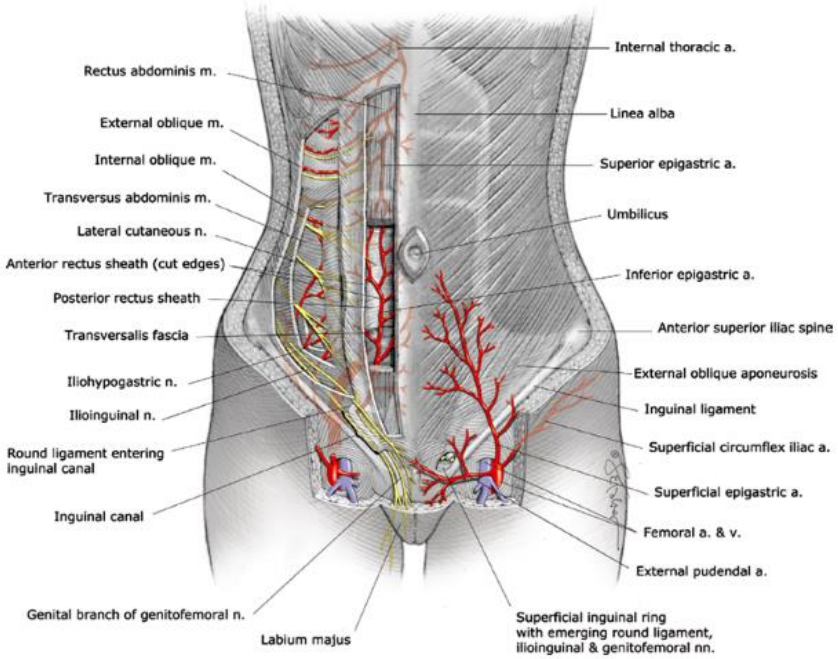
1.5 - Nerve Supply of the Anterior Abdominal Wall

The transversus abdominis plane contains the anterior rami of the lower six thoracic nerves (T7 to T12) as well as the first lumbar nerve. These nerves supply the skin, muscles and parietal peritoneum. The thoracic nerves from T7 to T11 enter this neurovascular plane at the costal margin and travel through it to enter the posterior wall of the rectus sheath and continue as anterior cutaneous branches supplying the overlying skin. Thoracic nerves T7 to T9 supply the skin superior to the umbilicus with T10 supplying the umbilicus and T11, T12, iliohypogastric nerve and ilioinguinal nerve supplying the skin to the umbilicus [165].

The iliohypogastric nerve arises from the L1 nerve root and runs in the plane between the internal oblique and transversus abdominis muscle. It subsequently pierces the internal oblique to lie between the internal oblique and external oblique and gives off cutaneous branches to supply the skin of the inguinal region.

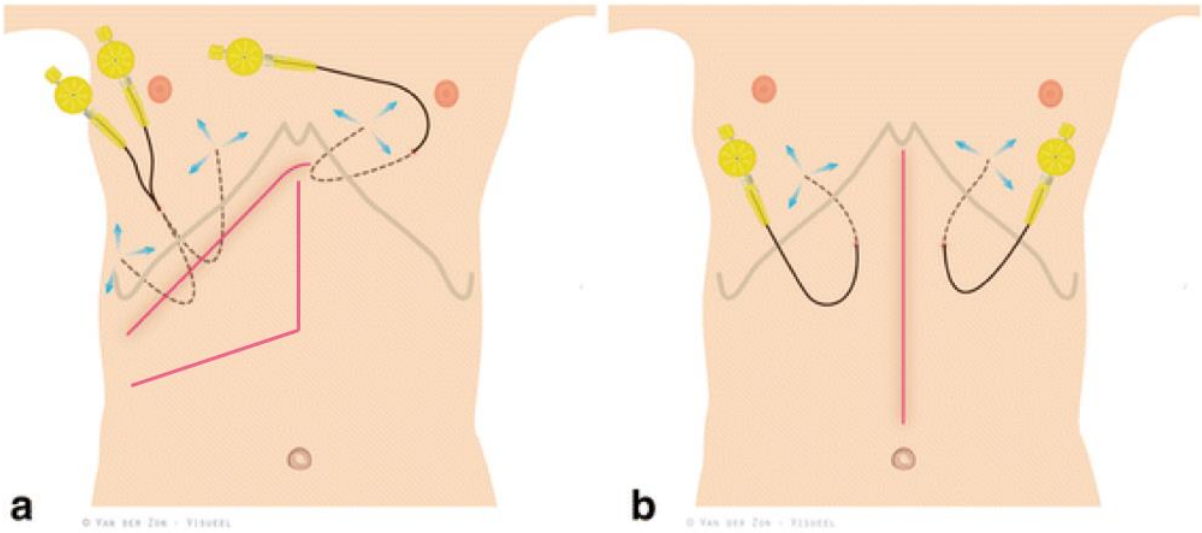
The ilioinguinal nerve also arises from the L1 nerve root and runs inferior to the iliohypogastric nerve, pierces the transversus abdominis muscle at the level of the iliac crest and runs medially in a deeper plane than the iliohypogastric nerve. This nerve supplies the medial aspect of the thigh and the anterior scrotum or labia [163-165]. See Figure 2.

Figure 2 – Nerve Supply of the Anterior Abdominal Wall



The three randomised studies comparing wound catheters with epidural have placed wound catheters in to the posterior rectus sheath and transversus abdominis plane to block these nerves. The most common placement location for these catheters is illustrated in Figure 3.

Figure 3: Location of Wound Catheter Placement. A) For 'Reverse L'/Subcostal Incision (Transversus abdominis plane laterally and posterior rectus sheath medially with an optional catheter in the left posterior rectus sheath. B) For Midline Incision (bilateral posterior rectus sheath catheters).



1.6 - Evidence in Hepato-Pancreato-Biliary Surgery

Epidural analgesia is used routinely during HPB surgery. It has been shown to allow earlier mobilisation plus a swifter recovery [166]. These advantages have resulted in this analgesic modality becoming part of enhanced recovery programmes, both in colorectal and liver surgery [94, 167]. Nevertheless, there is concern of potential serious complications such as epidural abscess and haematoma. Whilst these are rare, the postoperative coagulopathy sometimes associated with liver resection has sometimes been thought to increase this risk [168]. In addition, epidural associated hypotension may lead to: 1. increased fluid requirements intra and postoperatively during liver resection [114]. 2. increased need for postoperative

inotropes and subsequent need for level 2 facilities (HDU). These issues have led to the use of other modalities of postoperative anaesthesia such as local anaesthetic infiltration via wound catheters. These techniques have shown a significant reduction in opioid use following surgery, which is the obvious alternative to epidural [125], especially with use of continuous infusion of local anaesthetics [157]. Wound catheters are being increasingly used in liver surgery with satisfactory pain relief [114, 159, 169]. A recent meta-analysis comparing epidural with wound catheters in patients undergoing open abdominal surgery found comparable pain scores between the two groups [158]. Nevertheless, there is a paucity of data comparing epidural analgesia and wound catheters, in particular during liver surgery.

1.7 - Effect of Analgesia on the Systemic Inflammatory Response

Inflammation can be defined as the reaction of the host to injury and brings about the release of vasoactive mediators such as histamine and leukotrienes from mast cells. This causes vasodilatation, increased vascular permeability and leads to the typical signs of inflammation, redness (*rubor*), heat (*calor*) and the subsequent tissue oedema causing swelling (*tumour*). Interaction of these inflammatory mediators with the sensory system leads to pain (*dolor*). Significant tissue injury, such as that caused by surgery, leads to a systemic response or acute phase reaction which triggers two initial pathways [170]. The first is the release of cytokines and inflammatory mediators from injured tissues and the second is the stimulation of afferent neurones carrying information to the central nervous system. These two systems are not independent from each other and it is important to note that there is significant interaction between them. These pathways both activate the sympathetic system in the brainstem and the release of corticotrophin releasing hormone from the hypothalamus with a positive feedback system between the two [171]. This neuroendocrine response culminates in the release of cortisol, growth hormone and prolactin from the anterior pituitary and vasopressin from the posterior pituitary, as well as secretion of catecholamines from the adrenal medulla. The release of cortisol and catecholamines stimulate glycogenolysis and gluconeogenesis as well as reduced insulin secretion and increased insulin resistance. Cortisol also stimulates catabolism of protein and stored fat to ultimately produce more energy.

As described previously, the systemic inflammatory response (SIR) following surgery is a response that, mediated by activated leucocytes, fibroblasts and endothelial cells, produces a number of low molecular weight proteins called cytokines. These molecules are essential for cell-signalling and act on surface receptors of target cells to bring about their effect. The

earliest mediators of inflammation are interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α, with many other cytokines being subsequently released. Release of cytokines at the site of injury helps to coordinate the response to injury and induces neutrophil chemotaxis. Cytokines released locally include IL-1, IL-6 and TNF-α. These cytokines also cause lymphocyte proliferation, activate neutrophils and induce fever. The inflammatory response leads to macrophages, monocytes and polymorphonuclear granulocytes being recruited to the injured area. This systemic inflammatory response is essential for structural and functional repair of damaged tissues. However, excessive inflammation can heighten tissue damage [170].

Major surgery leads to a variety of metabolic, neuroendocrine and immune responses, which aim to maintain physiological stability and promote healing [172]. This response to the trauma of surgery leads to the activation of macrophages and neutrophils, which are produced as a response to pro-inflammatory cytokines, including TNF-α and the interleukins (IL) such as IL-1 and IL-6 [173, 174]. These cytokines subsequently alter the level of circulating acute phase proteins such as CRP, albumin and fibrinogen [175]. It has been reported that the circulating levels of cytokines and acute phase proteins corresponds to the size of the systemic inflammatory response. This inflammatory response is particularly relevant in liver surgery as pro- and anti-inflammatory cytokines coordinate a range of physiological and pathological pathways such as inflammation, organ failure and liver regeneration [176 – 178].

One of the most important cytokines to be released initially is IL-6 and this is the most frequently measured cytokine when investigating the SIR following surgery. This is often undetectable preoperatively, although rises quickly before reaching a peak plasma concentration at 24 hrs postoperatively [179]. However, there are multiple other cytokines, with

a variety of pro- and anti-inflammatory properties which have been reported in a variety of surgical specialities. These studies show that whilst the response pattern is generally similar, the size and duration of that response can be highly variable and dependent on many factors. Two of these factors include the type of surgical procedure, with larger, more extensive procedures producing a larger SIR and the development of postoperative complications also leading to a bigger response [180-182]. Also, of relevance to hepatic surgery is the impact tissue ischaemia and subsequent reperfusion has on increasing the cytokine response. In liver resection use of Pringle's manoeuvre is common and produces such an effect [183, 184].

There have been multiple studies looking at differing methods of pain relief and their influence on the inflammatory response. Differing methods of post-operative pain relief have been shown to modulate this inflammatory stress response, which may lead to improved outcomes. One of the most frequent methods of delivering post-operative pain relief is epidural analgesia and multiple studies, in a variety of surgical specialities have examined their impact on the systemic inflammatory response.

Initial studies compared outcomes between patients undergoing surgery with a general anaesthetic or general anaesthetic combined with intraoperative epidural. Several RCTs have been published, all demonstrating that epidural reduces the systemic inflammatory response. Dong et al compared outcomes following radical surgery for epithelial ovarian cancer. Lower levels of IL-1β and IL-8 and increased levels of IL-10 and IFN-γ were noted in the GA + EP group with the authors concluding that combined general anaesthetic (GA) and thoracic epidural (EP) promoted anti-tumorigenic cytokine responses [185]. Similarly, Hadimioglu et al compared the same groups undergoing renal transplantation in non-diabetics. A partly attenuated stress response was noted with the combined GA/EP approach with TNF-α and IL-6 levels being

significantly higher in the GA alone group (PCA for postoperative analgesia) [186]. In general surgery, intraoperative epidural was compared with intravenous opioid analgesia intraoperatively in patients undergoing major abdominal surgery with both groups receiving patient-controlled epidural postoperatively. The IFN-γ/IL-10 ratio was significantly higher in the epidural group from 2 hours to 1 day postoperatively. No differences were seen with IL-2. In this study, the use of Intraoperative EP reduced the stress response and prevented stress-induced perioperative impairment of pro-inflammatory lymphocyte function [187].

The majority of RCTs have compared epidural with systemic opioids, usually in the form of patient-controlled analgesia. Fant et al compared patients undergoing radical retropubic prostatectomy. This study found that cortisol and glucose levels in the initial period following surgery were significantly higher with PCA as was IL-17 at 24 and 72 hours. However, IL-6 and TNF-α were comparable. This showed that although epidural reduced the early postoperative stress associated with surgery, it did not reduce the acute inflammatory response [188]. Two studies within colorectal surgery showed slightly variable results with Day et al demonstrating no differences in circulatory IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IFN-γ, TNF-α or VEGF at any time point, although cortisol and glucose were lower at 3 hours post-surgery [189]. However, another study found that only IL-4 and IL-10 were higher at all time points with PCA, suggesting that EP attenuates the stress response [190]. Gu et al found the combination of total intravenous anaesthesia (TIVA) with intraoperative epidural and postoperative patient-controlled epidural inhibited the stress response with no significant increase in cortisol, IL-17 and IL-6 [191]. Hepatobiliary surgery patients undergoing hepatectomy for HCC had significantly lower IFN-γ and IL-4 with GA and EP and IL-17 levels remaining significantly lower up to day 7 post-surgery when compared to GA and PCA [192].

Only one RCT compared intraoperative intravenous lidocaine to epidural and placebo in a blinded study following colorectal surgery with all patients receiving postoperative analgesia via EP. Significant differences were noted in IL-6 and IL-8 between the 3 groups with the least increase in pro-inflammatory cytokines seen with intraoperative thoracic epidural [193].

A double blind RCT compared intraperitoneal infiltration of ropivacaine to saline placebo, although both arms in this study also received epidural postoperatively. The ropivacaine was infiltrated pre-dissection and continued up to 3 days following surgery via wound catheters. IL-6, IL-8 and TNF-α were all diminished at 8 and 20 hours, although only IL-6 was reduced at 48- and 72-hours post-surgery [194]. Fiorelli et al also randomised patients to receive either bupivacaine or saline wound infiltration via wound catheters up to 48 hours following lung resection with a muscle-sparing thoracotomy. Bupivacaine infiltration significantly decreased levels of IL-6, IL-10 and TNF-α when compared to placebo [195]. The only study to compare postoperative epidural with wound catheters following liver surgery was the LIVER-2 study which found that levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α peaked on day 1 from baseline and had improved but were not back to baseline by day 3. However, no differences in inflammatory response were noted between the 2 groups [159]. Interestingly, in abdominal surgery one study was able to associate an IL-6 level of greater than 432 pg/ml with an increased risk of post-operative complications following major abdominal surgery [196].

There is some evidence that the use of local anaesthetics may be able to modulate the systemic inflammatory response, with some laboratory studies having shown that amide local anaesthetics such as lidocaine or bupivacaine inhibit IL-1α in a dose-dependent manner [170]. As IL-1α stimulates chemotaxis, degranulation and phagocytosis by acting on polymorphonuclear granulocytes, inhibition of these effects by local anaesthetics may

contribute to an anti-inflammatory effect. TNF-α, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) are often described as 'priming' agents when they are exposed to polymorphonuclear granulocytes. This 'priming' is an essential regulatory mechanism involved in the overstimulation of inflammatory pathways, which can lead to tissue damage. Local anaesthetic agents have been shown to block priming of polymorphonuclear granulocytes and it is possible that this activity contributes to their anti-inflammatory actions.

The volume of evidence regarding the impact that different analgesic modalities have on the systemic inflammatory response is growing. As with other aspects of hepatobiliary surgery, the evidence base specific to this branch of surgery is limited, as is the evidence base looking at the impact of wound catheters on the systemic inflammatory response. Indeed, there is only one paper assessing the impact of wound catheters on the inflammatory response in liver surgery [159]. As such, this is an important area for further investigation. It is necessary to establish the impact that wound catheters have on the systemic inflammatory response prior to their recommendation over thoracic epidural.

Chapter 2

Wound Catheters in Open Liver Resection

2.1 Introduction

As described in Chapter 1 there is a paucity of data regarding the efficacy of wound catheters within hepato-biliary surgery with only limited studies published to date. To further evaluate this scenario, a systematic review and meta-analysis of the available literature regarding the use of wound catheters in liver surgery was performed comparing results between local anaesthetic infiltration via wound catheters versus epidural analgesia in patients undergoing open liver resection.

2.2 Methodology

Randomized and cohort studies (irrespective of language, country of origin, hospital, blinding, sample size or publication status) that compared the use of local anaesthetic infiltration via wound catheters with epidural catheters for elective liver resection were included. The Cochrane Colorectal Cancer Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, Embase and Science Citation Index Expanded were searched for articles published up to January 2018 using the medical subject headings (MeSH) terms ‘epidural, wound catheters, local anaesthetic infiltration and liver resection’. Equivalent free-text search terms, such as ‘epidural analgesia, local anaesthetic infiltration’, were used in combination with ‘liver resection’ and ‘hepatectomy’. The

references from the included studies were searched to identify additional studies comparing the two techniques.

Studies were restricted to those on human subjects; those reporting at least two study groups epidural and wound catheters in patients undergoing open liver resection for benign and malignant conditions including cirrhotic livers and those undergoing resection for living donor liver transplantation. Studies that failed to fulfil the above inclusion criteria were excluded from this study. Exclusion criteria were the following: review articles, letters, editorials, comments, case reports and studies reported from the same research group with the same data source.

Outcome Measures

The primary outcome measures were pain scores on postoperative days 1, 2, and 3. Secondary outcome measures were hospital stay, time to opening bowels, overall complications and analgesia-specific complications. To calculate opiate requirements, opiate doses were converted to morphine-equivalent doses.

Definitions

Overall, complications were defined as those directly related to the liver resection and to general ones such as renal, cardiorespiratory, pleural effusions, wound infections, deep vein thrombosis and pulmonary embolism.

Pain scores used were an 11-point scale (0-10). Those studies using a 101-point scale (0-100) were converted to an 11-point scale. Pain scores from comparable time points were used from each study.

Data extraction and quality assessment

Studies were systematically identified and data were extracted. The accuracy of the extracted data was further adjudicated as required.

Statistical analysis

Statistical analysis was performed using Review Manager Version 5.2 software (Cochrane Collaboration). The risk ratio (RR) with 95% confidence interval (CI) was calculated for binary data, and the mean difference with 95% CI for continuous variables. When median and range were reported instead of mean and variance, their mean and variance was calculated based on the methods described by Hozo and colleagues [197]. Random and fixed-effects models were used to calculate the combined outcomes of both binary and continuous data [198, 199]. In cases of heterogeneity, only the results of the random-effects model were reported. Heterogeneity was explored using the X^2 test, with significance set at $P < 0.05$. Low heterogeneity was defined as an I^2 value of 33% or less [200]. If standard deviation was not provided, it was calculated according to the guidelines of the Cochrane Collaboration [201]. This process involved assumptions that both groups had the same variance, which may not have been true, and variance was estimated either from the range or from the P value. Forest plots were used for graphical display of the results.

2.3 Results

Five studies fully met the inclusion criteria and formed the basis of this meta-analysis (see Figure 4) [114, 159, 202-204]. These included two randomised studies, one prospective study and two retrospective studies. All five studies combined had 798 patients; 215 patients were in the epidural analgesia group and 583 patients in the wound catheter group. The characteristics of the included studies are detailed in Table 1. Importantly 3 studies [114, 203, 204] provided a PCA in addition to AWC for postoperative pain relief in the AWC arm whereas the other 2 studies did not [159, 202]. The quality of the included studies is detailed in Tables 2 and 3. Pooled data were analysed by combining the results of the 5 studies.

Primary outcome measures

Postoperative day 1 (POD) pain scores

Data from 2 studies were included in this analysis [114, 204]. There was no significant heterogeneity between these trials (Tau^2=0.00, Chi^2=0.79, df=1 (P=0.37), I^2=0%. In a random-effects model, the pain scores were significantly higher in the wound catheter group with a mean difference of -0.90 [-1.29, -0.52] Z=4.61 (P<0.00001). See Figure 5.

Postoperative day 2 (POD) pain scores

Data from two studies was included in this analysis [114, 204]. There was no heterogeneity among the trials (Tau^2=0.00, Chi^2=0.03, df=1 (P=0.86), I^2=0%). In a random-effects model, the pain scores were similar between the 2 groups on day 2 (MD -0.29[-0.65, 0.07], Z=1.58 (P=0.11)).

Figure 4 - PRISMA Flow Diagram

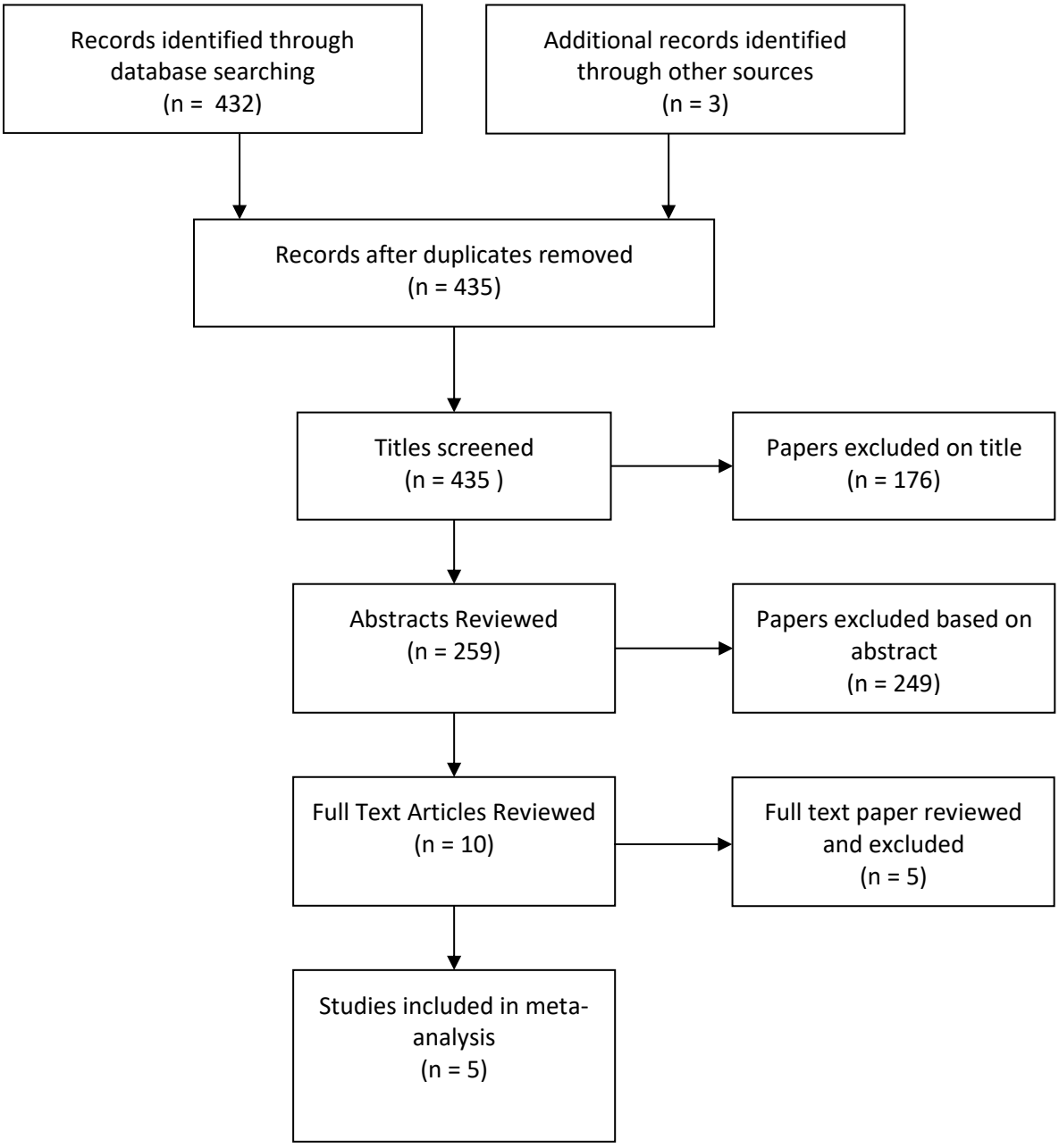


Table 1 – Summary of interventions

Reference	Operation	Incision	Analgesia Type	n per group	Age	Intervention	Drugs Administered	ERP	Additional drugs
Revie et al.	Open Liver resection	Right Subcostal	Wound Catheter	33	60	Dual wound catheter placed by surgeon in transversus abdominis plane and post. Rectus sheath	20ml 0.25% levobupivacaine bolus followed by continuous 0.375% levobupivacaine at 4ml/hr for 48hr	Yes	Paracetamol 1g QDS Ibuprofen 400mg TDS Oxycodone 10mg PRN IV morphine PCA
			Epidural	31	60	T7-8 Epidural	Continuous 0.1% bupivacaine and 2 mcg/ml fentanyl at 7-10ml/hr		
Soliz et al.	Open Liver Resection	Right subcostal or bilateral subcostal	Wound Catheter	72	53.7	Dual wound catheters above the fascia	Bolus of 10ml 1:1 1% lidocaine and 0.25% bupivacaine. Continuous 4ml/hr 0.5% ropivacaine	No	IV morphine PCA
			Epidural	71	54.3	T6-10 Epidural	0.075% or 1 % bupivacaine with hydromorphone 5mcg/cc or 2mcg/cc		
Stefancic et al.	Open liver Resection	Right Subcostal	Wound Catheter	15	-	30cm long multiholed catheter above fascia along wound length	10ml levobupivacaine bolus. 8ml/hr 0.25% levobupivacaine for 48hr	No	IV Diclofenac 75mg BD IV morphine PCA
			Epidural	14	-	T8-11 Epidural	Levobupivacaine 0.5% 5-7ml and 100mcg fentanyl bolus. Continuous 0.125%		

							levobupivacaine and fentanyl 2mcg/ml at 6ml/hr		
Wong –Lun-Hing et al.	Open Liver Resection	Reverse L	Wound Catheter	429	63	Dual wound catheter placed by surgeon in transversus abdominis plane and post. Rectus sheath	10ml bolus of 0.25% bupivacaine. Continuous 0.25% bupivacaine at 3ml/hr for 72hr	No	Morphine/Fentanyl PCA PO paracetamol, NSAID and opioid available to all patients
			Epidural	69	63	T5-12 Epidural	20ml 0.25% bupivacaine bolus. 0.1% bupivacaine and 2mcg/ml fentanyl at 5-15ml/hr		
Hughes et al.	Open Liver Resection	Right Subcostal	Wound Catheter	49	62.8	Dual Limb 12.5cm in transversus abdominis plane and posterior rectus sheath	40ml 0.125% levobupivacaine bolus. Infusion of 0.375% levobupivacaine at 4ml/hr for 48hr	Yes	1g Paracetamol QDS
			Epidural	44	62.6	T8-9 Epidural	4ml 2% lidocaine followed by 10ml levobupivacaine with 100mcg fentanyl. Infusion of 0.1% levobupivacaine with 2mcg/ml fentanyl		

Postoperative day 3 (POD) pain scores

Data from 2 studies were included in this analysis [114, 204]. There was significant heterogeneity among the trials (Tau2=0.59, Chi^2=5.60, df=1 (P=0.02), I^2=82%). In a random-effects model, the pain scores were similar between the 2 groups on day 2 (MD -0.33 [-0.84, 1.49], Z=0.55 (P=0.58)).

Secondary outcome measures

Time to opening bowels

Data from 3 studies were included in this analysis [159, 203, 204]. There was heterogeneity amongst the included studies (Tau^2=0.59, Chi^2=9.11, df=2 (P=0.01), I^2=78%). In a random-effects model, time to opening bowels was similar between the 2 groups (MD 0.24[-0.74,1.23]; Z=0.48 (P=0.63)).

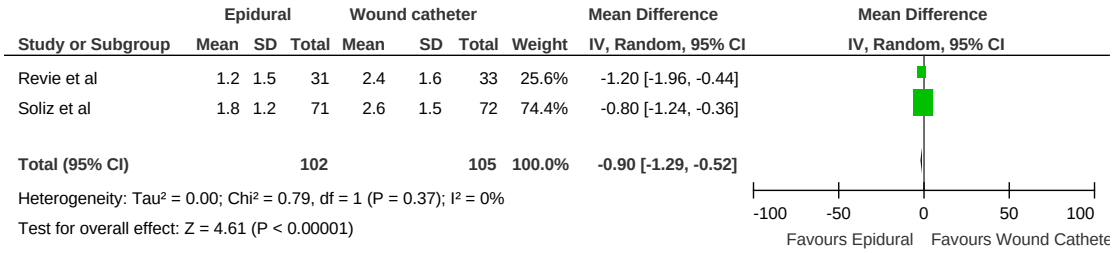
Opioid use

Data from 3 studies were included in the analysis [159, 202, 203]. There was heterogeneity amongst the included studies (Tau^2 = 1403.39; Chi^2 = 15.56, df = 2 (P = 0.0004); I^2 = 87%). In a random-effects model, the opioid use was similar between the 2 groups (MD -6.46 [-56.60, 43.69] Z = 0.25 (P = 0.80)).

Overall complications

Data from 3 studies were included in this analysis [114, 159, 202]. There was no heterogeneity amongst the included studies. In a fixed effect model, the overall complication rate was higher in the epidural group, 52% versus 30% (RR 1.39 [1.13, 1.72]; Chi^2 = 0.60, df = 2 (P = 0.74); I^2 = 0%; Z=3.06 (P=0.002)). See Figure 6.

Figure 5: Forest Plot of Postoperative pain score - day 1



Length of hospital stay

Data from four studies were included in the analysis [114, 159, 202, 204]. There was no heterogeneity amongst the included studies. In the fixed-effect model, the length of hospital stay was similar in both groups (MD 0.78[-0.35, 1.91] X^2=0.07, df=3 (P=0.99), I^2=0%; test for overall effect Z=1.35(P=0.18)).

Figure 6: Forest Plot of Overall Complications

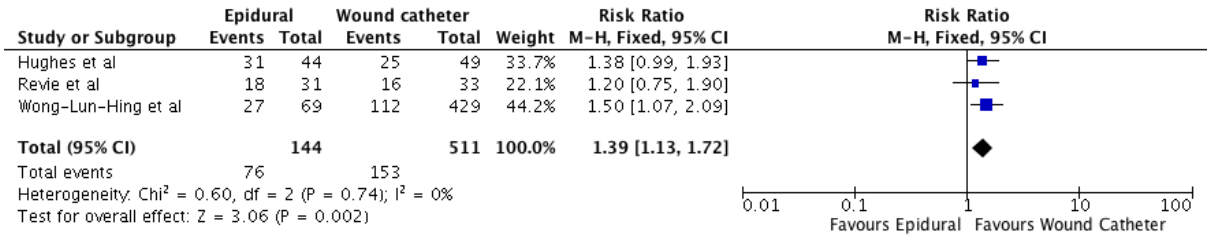


Table 2 – Characteristics of Included studies

Study	Year	Centre	Inclusion Period	Country	Number of epidural patients	Number of wound catheter patients	Newcastle Ottawa Score
Revie et al	2012	Single	Aug 2009 – July 2010	UK	31	33	See Table 3
Wong-Lun-Hing et al	2013	Single	July 2004 – July 2011	UK	69	429	7
Stefancic et al	2013	Single	2012 - 2013	Croatia	14	15	4
Soliz et al	2012	Single	July 2005 – July 2010	USA	71	72	5
Hughes et al	2015	Single	Dec 2012 – June 2014	UK	44	49	See Table 3

Table 3 – Quality Assessment of included trials						
Study	**End Point**	**Randomisation Technique**	**Concealment**	**Blinding**	**Power Calculation**	**Jadad Score**
Revie et al	Length of stay	Sealed envelopes	Sealed envelope	Single Blind	Yes	3
Hughes et al	Functional recovery	Sealed envelopes	Sealed envelope	Open label	Yes	4

2.4 Discussion

Debate continues regarding optimal pain management following liver resection. Over the years, epidural analgesia has formed the mainstay of pain management over patient-controlled analgesia (PCA) alone but this has had issues such as inadequate pain relief in 20-30% of patients [125]. Epidurals can make perioperative hemodynamic management more complex. There is an increased fluid requirement postoperatively because of epidural induced hypotension and this may also require inotropic support [114]. In addition, particularly in patients undergoing liver resection, there is an increased risk of requiring transfusion [113]. In the last few years, several RCTs and case-controlled trials compared epidural analgesia and wound catheters for analgesia with varying results. The results from this pooled analysis have shown that epidural provides better pain management in the first postoperative day with comparable pain relief subsequently. The overall complication rate appeared to be higher in the epidural group. However, opioid requirements, time to moving bowels and hospital stay were comparable between the 2 groups. However, these results need to be interpreted with caution given the heterogeneity of the data.

In conclusion, this meta-analysis appears to show that wound catheters provide largely comparable pain relief with a lower complication rates and no difference in length of stay when compared to epidural catheters. Although some of these studies are well designed more data from well-designed studies is required to draw firm conclusions. There are significant limitations in this meta-analysis. The studies included vary in the position of the wound catheters, postoperative analgesic regimes and even wound incisions. There is, however, no current consensus available regarding the optimal site for wound catheters and we therefore included all studies. There was no comparable data available to assess

complication rates with each catheter technique, failure rate and postoperative fluid requirements. Studies involving a small number of patients in this meta-analysis may not have had sufficient power to recognize small differences in pain scores and complications outcomes between epidural and wound catheter groups. While this meta-analysis does not provide data on cost-benefit analysis, results suggest wound catheters provide adequate pain relief comparable to epidurals with a lower complication rate.

In general, the quality of some studies investigating the effects of wound catheters following liver surgery that are included in this study are poor with only two randomised studies [114, 159], both of which were carried out in the same institution. Further randomised studies evaluating the impact wound catheters have on perioperative outcomes, including pain scores, complications and length of stay, are needed.

Justification, Hypothesis and Objectives

Justification

Good post-operative analgesia is an integral part of ERAS protocols and has the potential to improve recovery following surgery. The ideal method of delivering such analgesia would provide effective analgesia without side effects. Whilst epidural analgesia can provide good analgesia, it is not without unwanted side effects and concern regarding sympathetic blockade remains. There are also several alternatives available. Local anaesthetic infiltration via abdominal wound catheters in combination with an opioid based PCA is one multi-modal approach to analgesia that aims to provide good pain control without the systemic side effects associated with thoracic epidurals. The combination of two different modalities also aims to minimise opioid use associated with patient-controlled analgesia alone and its accompanying side-effects. However, high-quality evidence for their use in patients undergoing liver resection is limited with experience from our colleagues in Edinburgh being instrumental. There is also very limited evidence evaluating the impact that local anaesthetic infiltration via abdominal wound catheters has on the systemic inflammatory response, particularly in hepatobiliary surgery. We have designed this study to compare thoracic epidural, the current gold standard for postoperative analgesia, with a multimodal regime consisting of local anaesthetic infiltration via abdominal wound catheters combined with an opioid based patient-controlled analgesia.

Hypothesis

We hypothesized that patients receiving thoracic epidural following open liver resection would not experience a better recovery to those receiving AWC with PCA and, in fact, recovery may be improved with the use of AWC by eliminating the systemic side effects of EP. Specifically we hypothesized that:

1. Patients receiving AWC-PCA for post-operative pain relief would not have an inferior recovery following open liver resection to those receiving thoracic epidural analgesia, which is the current standard of care.
2. The use of AWC-PCA for post-operative pain relief following open liver resection would not be associated with an increased morbidity when compared to patients receiving thoracic epidural analgesia.
3. The use of AWC-PCA for post-operative pain relief following open liver resection will not be associated with an inferior systemic inflammatory response when compared to patients receiving thoracic epidural analgesia.

Objectives

To test our hypotheses, we set the following objectives.

1. To demonstrate that overall recovery was not inferior with the use of AWC-PCA we set overall hospital length of stay as the primary endpoint. Additionally, we monitored HDU stay and functional recovery as other variables of recovery.

2. In order to capture potential morbidity, we measured anaesthetic and surgical times, pain scores, peak flow, analgesic requirements, intravenous fluid requirements, vasopressor requirements, nausea and sedation scores, complications (stratified according to Clavien-Dindo Classification), return to theatre rates and readmission rates within 90 days of surgery as well as treatment failure rates. Postoperative mortality within 90 days was also recorded.

3. To measure the systemic inflammatory response whole blood samples were collected from participants on Day 0, 24- and 72- hours post-operatively. Cytokine levels were measured using a cytometric fluid-phase multiplex immunoassay.

Chapter 3

Clinical Trial

3.1 Methodology

The study and ERAS protocols were written and submitted for ethical approval using the integrated research application system (IRAS). After some minor amendments this RCT was approved by the Yorkshire and Humber Research Ethics Committee and was registered with the ISCRCTN registry (16447784). Recruitment commenced in April 2015 and was completed in November 2017. The study was also approved by the Leeds Teaching Hospitals NHS Trust Research and Development Department.

Patients

All patients scheduled to undergo open liver resection (OLR), including live liver donation, at St James's University Hospital, Leeds, UK were eligible for inclusion and were approached in outpatients by members of the medical or nursing team to discuss participation. Patients were provided with written information prior to attendance for surgery. Written informed consent was obtained on the morning of surgery. Patients were randomized 1:1 after consenting to receive either EP or AWC-PCA according to a computer-generated random sequence with concealed allocation. No blinding took place as this was not felt to be practical [114].

Exclusion criteria included patients with a known contraindication to either epidural or local anaesthetic, inability to give informed consent, aged less than 18, liver resection combined with a second surgical procedure, laparoscopic procedures,

pregnant or lactating women, prisoners and patients with a history of chronic pain issues requiring regular opioid analgesia.

Perioperative Care

Patients were fasted for 6 hours prior to surgery and allowed clear fluids up to 2 hours before.

All patients underwent a standard anaesthetic by a team of experienced liver resection/transplant anaesthetists. This involved induction of general anaesthesia using fentanyl 1-2microgram/kg, sleep dose of propofol and non-depolarising muscle relaxant to facilitate endotracheal intubation. Anaesthesia was maintained with mixture of oxygen, air and inhalational agent (sevoflurane, desflurane). Patients were monitored with electrocardiogram, pulse oximetry, capnography, arterial blood pressure and central venous pressure. Nasogastric tube were not routinely used and if used was removed at end of procedure. Maintenance fluid (0.18% sodium chloride/4% dextrose) was used to achieve desired central venous pressure. The need for intravenous crystalloids was determined by the use of Lidco© in theatre based on stroke volume variation. Vasopressors were administered to maintain blood pressure within 20% of preoperative range. If patients are hypotensive (systolic blood pressure < 20% of preoperative level) despite adequate volume resuscitation then vasopressors (noradrenaline as a single strength solution) would be commenced. Hartmann's solution was used for intraoperative volume replacement after completion of liver transection, with vasopressors given at the discretion of the anaesthetist. All patients received dexamethasone 8 mg for antiemetic prophylaxis.

The type of incision was left to the operating surgeon's discretion. Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; ValleyLab, Boulder, Colorado, USA).

According to randomisation, epidural catheter or wound catheters plus PCA were commenced in theatre according to the study protocol:

Epidural

Prior to anaesthetic induction, EP patients received a thoracic epidural at the level of T6-10. Epidural infusion was started intraoperatively and consisted of fentanyl (2 µg/ml) and local anaesthetic (0.15% bupivacaine) at 6-10 ml/hr.

Wound Catheter

Patients randomized to the AWC-PCA group received an anaesthetic according to the same protocol. Prior to abdominal closure, two multi-perforated Painkwell (PeakMedical©) catheters were inserted into the transversus abdominis plane laterally and the posterior rectus sheath medially. A 20 ml 0.5% bupivacaine bolus (10 ml per catheter) was followed by an infusion of 0.25% bupivacaine at 4 ml/h per catheter for 60 h (POD 3) via an elastomeric pump. Patients in the AWC-PCA group also received a morphine based PCA for breakthrough pain with a 5 minute 'lock-out'. Both EP and AWC-PCA provided analgesia for 60 h postoperatively.

Local anaesthetic toxicity can rarely occur with rapid absorption into the blood stream, or if inadvertently administered intravenously. Symptoms of local anaesthetic toxicity include:

1. Mild - restlessness/confusion, light-headedness, numbness of tongue and lips, tinnitus, double vision, blurred vision

2. Moderate – heaviness of limbs, muscular twitching, convulsions

3. Severe – cardiac arrhythmias, hypotension, respiratory arrest, cardiac arrest

Recognition and assessment of local anaesthetic toxicity was managed as below:

1. If symptoms are mild (1);

    1 Stop local anaesthetic infusion and inform medical team

    2 Attach ECG and monitors

    3 Maintain oxygenation and BP

    4 Consult with Pain Team or on call anaesthetist

    5 Continue to observe closely

2. If symptoms are moderate or severe (2 or 3):

    1 Stop local anaesthetic infusion

    2 Attach ECG and monitors

    3 Phone for help immediately – Bleep ---- medical team / anaesthetist or cardiac arrest 2222

    4 Maintain airway and give high flow oxygen.

    5 Hypotension will be treated with IV fluids

    6 Convulsions will be treated with diazepam

    7 Commence CPR if in cardiac arrest

Emergency Treatment of Local Anaesthetic Toxicity

1 Collect Lipid Rescue Box from the nearest recovery area or operating theatre if patient is in local anaesthetic induced cardiac arrest.

2 Treatment will require intravenous Intralipid 20% (from the lipid rescue box). The initial dose is 1.5ml/kg over 1 minute, followed by an intravenous infusion of 15ml/kg over 1 hour.

3 For a 70kg adult this means 100mls over 1 minute followed by 1000mls over 1 hour.

4 Refer to The Association of Anaesthetists of Great Britain and Ireland safety guideline 'Management of Severe Local Anaesthetic Toxicity'.

Perioperatively, patients were managed according to an ERAS Protocol. Patients were warmed pre- and intra-operatively with 3M™Bair Hugger™ Normothermia system. Patients were given high carbohydrate drinks preoperatively except in patients with a past medical history of diabetes. Patients received perioperative intravenous antibiotics prior to skin incision and routine venous thromboprophylaxis. Nasogastric tube and intraperitoneal drains were used at the surgeon's discretion. Epidural failure was managed with conversion to PCA. Treatment failure was judged by the acute pain team independent from the study. It was defined as accidental dislodgment of the EP/AWC requiring removal or significant pain scores needing PCA. These patients were kept in the trial for the purposes of the intention to treat analysis.

Postoperative

Patients were transferred from the theatre complex to the surgical high-dependency unit (HDU) where they remained until discharge to ward criteria were met. These included:

- Respiratory
    - Requiring less than 40% Oxygen
    - Respiratory rate <20 >10
    - SpO2 >94%
- Cardiovascular
    - No CVP/invasive BP monitoring required
    - ECG monitoring not required
    - No vasopressor requirements or large boluses of fluid
- Renal
    - Stable renal function on biochemistry
    - Urine output >25ml/hr
- Analgesia
    - Pain control adequate with current method of analgesia
- Blood tests
    - Improving
- General
    - Able to mobilise out of bed

A standard oral analgesic scheme was followed for all patients from the first postoperative day. This included paracetamol (1gm four times daily), ibuprofen (400mg three times daily for 72 hours) and codeine (30-60 mg/qds) or tramadol (100mg four times daily) once the PCA had been discontinued. Ondansetron (4 mg three times daily) was used as antiemetic prophylaxis. All patients who are euvolaemic and haemodynamically stable will be encouraged to return to oral fluid administration as soon as possible.

Similarly, patients remained on the ward until discharge home criteria were fulfilled. These included:

- Adequate pain control on oral analgesia.

- Eating and drinking with no requirement for intravenous fluids in previous 24 hours.
- Independently mobile (can mobilise independently to toilet).
- Able to perform activities of daily living (washing, dressing) without help from nursing staff.
- Blood tests returning to normal range.
- Patient willing to go home.

Outcomes

To investigate the hypothesis the following outcome measures were defined:

Length of Stay

The primary outcome was the length of stay (from admission to discharge), which was assessed twice daily by a senior clinician independent from the study. In addition, days to meet 'medically fit for discharge' criteria functional recovery and length of high dependency (HDU) stay were also recorded.

Assessment of Pain

Pain scores at rest on a scale from 0 to 10 at 6 h postoperatively (Day 0) and then twice a day at 08:00-09:00 and 16:00-17:00. Scores were recorded by nursing staff independent of the study. PCA use, including attempted use, was recorded in addition to oral analgesia requirements and were converted to intravenous opiate equivalent.

Other Outcomes

Nausea and sedation scores were recorded at the same time points as pain scores. Peak flow measurements (best of 3) as a surrogate of pain were recorded pre-

operatively and twice a day for the first 3 days. Total volumes of intravenous fluid and the need for vasopressor support postoperatively were also monitored daily as were time to open bowels and time to sit out of bed.

Complications

Patients were monitored for complications routinely during their recovery. Complications were graded according to the Clavien-Dindo classification [205].

Statistical Analysis

A sample size calculation based on a mean historical length of stay of 9.8 days (SD 8.2)(median 7) with a clinically significant difference of one day. To achieve a significance of 0.05 and 80% power, 40 patients per arm were required. Given the nature of the study very few patients were expected to drop-out or be lost to follow up. Continuous data was compared using the Mann-Whitney U test and categorical data was compared using χ^2. Analysis was performed on an intention to treat basis. SPSS® Version 25 was used for statistical analysis.

3.2 Results

The trial commenced in April 2015 and was completed in November 2017. A total of 153 patients were approached to participate. A CONSORT flow diagram is shown in Figure 7. No patients were lost to follow up. Among the patients approached 83 patients were eligible and consented to participation. These were randomly allocated to either epidural (n=41) or abdominal wound catheters groups (n=42).

Patient Characteristics

Patients in both groups were comparable with regards to age, sex, body mass index, baseline peakflow and American Society of Anaesthesiologists (ASA) grade. Indications for surgery were colorectal liver metastases (CRLM, 50, 60%), hepatocellular carcinoma (HCC, 12, 14%), cholangiocarcinoma (CCA, 8, 10%), benign disease (9, 11%) and other causes (4, 5%). There were no significant differences between the two groups with regards to baseline characteristics. Operatively, the proportion of patients requiring a 'major' liver resection was comparable as were the median number of segments resected. There was no difference between the two groups regarding wound shape or length. Patient characteristics are shown in Table 4.

Table 4: Baseline Characteristics

	EP (n=41)	% or Range	AWC (n=42)	% or Range	P Value
Age, median (year)	67.3	25-85	65	24-79	0.133
Sex (Female)	12	29%	15	36%	0.348
ASA II	16	39%	17	40%	0.830
BMI (median, kg/m^2)	26	18-41	28	23-42	0.115
Baseline Peakflow Median (L/min)	395	(170-700)	415	(210-800)	0.379
Diagnosis CRLM HCC CCA Benign Other	 27 5 5 3 1	 66% 12% 12% 7% 3%	 23 7 3 6 3	 55% 17% 7% 14% 7%	0.534
PVE	2	5%	2	5%	0.683
Major Resection	23	56%	24	57%	0.574
Anatomical resection	21	51%	23	55%	0.298
Number of Segments (median)	4	(0-6)	3	(0-5)	0.291
Wound Shape Reverse 'J' Kocher Midline	 36 1 4	 88% 2% 10%	 36 1 5	 86% 2% 12%	0.559
Wound Length (median, cm)	28	17-45	27.5	15-36	0.458
Prior Abdo. Surgery	27	66%	23	55%	0.302
Redo Liver Resection	6	14%	3	7%	0.272
Intraop. Transfusion	2	5%	0	0%	0.147

ASA - American Society of Anaesthesiology, BMI - Body Mass Index, CRLM – colorectal liver metastases, HCC – hepatocellular carcinoma, CCA – cholangiocarcinoma, PVE – portal vein embolisation

Primary End Point: Length of stay

The overall length of stay (median) was comparable between the two groups (EP 6 days (3-27) vs 6 days (3-66), p=0.886). The median number of days to meet 'medically fit for discharge' criteria between the two groups was also comparable (EP, 5 days (3-27) vs. AWC 5 days (3-66), p=0.611).). The median length of stay on HDU between the two groups was comparable (EP 1 day (1-6) vs. AWC 1 day (0-6), p=0.097).

Perioperative Outcomes

The median anaesthetic time in the AWC group was shorter (AWC 49 min (20-115) vs. EP 62 min (20-126), p=0.003) but there was no significant difference in median surgical time (AWC 203 min (90-402) vs. EP 170 min (80-390), p=0.095) despite the potential complexity of inserting the AWC at the end of the procedure. The volume of intra-operative fluid and the proportion of patients requiring HDU admission post-surgery. Intraoperatively patients in the AWC group were more likely to require metaraminol boluses to maintain blood pressure whereas the EP group required noradrenaline infusion (p=0.01). See Table 5.

Postoperative Outcomes

Patients randomised to the EP group required significantly more vasopressor support on day 0 (AWC 14% vs. EP 54%, p = <0.001) and day 1 (AWC 5% vs. EP 23%, p=0.021). Intravenous fluid requirements were comparable until post-operative day 3 when approximately one-third of patients in the EP group required IV fluid (p=0.001). Median pain scores were worse on day 0, afternoon of day 1 and the morning of day 2 in the AWC group but not beyond this. Median pain scores in both groups at all time points were <3 and were thus considered to be low. See Table 5 and Figure 8.

No difference was noted in baseline peak flow between the two groups. However, reduction in peak flow from baseline was greater in the AWC group up to Day 3. Opioid requirements (IV morphine equivalent, mg) were greater in the AWC group on Day 0, Day 1 and Day 2. See Table 7.

Other Outcomes

In the EP group, 8 (20%) patients experienced treatment failure versus 3 (7%) patients in the AWC group (p=0.09). No differences were noted in nausea or sedation scores at any time point throughout the study. The number of days to open bowels was also comparable, both median 3 days (p=0.145) as was the time to first sit out (p=0.563). Complication rates were comparable between the EP and AWC groups being 29% vs 31% respectively (p=0.867). Similarly, no difference was noted in severe complications (Clavien-Dindo >3). Perioperative mortality was 2% in each group (p=0.747). See Table 5.

Figure 7: CONSORT Diagram

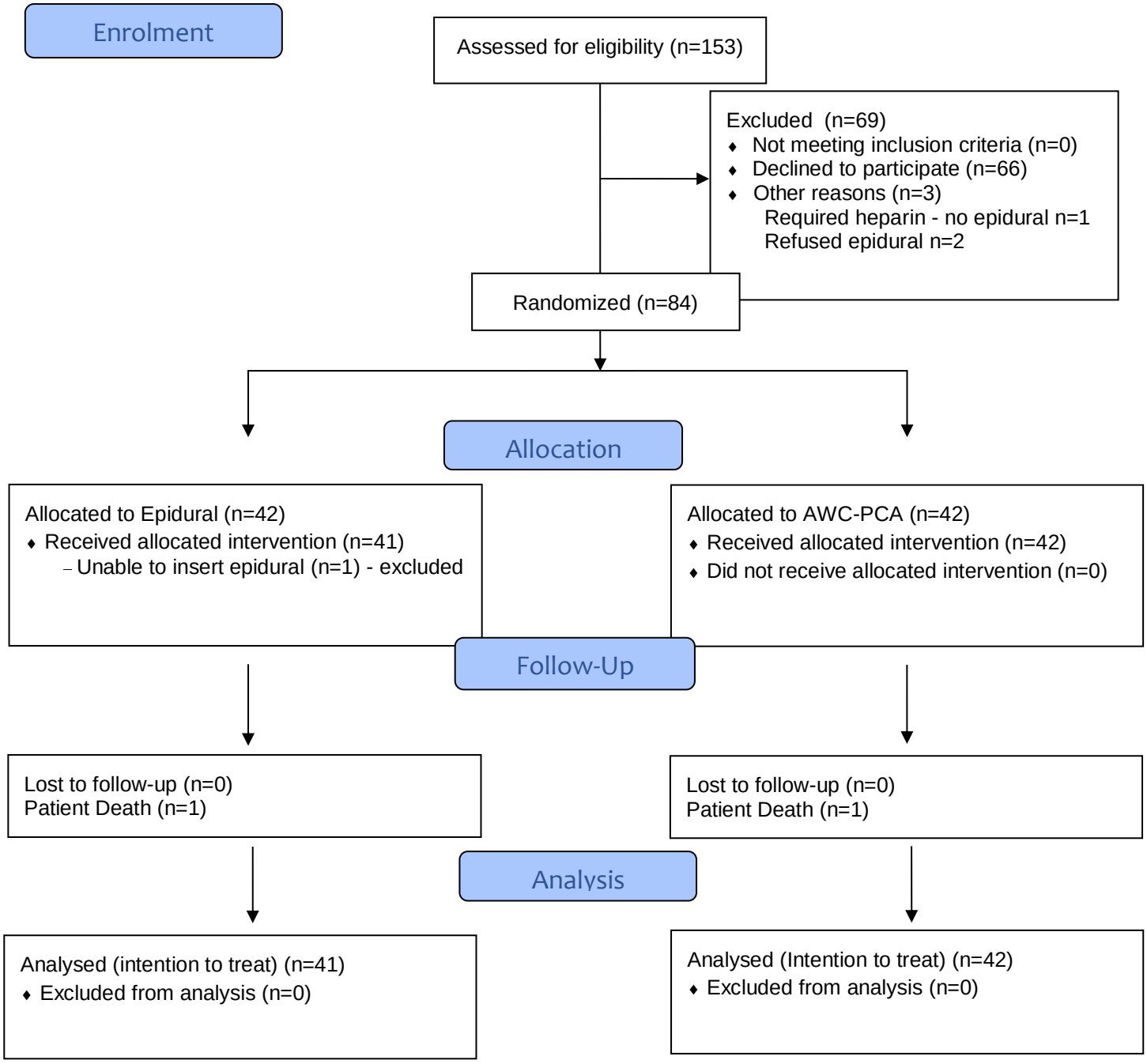


Figure 8: Pain Scores

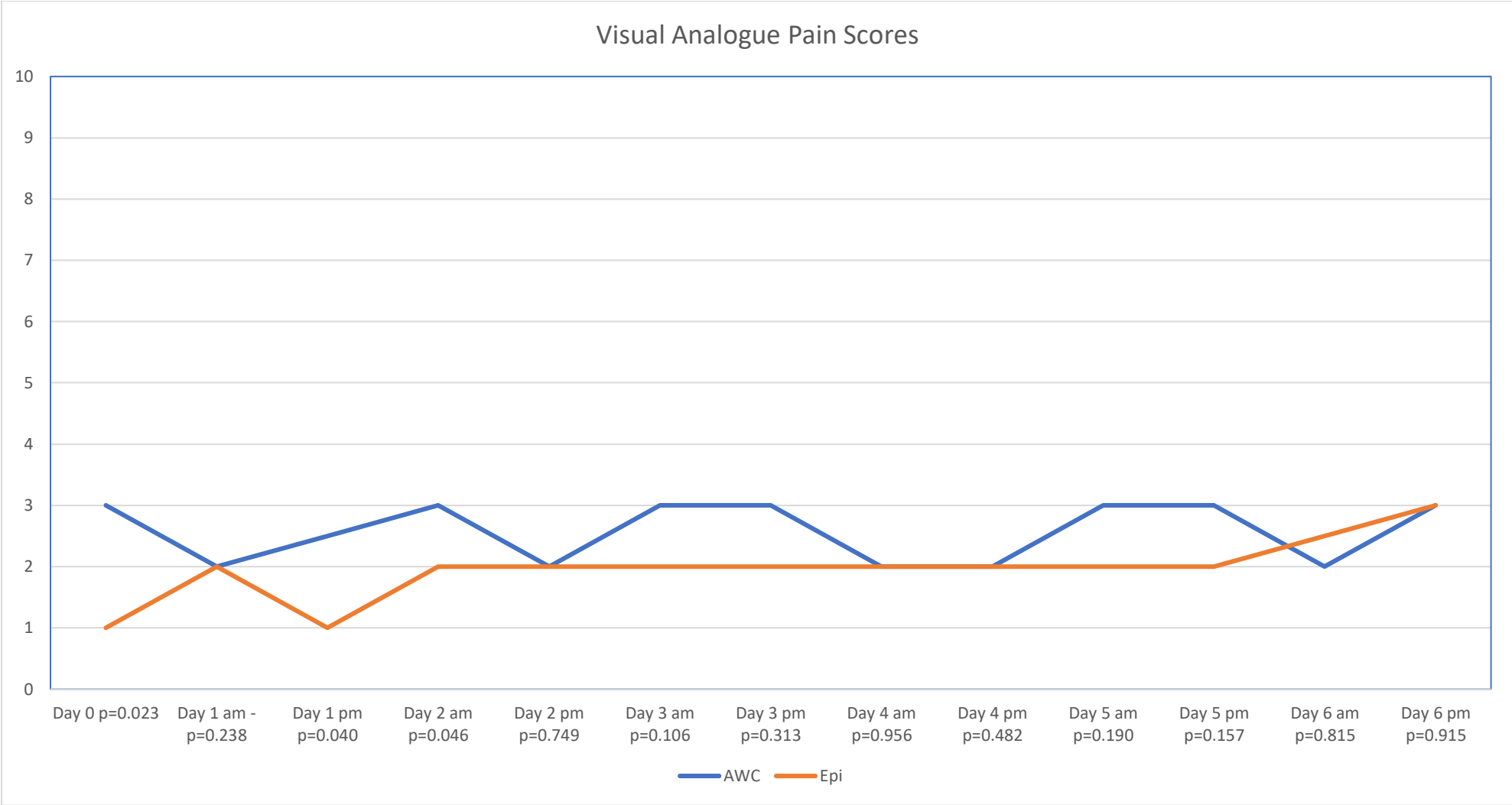


Table 5: Peri- and Post-Operative Outcomes

	EP (n=41)	% or Range	AWC (n=42)	% or Range	P Value
Anaesthetic Time (min)					
(median, range)	62	20-126	49	20-115	0.003
(mean, SD)	64	23	50	19	
Surgical Time (min)					
(median, range)	170	80-390	203	90-402	0.095
(mean, SD)	187	75	212	81	
Intraoperative Opioid					
(IV Morphine Equivalent, mg)	15	3-30	13.5	0-45	0.548
Intraoperative Vasopressors					
None	13	32%	19	45%	
Noradrenaline Infusion	23	56%	10	24%	0.001
Metaraminol	5	12%	13	31%	
Intraoperative fluid (ml)					
(median, range)	2000	1000-6000	2000	1000-6000	0.579
(mean, SD)	2267	1178	2262	989	
HDU Admission	38	93%	39	93%	0.644
Requirement for Vasopressors					
Day 0	22	54%	6	14%	<0.001
Day 1	9	22%	2	5%	0.021
Day 2	3	7%	1	2%	0.305
Intravenous Fluid Requirement (ml)					
Day 0 (median, range)	1650	600-3826	1663	664-3596	
(Mean, SD)	1675	742	1890	740	0.282
No. requiring IVI	41/41	100%	42/42	100%	
Day 1 (median, range)	1550	100-4650	1437	250-4667	
(Mean, SD)	1787	1057	1503	915	0.294
No. requiring IVI	41/41	100%	42/42	100%	
Day 2 (median, range)	490	0-4639	80	0-3246	
(Mean, SD)	890	1094	623	883	0.177
No. requiring IVI	27/41	66%	22/42	52%	
Day 3 (median, range)	0	0-3000	0	0-2000	
(Mean, SD)	552	866	65	359	0.001
No. requiring IVI	13/41	32%	1/42	2%	
Peak Flow from baseline (L/min)					
Day 0	80	-10-450	160	10-260	0.015
Day 1 am	150	-30-580	170	0-500	0.012
Day 1 pm	100	-60-500	180	0-400	0.005
Day 2 am	120	-10-350	215	0-500	0.001
Day 2 pm	110	-60-590	180	0-450	0.039
Day 3 am	100	-20-610	180	0-450	0.033
Day 3 pm	110	-60-590	145	0-300	0.291
Other Variables					

Days to Bowels Open (days)					
(median, range)	3	1-7	3	0-8	0.145
(mean, SD)	3	1.4	3.5	1.6	
Time to sit out (hr)					
(median, range)	17	15-26	16.5	4-20	0.563
(mean, SD)	17.3	1.4	16.7	3.2	
Length of Stay HDU (days)					
(median, range)	1	1-6	1	0-6	0.097
(mean, SD)	1.8	1.4	1.3	1	
MFFD (days)					
(median, range)	5	3-27	5	3-66	0.611
(mean, SD)	6.8	4.8	8.2	11	
Length of Stay (days)					
(median, range)	6	3-38	6	3-66	0.886
(mean, SD)	7.2	6	8.7	11.7	
Complications	12	29%	13	31%	0.867
Clavien-Dindo					
I	2	5%	2	5%	
II	4	10%	4	10%	
IIIa	2	5%	0	0%	0.506
IIIb	2	5%	1	2%	
Iva	1	2%	3	7%	
Ivb	0	0%	2	5%	
V	1	2%	1	2%	
Treatment Failure	8	20%	3	7%	0.07
Re-Operation	3	7%	3	7%	0.500
90-Day Readmission	2	5%	7	16%	0.077
90-Day Mortality	1	2%	1	2%	0.747

IV – Intravenous, HDU – High Dependency Unit, MFFD – medically fit for discharge

Table 6: Visual Analogue Pain Scores at all Time Points

	Day 0	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6	
		am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
EP (n=41) (median, range) (mean, SD)	1 (0-8) 1.6 (2.1)	2 (0-9) 2.7 (2.4)	1 (0-8) 2 (2.1)	2 (0-8) 2.6 (2.5)	2 (0-10) 2.5 (2.7)	2 (0-9) 2.5 (2)	2 (0-8) 2.6 (2.3)	2 (0-9) 3 (2.0)	2 (0-9) 2.5 (2.1)	2 (0-8) 2.8 (2.4)	2 (0-6) 2.1 (1.9)	2.5 (1-6) 3.1 (1.8)	3 (0-6) 3 (1.9)
AWC (n=42) (median, range) (mean, SD)	3 (0-6) 2.3 (1.8)	2 (0-8) 3.1 (2.2)	2.5 (0-8) 3.0 (2.4)	3 (1-10) 3.4 (2.4)	2 (0-8) 2.4 (2.0)	3 (0-8) 3.2 (2.2)	3 (0-7) 3.0 (2.1)	2 (0-8) 3.2 (2.6)	2 (1-8) 3.2 (2.3)	3 (1-8) 3.6 (2.1)	3 (0-10) 3.6 (2.9)	2 (0-10) 3.2 (2.4)	3 (0-10) 3.6 (3.6)
P Value	0.023	0.238	0.040	0.046	0.749	0.106	0.313	0.956	0.482	0.190	0.157	0.815	0.915

Table 7: Total Analgesic Requirements (IV Morphine Equivalent, mg)

	Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
AWC-PCA (n=42)						
Median (Range)	18.5 (0-76)	14 (0-81)	2 (0-129)	1 (0-10)	0.25 (0-5)	0 (0-5)
Mean (SD)	20 (16)	21 (22)	11 (25)	1 (1.9)	1.1 (1.4)	1 (1.5)
EP (n=41)						
Median (Range)	0 (0-70)	0 (0-89)	0 (0-128)	2 (0-80)	1 (0-96)	0 (0-8)
Mean (SD)	3 (13)	10 (22)	8.7 (24)	7 (16)	4 (15)	1 (1.5)
EP Failure (n=8)						
Median (Range)	2 (0-70)	43 (12-89)	16 (1-128)	0.5 (0-80)	1 (0-2)	0.25 (0-2)
Mean (SD)	19 (28)	46 (30)	33 (44)	5 (12)	1 (1.1)	1 (1)
P Value	<0.001	<0.001	<0.001	0.004	0.455	0.712

Kruskal-Wallis on median, EP Failure was managed with PCA alone

Chapter 4

Analysis of Systemic Inflammatory Response

4.1 Methodology

Analysis of the Systemic Inflammatory Response

A substantial ethical amendment was submitted to the Yorkshire and Humber Research Ethics Committee to approve the systemic inflammatory response analysis work in April 2016. This was approved in June 2016 and, following local R&D approval, sample collection began in August 2016. Patients from the first half of the study were therefore not included in the systemic inflammatory response analysis work and therefore the subsequent 30 patients were recruited. Whole blood was collected in an EDTA tube using a standard technique from participants in the second half of the RCT. Samples were collected at Day 0 (day of surgery), 24 and 72 h post-operatively. Samples were transferred to the laboratory on ice before being centrifuged (4°C at 900g for 10 minutes). The separated plasma was then stored at -80°C after being divided into 0.5ml aliquots. Cytokine levels were measured using Bio-Plex Pro ™ (Human Cytokine 27-plex Assay, Bio-Rad Laboratories, Hemel Hempstead, UK) in a batch analysis once all samples had been obtained. Cytokines analysed for were IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α and VEGF.

Initial preparation for the cytokine analysis involved bringing the assay buffer, wash buffer and sample diluent to room temperature and thawing the samples. Thawed samples were diluted at a ratio of 4:1 with Bio-Plex sample diluent HB. The wash station was primed and wash buffer prepared and diluted 1-part 10x wash buffer (60ml) with 9 parts dH_20 (540ml). The Bio-Plex system was then calibrated. A single vial of standards was reconstituted in 500µl

of standard diluent HB and then vortexed for 5 seconds before incubating on ice for 30 minutes. A fourfold standard dilution series was prepared with 5 seconds of vortex between liquid transfers. The coupled beads were then vortexed for 30 seconds and diluted in Bio-Plex Assay Buffer. This was then protected from light. The diluted beads were then vortexed for 10-20 seconds before adding 50µl to each well of the assay plate. The plate was then washed twice with 100µl Bio-Plex Wash Buffer. Samples were then vortexed and 50µl added to each well. The plate was then covered with sealing tape and incubated on a shaker at 850 rpm at room temperature for 30 minutes.

With 10 minutes remaining in the incubation, the detection antibodies were vortexed for 5 seconds, quick spun and liquid collected before diluting to 1x concentration (300µl detection antibody:2700µl detection antibody diluent HB). The plate was washed with three times with 100µl of buffer, the diluted detection antibodies vortexed and 25µl added to each well. The plate was then covered and incubated on the shaker at 850rpm for 30 minutes at room temperature. The standard S1 values from the assay kit were entered into the Bio-Plex manager Software. With approximately 10 minutes left in the incubation process, the 100x streptavidin-phycoerythrin (SA-PE) was vortexed for 5 seconds, quick spun and the fluid collected. This was diluted to 1x by mixing 60µl SA-PE with 5940µl of assay buffer. The plate was washed three times with 100µl wash buffer and 50µl of vortexed diluted SA-PE added to each well. The plate was again covered, shaken at 850rpm for 10 minutes at room temperature. The plate was then washed three times with 100µl of wash buffer. The beads were resuspended in 125µl assay buffer, the plate covered and shaken at 850 rpm for 30 seconds. The plate was then read using low PMT, RP1 settings for the Bio-Plex 3D System (Bio-Rad Laboratories, Luminex Corporation).

The effect of time and analgesic modality on cytokine response was analysed using two-way ANOVA with repeated measures after testing for normal distribution using SPSS version 25.

4.2 Results

Thirty patients were recruited into the cytokine analysis. There were more patients in the AWC group (n=17) than the EP group (n=13). Patients in the EP group were more likely to be ASA II and have a larger portion of liver resected. The AWC-PCA group had a significantly shorter anaesthetic time and longer surgical time. There was a non-significant trend towards more serious complications (Clavien-Dindo grade $\geq$3) in the AWC-PCA group, 4/8 complications versus 0/4 complications in the EP group. The demographics for patients enrolled in the cytokine analysis are available in Table 8.

The level of IL-9 and MIP-1β were significantly lower over time in the AWC-PCA group. Levels of these two cytokines fell from baseline levels at the two other timepoints in the AWC-PCA group whereas levels in the EP group rose. There were no other significant differences with regards to the systemic inflammatory response when taking into account time and analgesic modality. These results are summarised in Table 9 and Figure 9.

Table 8: Demographics For Patients in Cytokine Analysis

	EP (range/%) (n=13)	**AWC (Range/%) (n=17)**	**P Value**
Age, median (year) (Mean (SD))	63 (57-81) 66 (8)	58 (42-75) 61 (10)	0.116
Sex (Female)	5 (38%)	5 (29%)	0.602
ASA II	11 (85%)	6 (35%)	0.005
BMI (median, kg/m^2)	26 (22-37) 27 (5)	27 (25-35) 29 (4)	0.537
Baseline Peakflow Median (L/min)	390 (240-500) 387 (93)	400 (250-640) 455 (127)	0.198
Diagnosis CRLM HCC CCA Benign Other	 8 3 2 0 0	 10 0 4 2 1	0.167
Major Resection	9 (69%)	7 (41%)	0.127
Anatomical resection	9 (69%)	9 (53%)	0.611
Number of Segments	4 (2-6) 4 (1)	2 (1-4) 2 (1)	0.03
Wound Shape Reverse 'L' Kocher Midline	 10 (77%) 1 (8%) 2 (15%)	 14 (82%) 2 (12%) 1 (6%)	0.587
Wound Length (cm)	29 (17-34) 27 (5)	27 (16-32) 27 (4)	0.251
Prior Abdo. Surgery	6	9	0.713
Redo Liver Resection	1	3	0.427
Anaesthetic Time (min)	60 (41-126) 71 (25)	41 (20-115) 45 (22)	0.002
Surgical Time	180 (110-330) 180 (63)	213 (100-375) 254 (94)	0.036
Complications	4 (31%)	8 (53%)	0.367
Clavien-Dindo I II III IV V	 0 4 0 0 0	 1 3 0 3 1	0.083*

*comparison of serious complications (Clavien-Dindo $\geq$3)

Table 9: Assessment of the systemic inflammatory response between Abdominal Wound Catheters + PCA versus Thoracic Epidural following Open Liver Resection

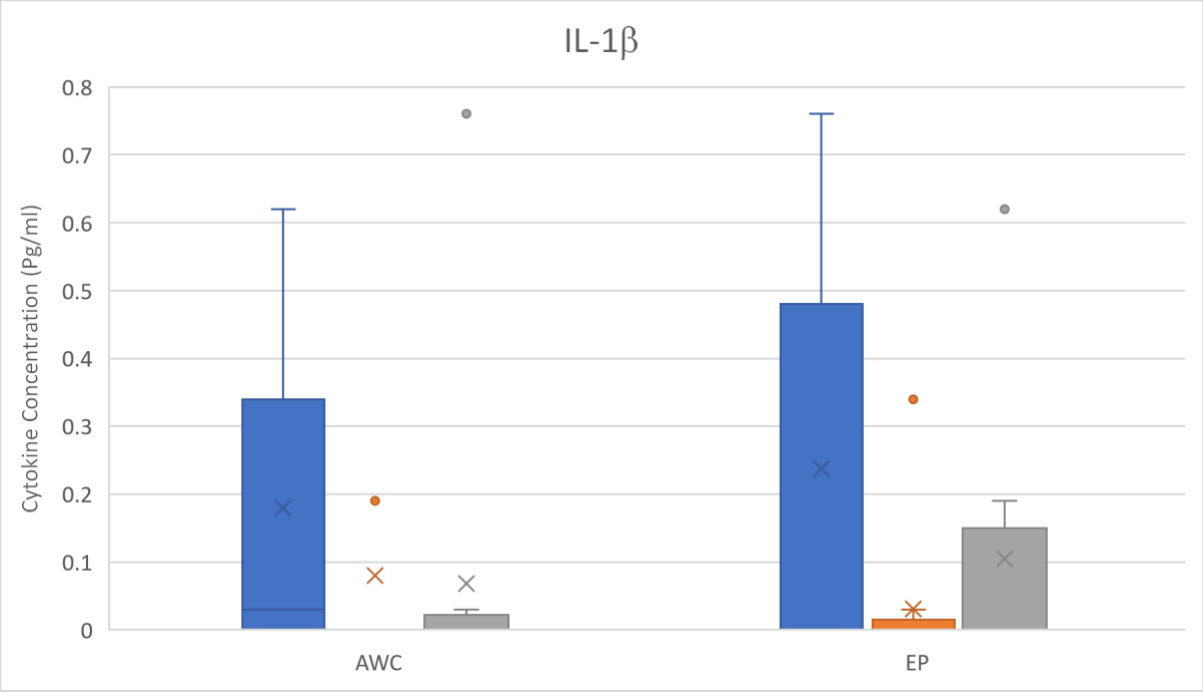
		Day 0 (pg/ml)	**Day 1 (pg/ml)**	**Day 3 (pg/ml)**	**P value***
IL-1β	AWC-PCA	0.03 (0-1.03) 0.18 (0.29)	0 (0-1.17) 0.08 (0.28)	0 (0-0.76) 0.07 (0.22)	0.336
	EP	0 (0-0.76) 0.22 (0.29)	0 (0-1) 0.10 (0.27)	0.03 (0-637) 65 (191)	
IL-1ra	AWC-PCA	73 (47-485) 146 (132)	98 (40-344) 120 (78)	119 (44-288) 149 (80)	0.287
	EP	52 (34-101) 63 (23)	71 (23-740) 130 (192)	78 (31-637) 169 (198)	
IL-2	AWC-PCA	3.2 (1.1-4.3) 3.2 (1.1)	2.7 (0.1-7.1) 2.6 (1.6)	2.3 (0.1-5.7) 2.4 (1.7)	0.051
	EP	3.2 (0.1-1) 3.3 (2.4)	2.7 (0.1-4.9) 2.4 (1.4)	3.2 (0-4.3) 2.9 (1.4)	
IL-4	AWC-PCA	1.1 (0.3-1.5) 1 (0.38)	0.88 (0.2-3.4) 0.97 (0.77)	0.69 (0.3-3.2) 1 (0.86)	0.564
	EP	0.9 (0.3-3.2) 3.2 (1.1)	0.7 (0.2-1.3) 0.79 (0.4)	1.1 (0.4-2.3) 1.2 (0.6)	
IL-5	AWC-PCA	7.2 (2.3-15.2) 7.3 (3)	5.9 (1.2-15.1) 6.2 (3.6)	4.7 (0.3-16.5) 5.8 (4.5)	0.064
	EP	7.2 (1.2-35.6) 8.7 (8.5)	3.5 (0.7-16.5) 5.9 (4.5)	8.5 (0-12.4) 8.4 (3.7)	
IL-6	AWC-PCA	3.6 (1.4-8.8) 3.7 (2.1)	6.5 (1-13.4) 6.2 (3.7)	5.3 (1-9.4) 4.4 (3)	0.830
	EP	2.5 (0.5-6.6) 2.2 (1.6)	5.8 (0.5-31.1) 2 (8.5)	7.7 (0.9-27) 3.6 (9)	
IL-7	AWC-PCA	10 (0-48.3) 14.4 (13.2)	6.2 (0-102.2) 15.2 (24.7)	6.2 (0-94.5) 17.5 (28.1)	0.341
	EP	13.8 (0-59.8) 15.7 (16.7)	0 (0-48.3) 8.7 (13.8)	6.2 (0-40.6) 15.4 (16.6)	
IL-8	AWC-PCA	6.4 (2.1-16) 6.9 (3.7)	9.2 (3.7-23.6) 10.6 (6)	11.7 (1.6-21) 12.2 (6.7)	0.445
	EP	3.7 (1.1-27.5) 6.5 (7.4)	7 (1.6-53.6) 12.3 (14.5)	9.9 (1.6-46.5) 16 (14.8)	
IL-9	AWC-PCA	99 (61-119) 94 (18.5)	80.5 (46-123) 84 (22.9)	82.9 (54-142) 85.3 (25.4)	0.005
	EP	79.7 (70-116) 90 (18)	78 (49-121) 83 (22)	95 (67-133) 101 (24)	
IL-10	AWC-PCA	1.7 (0-49) 6.2 (13)	2.8 (0-8.1) 3.1 (2.6)	1.2 (0-5.4) 1.9 (2)	0.255
	EP	0.4 (0-5.7) 1 (1.6)	0.8 (0-5.4) 1.5 (1.7)	2.1 (0-6.1) 2.1 (2.3)	
IL-12	AWC-PCA	0.82 (0-2.9) 0.95 (0.9)	0 (0-5.6) 0.8 (1.5)	0 (0-2.9) 0.5 (1.0)	0.857

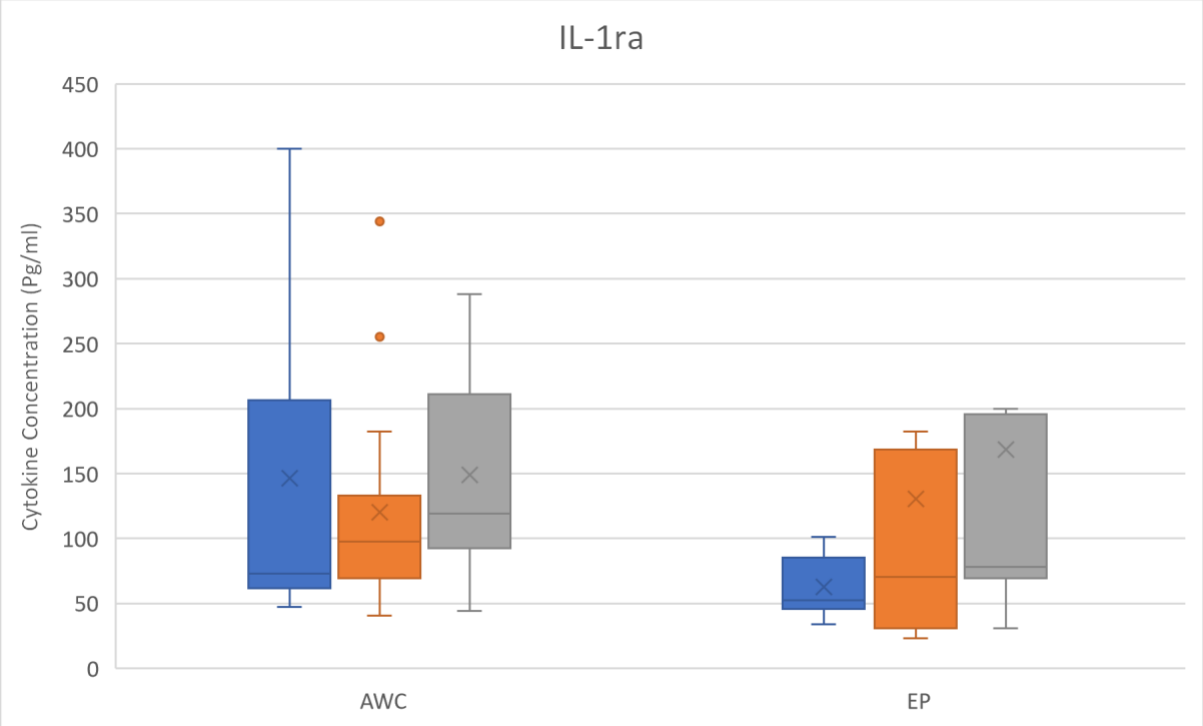
	EP	0.4 (0-17) 1.4 (3.1)	0 (0-5.6) 0.8 (1.4)	0 (0-2.9) 0.6 (0.9)	
IL-13	AWC-PCA	1.2 (0.9-2) 1.3 (0.3)	1.0 (0.7-2.5) 1.1 (0.4)	0.9 (0.7-2.3) 1.1 (0.4)	0.060
	EP	1.3 (0.8-1.5) 1.2 (0.3)	1.2 (1-1.2) 1.1 (0.1)	1.2 (1.2-1.7) 1.3 (0.3)	
IL-15	AWC-PCA	0 (0-0) 0(0)	0 (0-0) 0 (0)	0 (0-0) 0 (0)	0.999
	EP	0 (0-52) 4 (14.5)	0 (0-0) 0 (0)	0 (0-0) 0 (0)	
IL-17	AWC-PCA	7.3 (5-10.6) 7.3 (1.4)	6.3 (3.2-10.6) 6.3 (2.1)	5.3 (3.2-12.1) 6 (2.6)	0.367
	EP	6.9 (5-12) 7.5 (2.3)	6.3 (3.8-9.8) 6.3 (1.6)	6.4 (3.8-9.1) 6.6 (1.6)	
Eotaxin	AWC-PCA	9.0 (4.4-26.2) 10.1 (5.0)	7.0 (2.3-18.2) 7.3 (3.8)	5.3 (2.4-9.8) 5.6 (2.8)	0.407
	EP	10.3 (5.5-17.8) 10.7 (4.0)	7.3 (2.4-24.5) 9.9 (7.2)	7.1 (3.1-23.6) 9.1 (6.3)	
FGF Basic	AWC-PCA	10.8 (3.6-21.3) 10.9 (4.6)	6.3 (0-21.3) 6 (6)	0 (0-18.1) 5 (7.1)	0.317
	EP	10.8 (0-24.4) 10.5 (7.3)	6.3 (0-14.6) 6.2 (5.1)	8.6 (0-18.1) 9.3 (7.3)	
G-CSF	AWC-PCA	24.3 (8.9-61.1) 29.6 (17.2	40.4 (14-136) 50.8 (32.2)	32.9 (7-142) 56.6 (48.7)	0.397
	EP	22.7 (4.8-85.8) 30.2 (23.8)	29.3 (11-86) 39.9 (26.2)	46.6 (7-102) 48.4 (32.3)	
GM-CSF	AWC-PCA	0.1 (0-0.9) 0.2 (0.3)	0 (0-0.8) 0.1 (0.2)	0 (0-0.8) 0.1 (0.3)	0.790
	EP	0.2 (0-3.8) 0.5 (1)	0 (0-0.9) 0.2 (0.3)	0.3 (0-0.9) 0.4 (0.3)	
IFN-γ	AWC-PCA	5.3 (1.1-12) 5.3 (2.7)	3.8 (0.3-12.9) 4.6 (3)	3.4 (0.6-14.7) 4.8 (5.3)	0.150
	EP	4.5 (1.1-19.5) 5.8 (4.7)	3.8 (0.6-9.4) 4.1 (2.7)	5.3 (0.6-8.1) 5.3 (2.4)	
IP-10	AWC-PCA	82 (46-190) 87 (38)	52 (24-120) 57 (22)	50 (40-78) 53 (12)	0.118
	EP	96 (48-1034) 168 (263)	56 (24-1185) 145 (313)	67 (50-149) 82 (35)	
MCP-1	AWC-PCA	17.7 (4.8-113) 28.4 (29.5)	25.9 (7.3-88) 31.1 (20.5)	21 (8.7-36) 23.4 (9.4)	0.147
	EP	17.4 (5.5-54) 19.3 (13.5)	17 (3-80) 24.7 (25.3)	17 (4-84) 28 (25)	
MIP-1α	AWC-PCA	0.7 (0.3-2) 0.8 (0.4)	0.6 (0-2.3) 0.8 (0.6)	0.6 (0.2-2.3) 0.9 (0.7)	0.109
	EP	0.8 (0.2-2.3) 0.8 (0.5)	0.6 (0-2) 0.8 (0.5)	0.9 (0.1-2) 1 (0.6)	

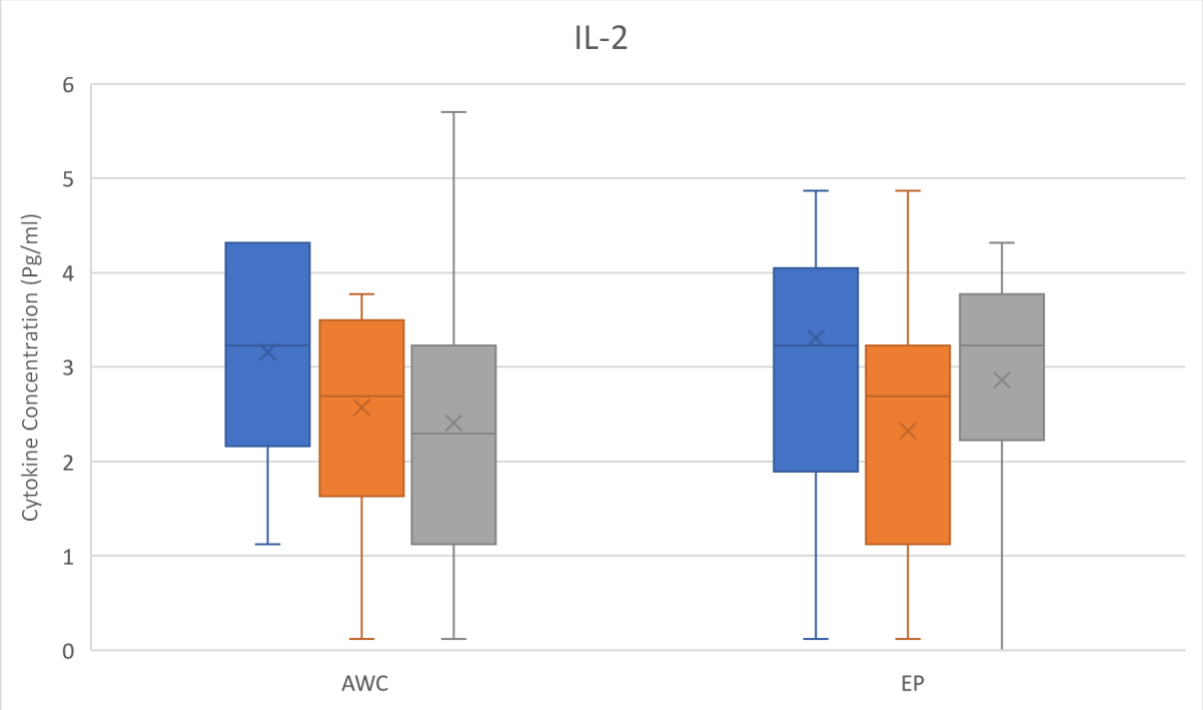
PDGF-bb	AWC-PCA	357 (152-2406) 588 (604)	100 (0-1093) 213 (288)	44 (4-547) 139 (167)	0.933
	EP	428 (94-1008) 449 (320)	237 (44-1638) 375 (424)	242 (0-942) 333 (293)	
MIP-1β	AWC-PCA	50 (32-74) 50 (12)	47 (24-66) 46 (12)	41 (28-61) 42 (11)	0.002
	EP	48 (33-65) 47 (10)	51 (30-65) 49 (11)	52 (32-74) 53 (13)	
TNF-α	AWC-PCA	22 (12-37) 22 (7)	20 (7-46) 21 (11)	18 (9-48) 23 (12)	0.385
	EP	20 (10-44) 22 (8)	20 (7-31) 19 (7)	22 (10-35) 24 (8)	
VEG-F	AWC-PCA	0.5 (0-90) 18 (27)	0.5 (0-66) 11 (19)	0 (0-61) 9 (18)	0.741
	EP	25 (0-86) 26 (25)	0 (0-45) 9 (16)	17 (0-49) 18 (18)	

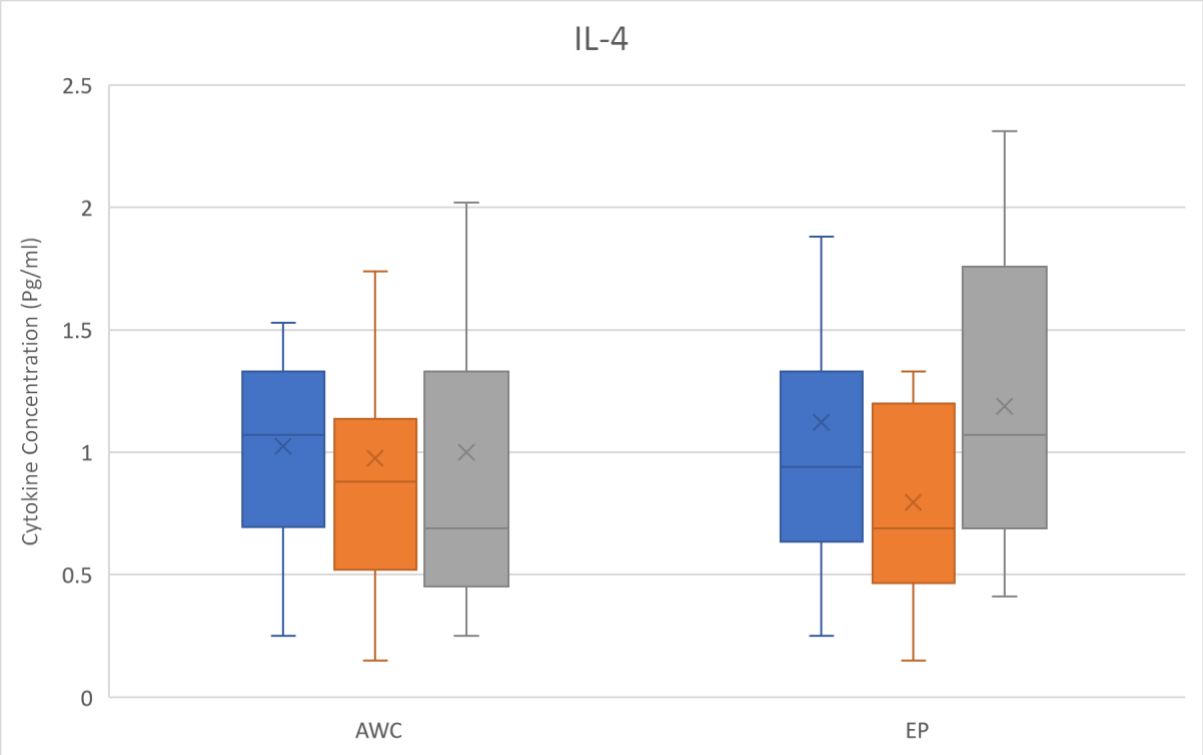
Comparison using 2-Way ANOVA with repeated measures.

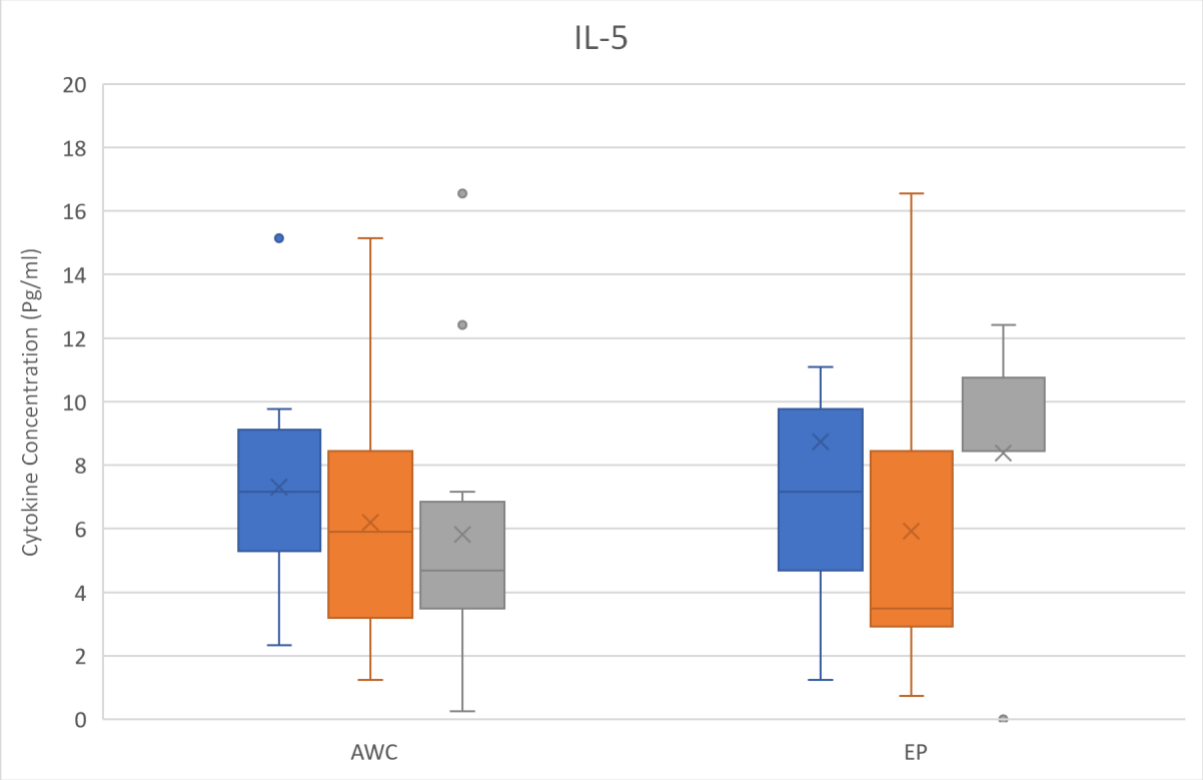
Figure 9: Graphs Comparing Systemic Inflammatory Response between Abdominal Wound Catheters and Thoracic Epidural

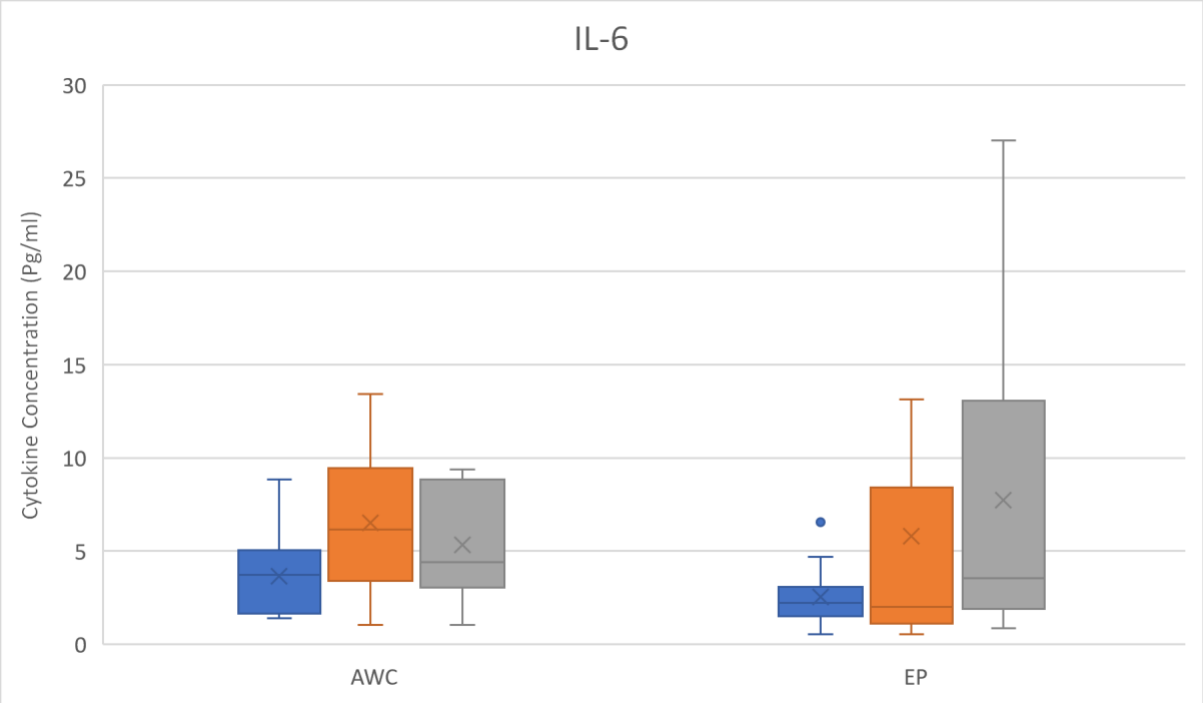


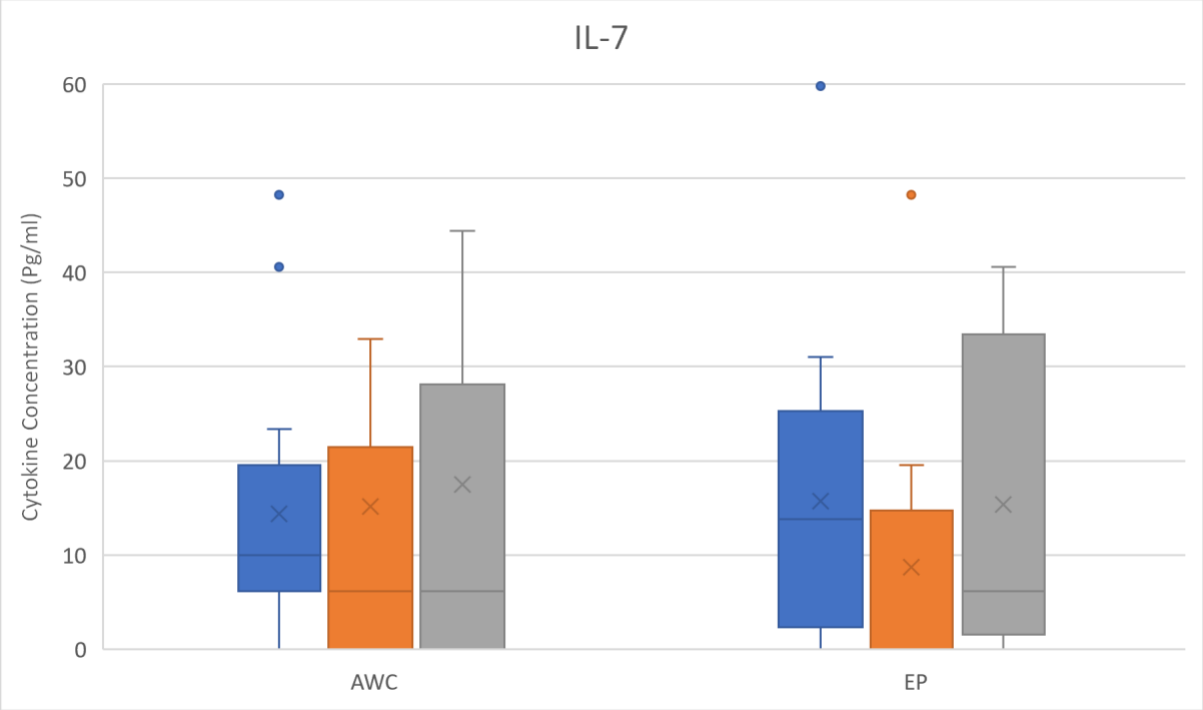


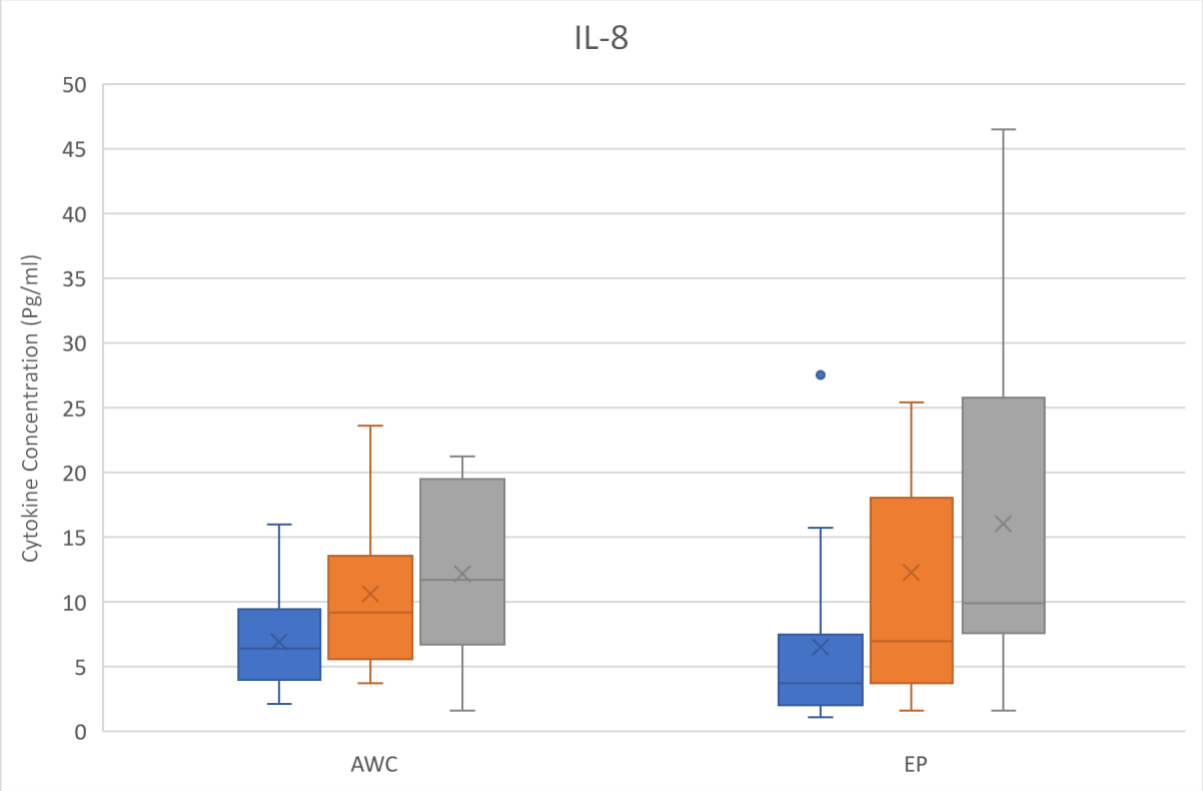

IL-2
Cytokine Concentration (Pg/ml)
6
5
4
3
2
1
0
AWC
EP

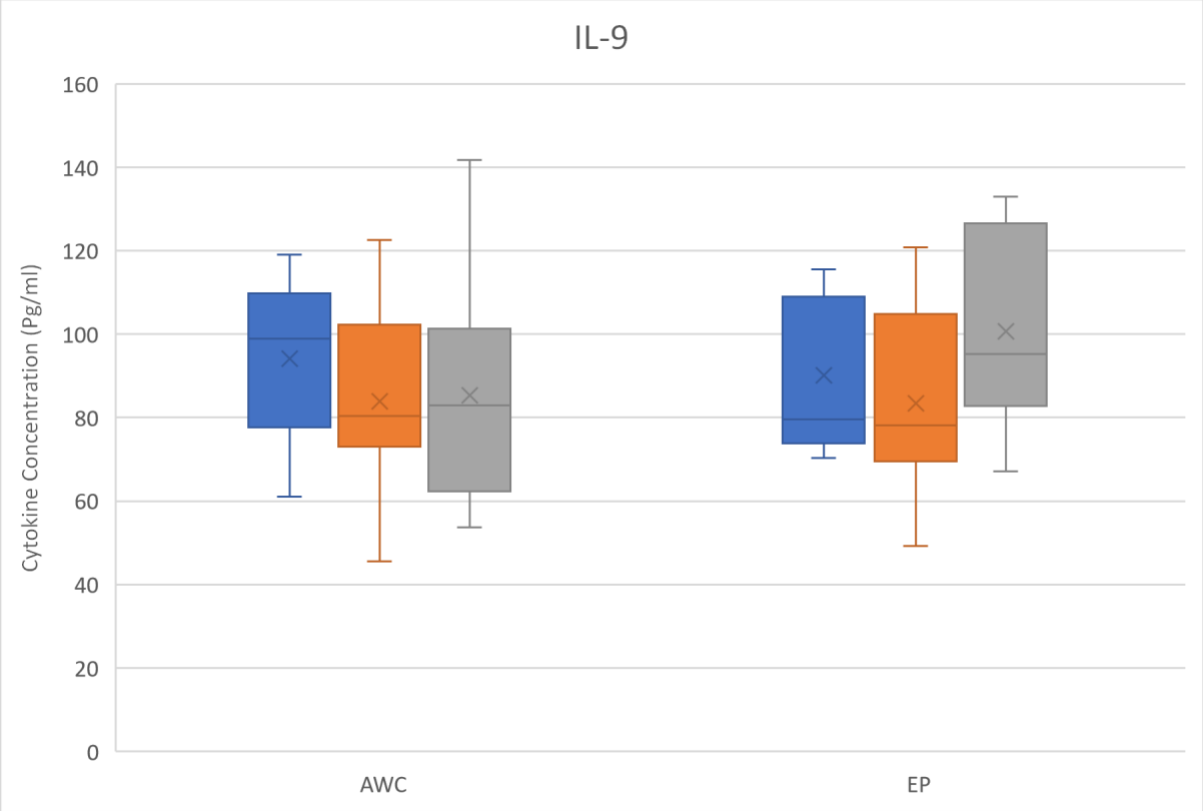

IL-4
Cytokine Concentration (Pg/ml)
2.5
2
1.5
1
0.5
0
AWC
EP

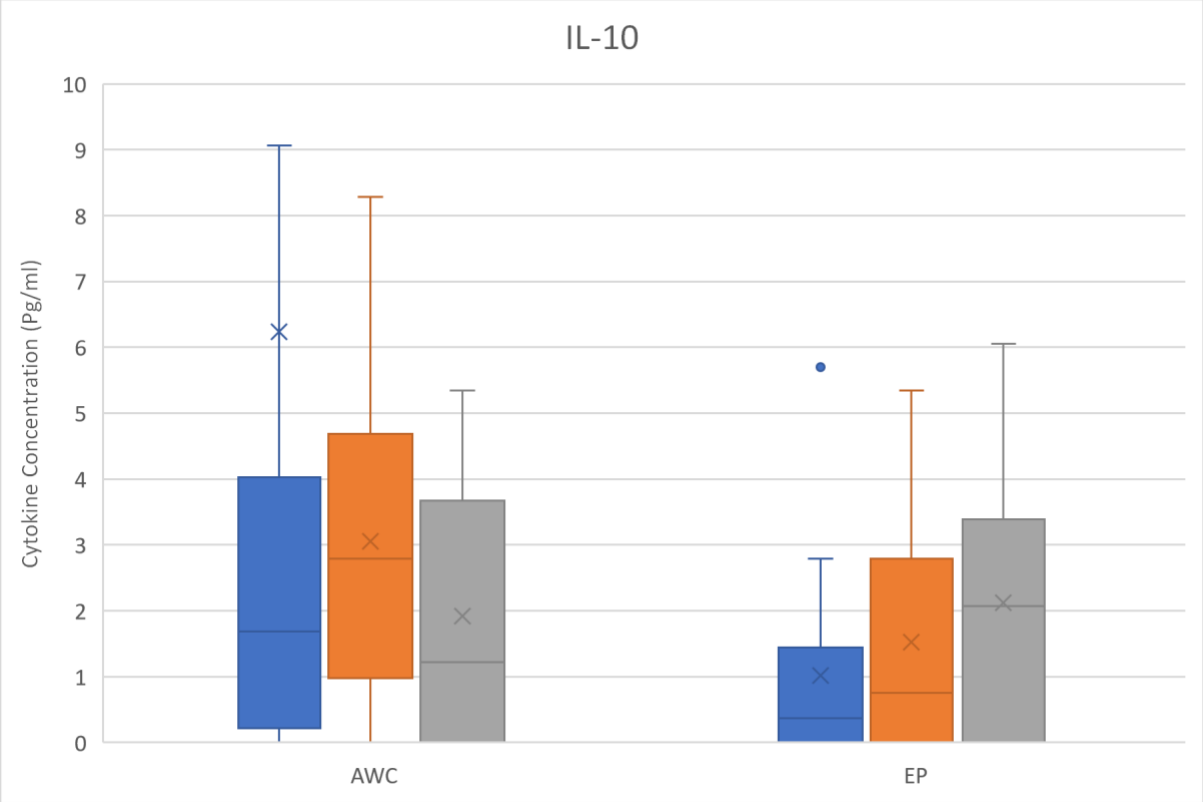

IL-5
Cytokine Concentration (Pg/ml)
20
18
16
14
12
10
8
6
4
2
0
AWC
EP

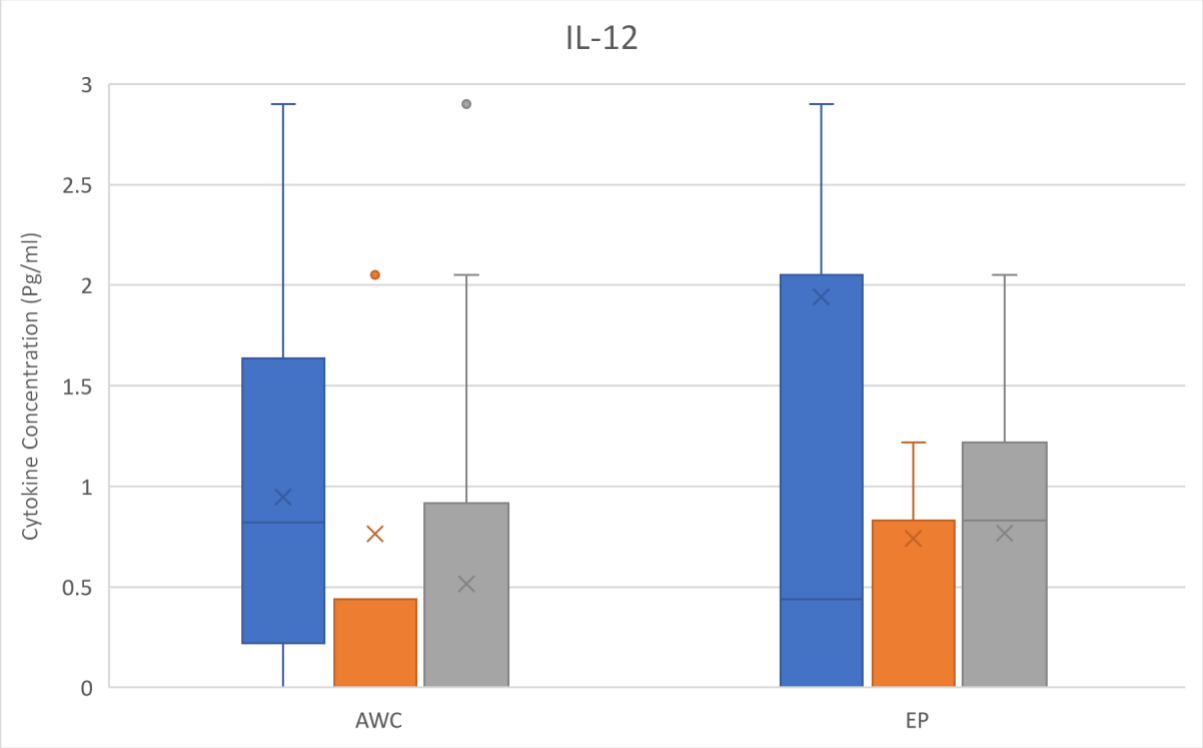

IL-6
Cytokine Concentration (Pg/ml)
30
25
20
15
10
5
0
AWC
EP

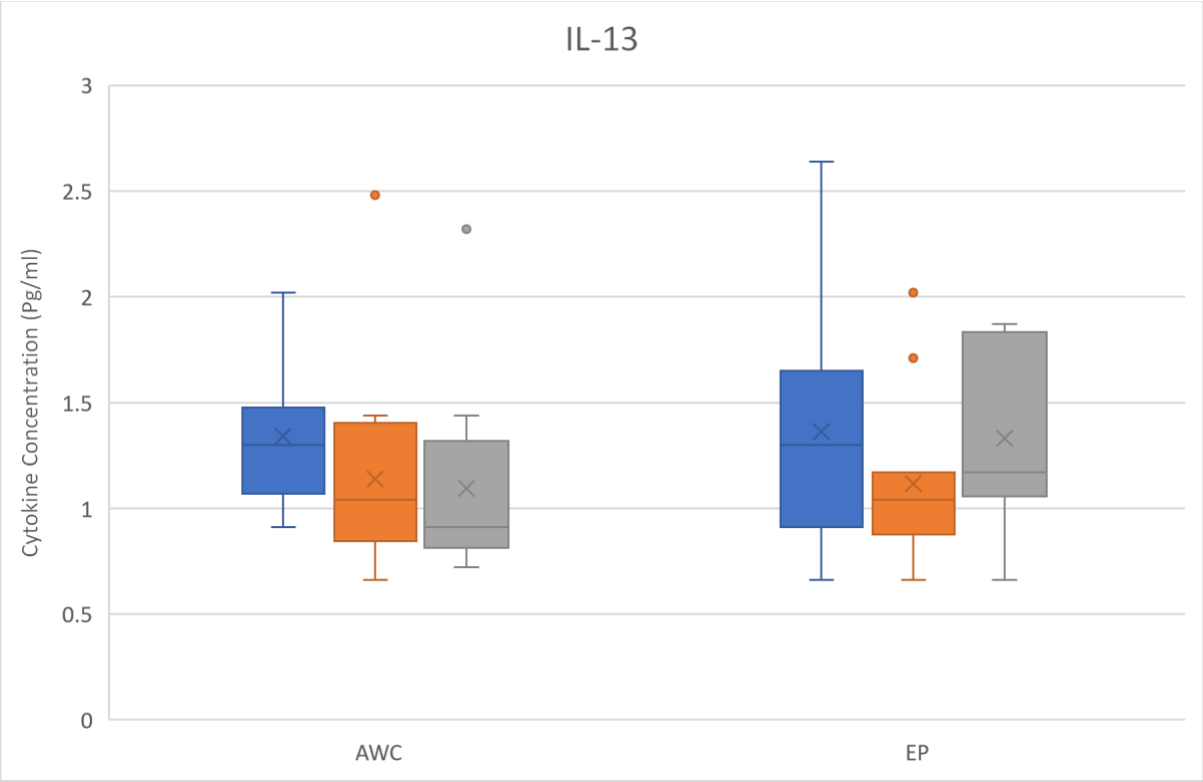

IL-7
Cytokine Concentration (Pg/ml)
60
50
40
30
20
10
0
AWC
EP

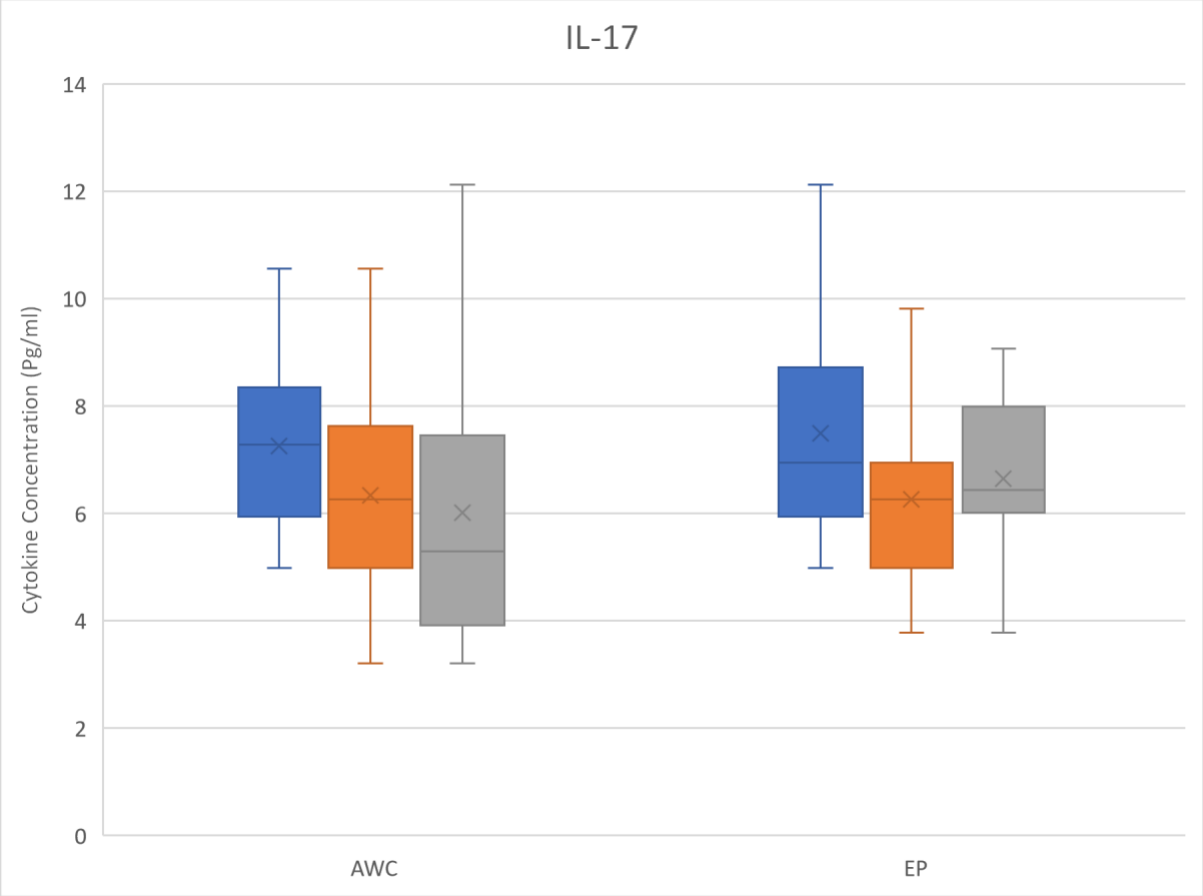

IL-8
Cytokine Concentration (Pg/ml)
50
45
40
35
30
25
20
15
10
5
0
AWC
EP

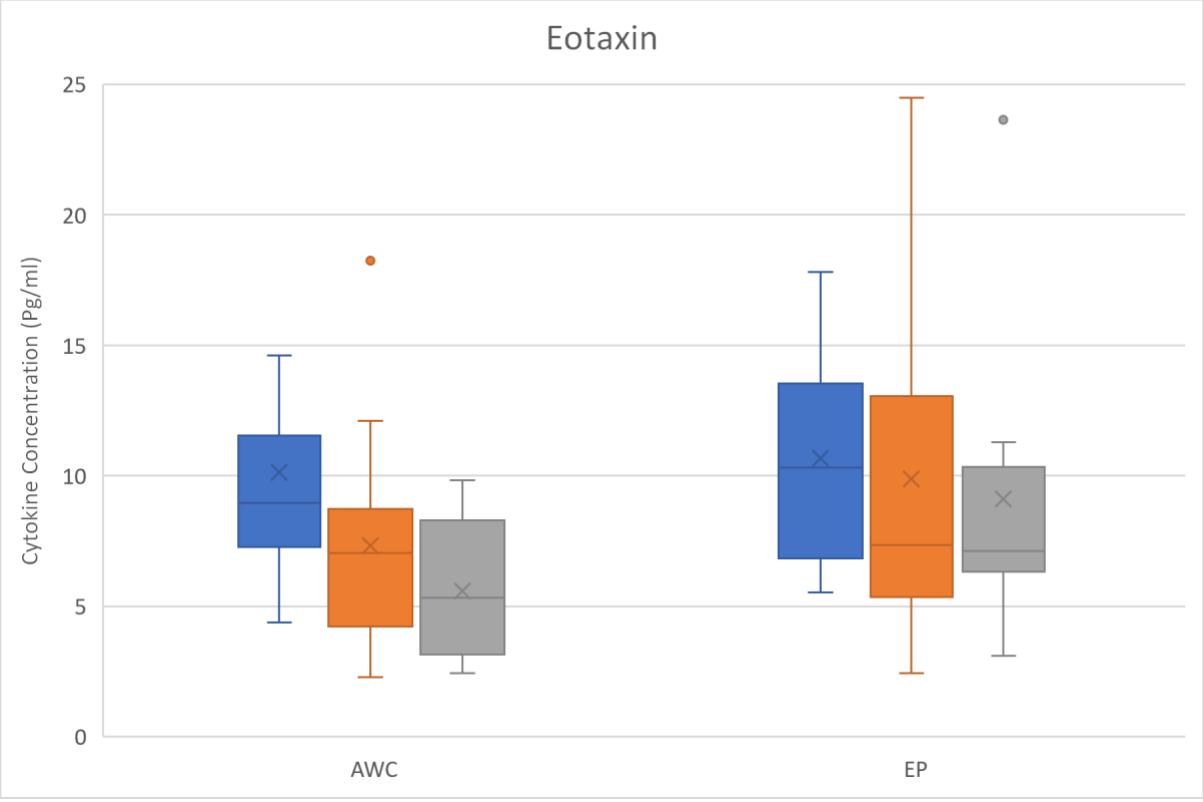

IL-9
Cytokine Concentration (Pg/ml)
160
140
120
100
80
60
40
20
0
AWC
EP

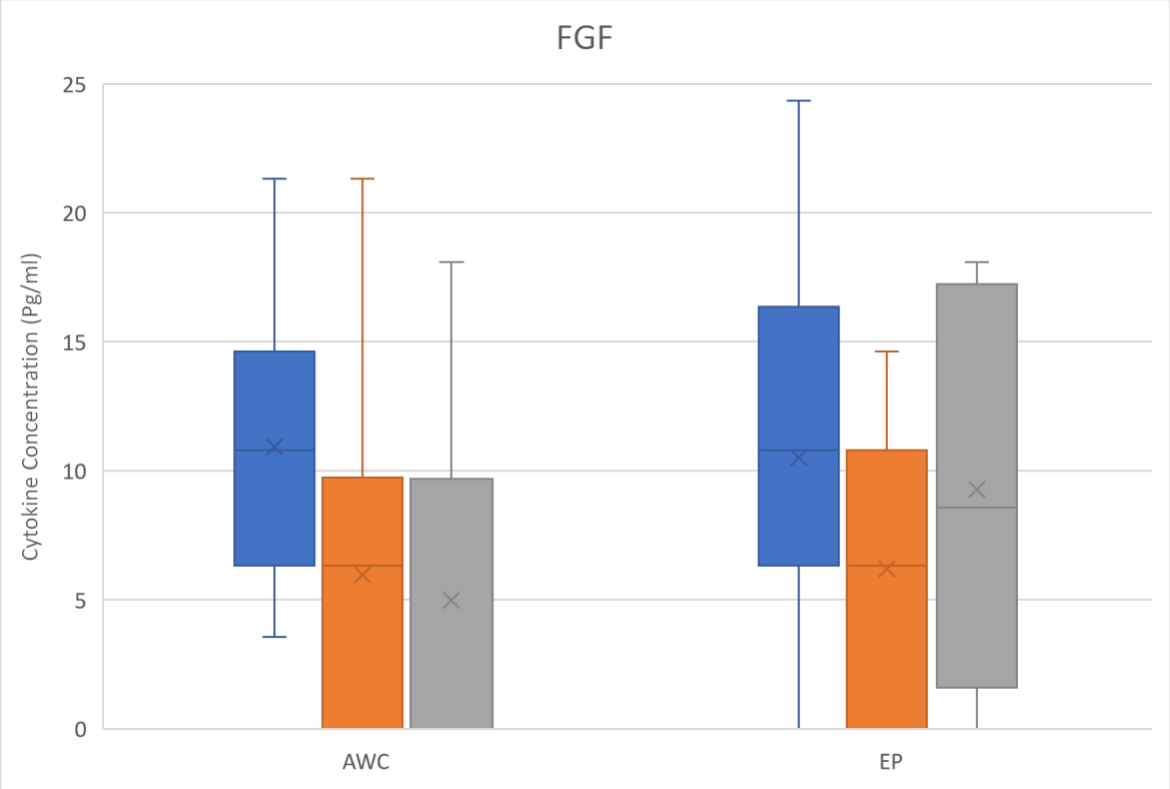

IL-10
Cytokine Concentration (Pg/ml)
10
9
8
7
6
5
4
3
2
1
0
AWC
EP

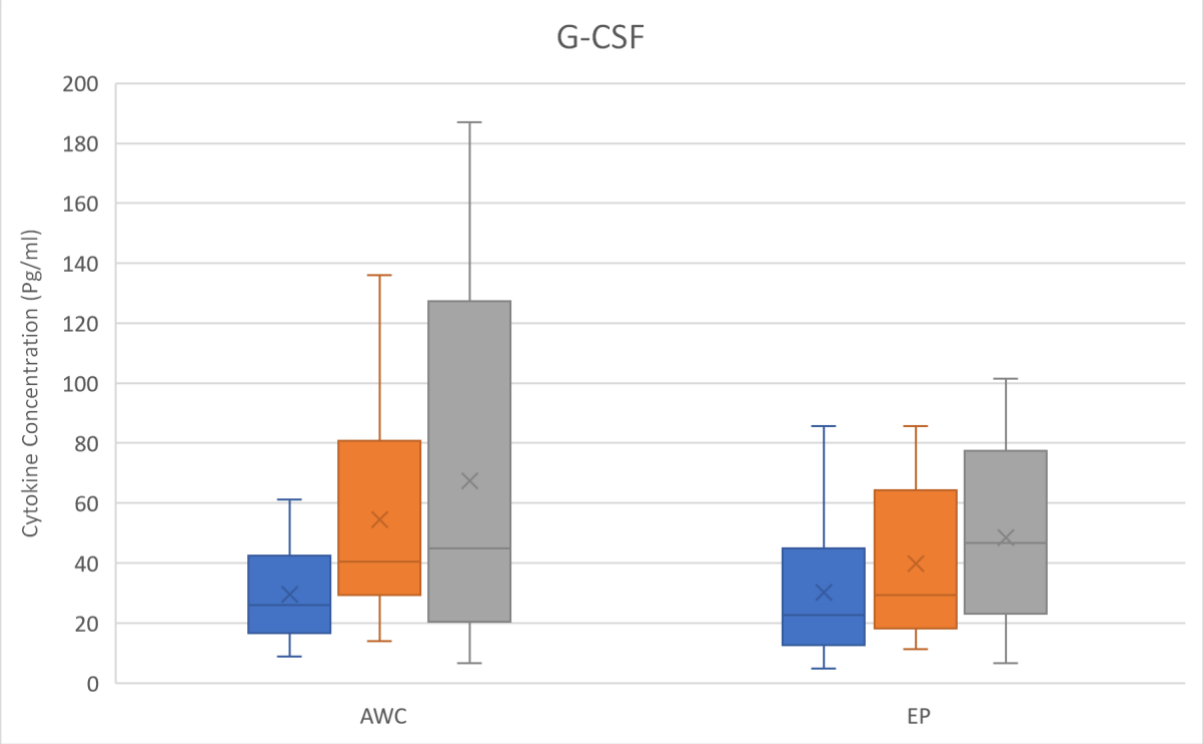

IL-12
Cytokine Concentration (Pg/ml)
3
2.5
2
1.5
1
0.5
0
AWC
EP

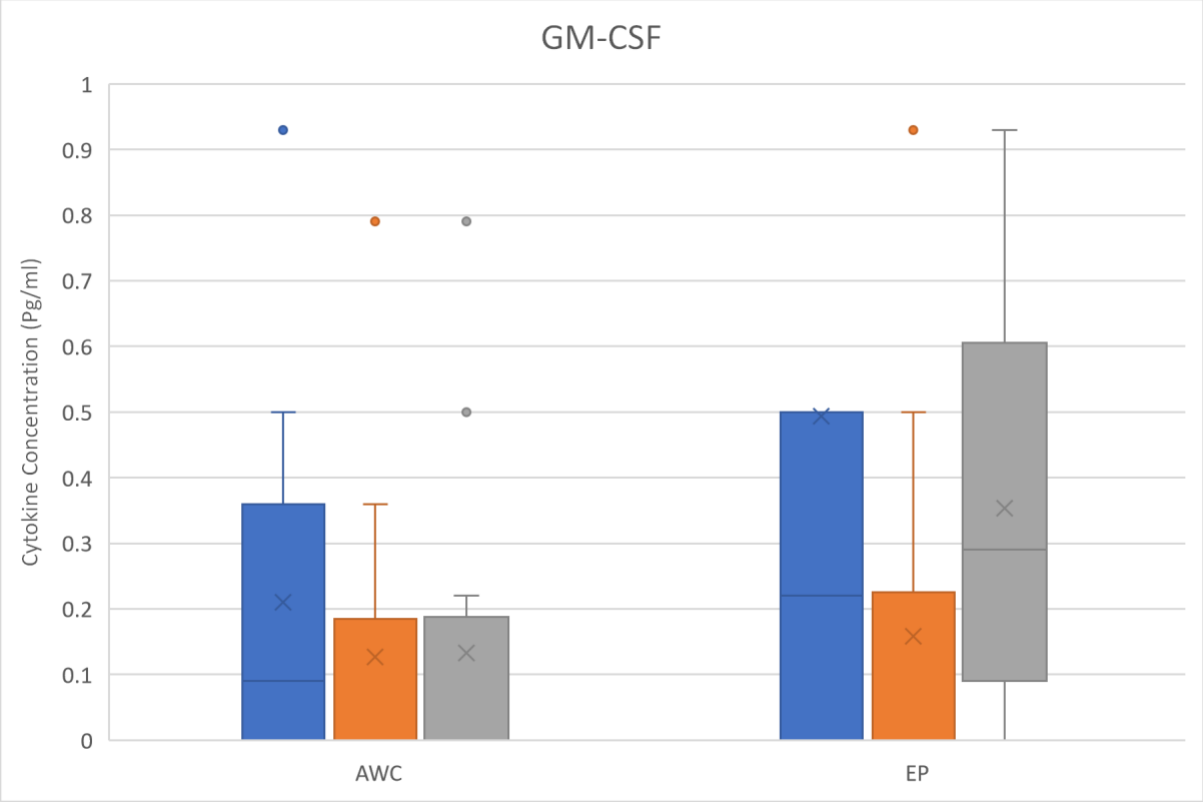

IL-13
Cytokine Concentration (Pg/ml)
3
2.5
2
1.5
1
0.5
0
AWC
EP

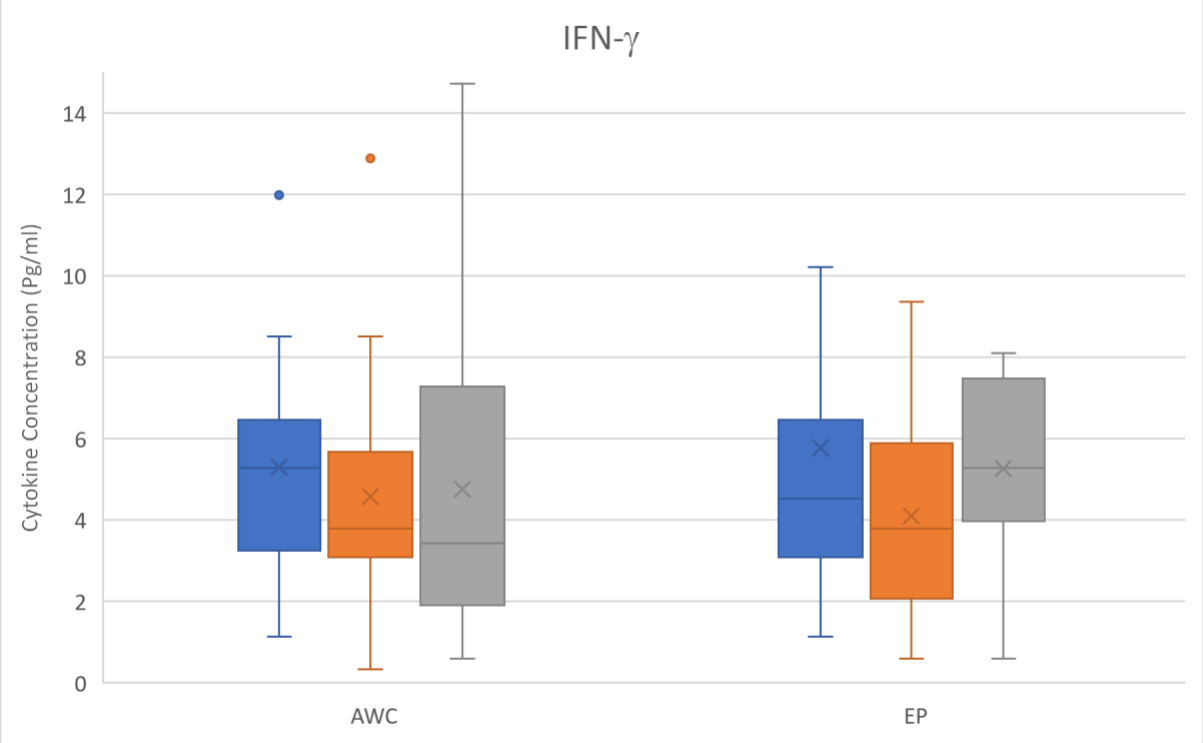

IL-17
Cytokine Concentration (Pg/ml)
14
12
10
8
6
4
2
0
AWC
EP

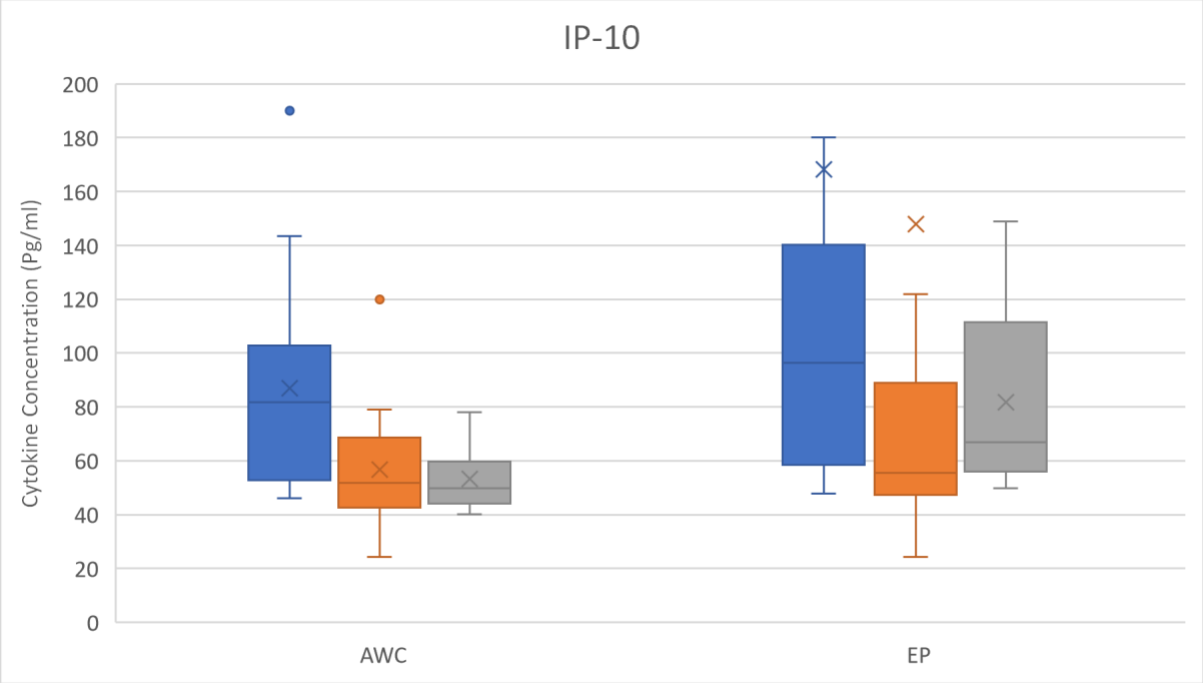

Eotaxin
Cytokine Concentration (Pg/ml)
25
20
15
10
5
0
AWC
EP

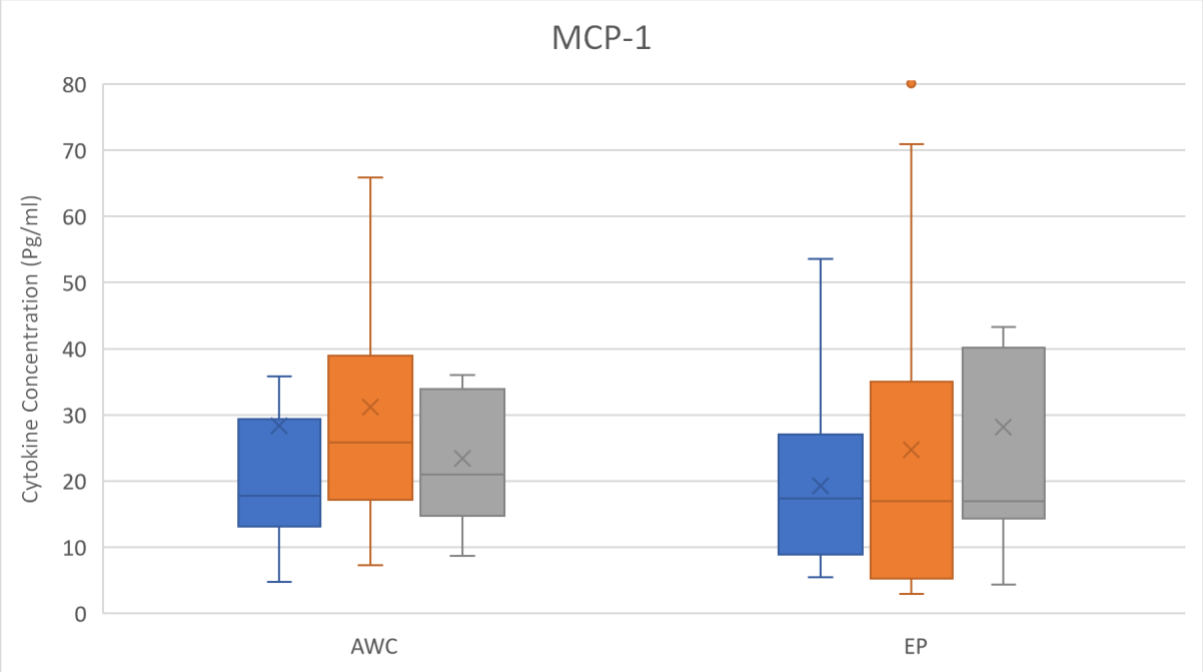

FGF
Cytokine Concentration (Pg/ml)
25
20
15
10
5
0
AWC
EP

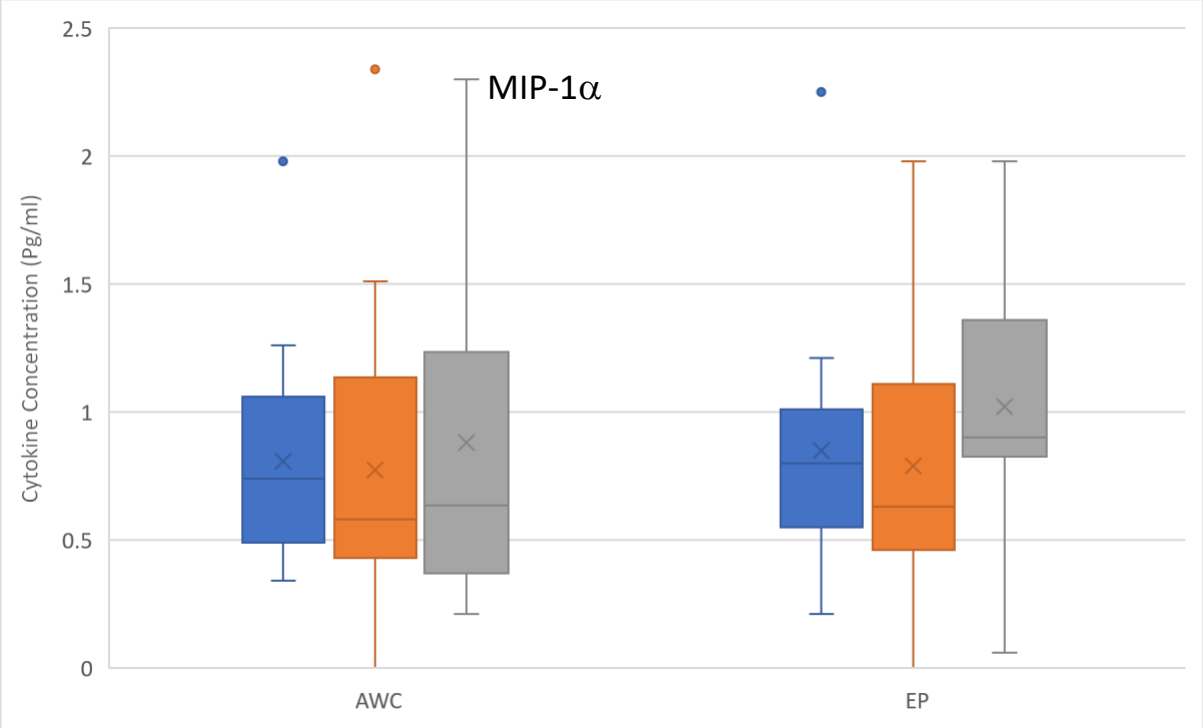

G-CSF
Cytokine Concentration (Pg/ml)
200
180
160
140
120
100
80
60
40
20
0
AWC
EP

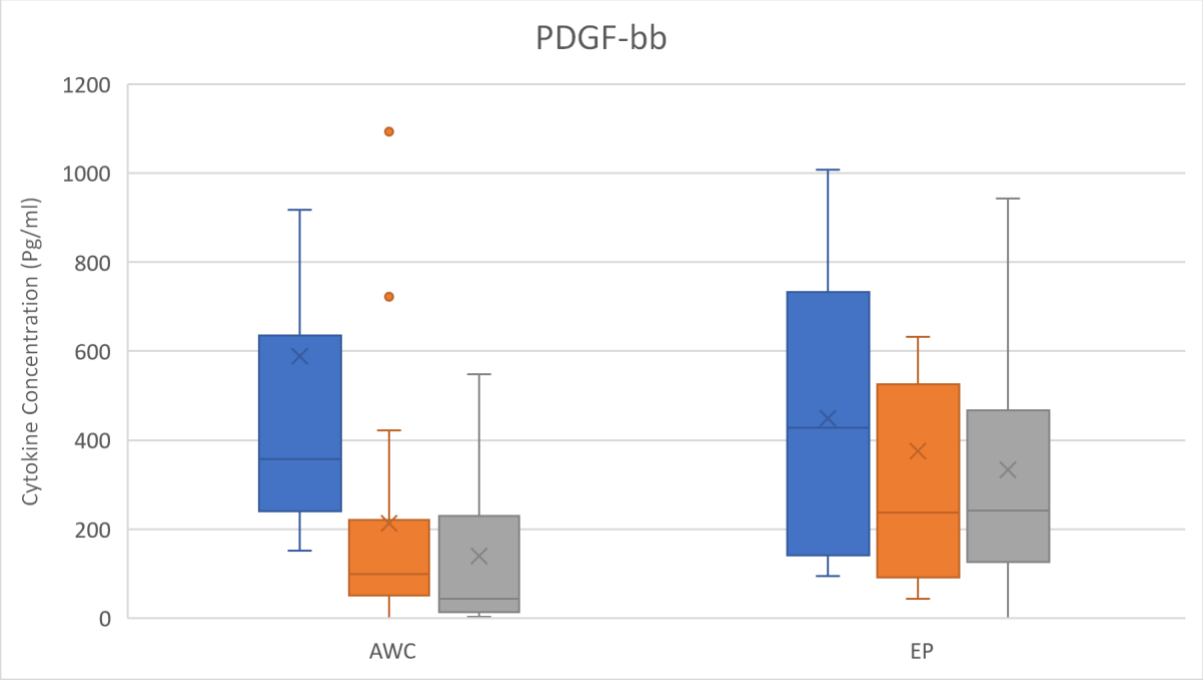

GM-CSF
Cytokine Concentration (Pg/ml)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
AWC
EP

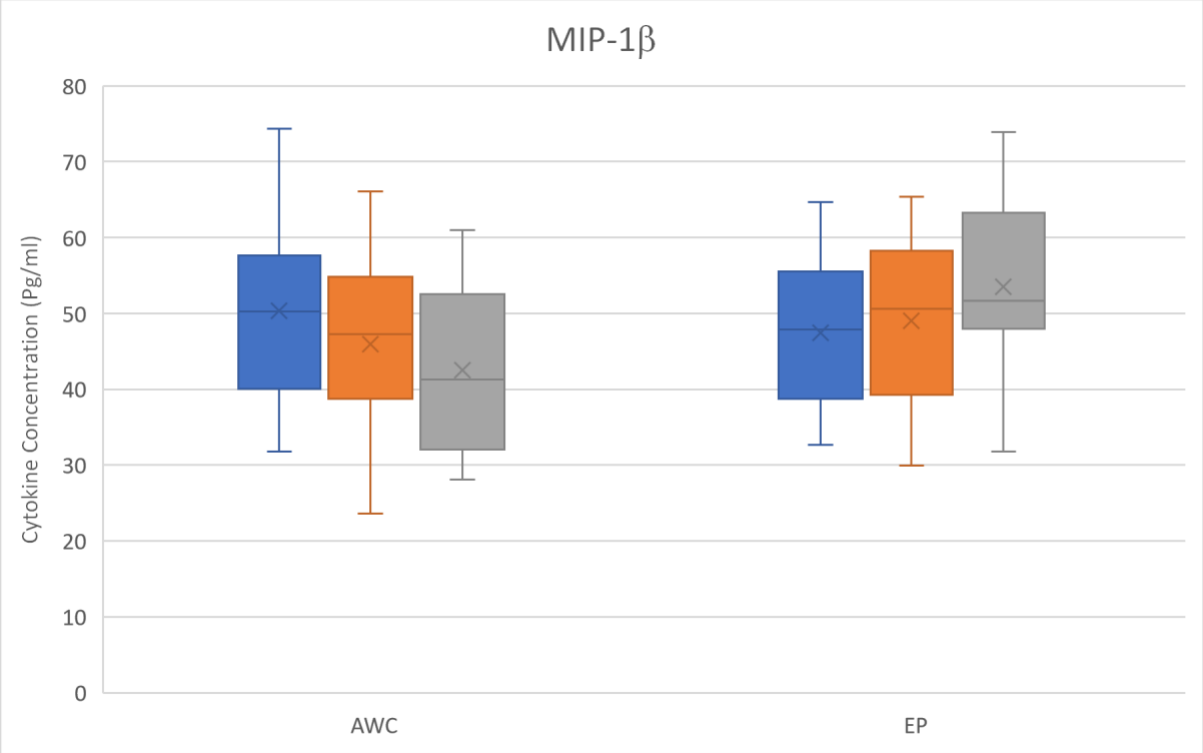

IFN-γ
Cytokine Concentration (Pg/ml)
14
12
10
8
6
4
2
0
AWC
EP

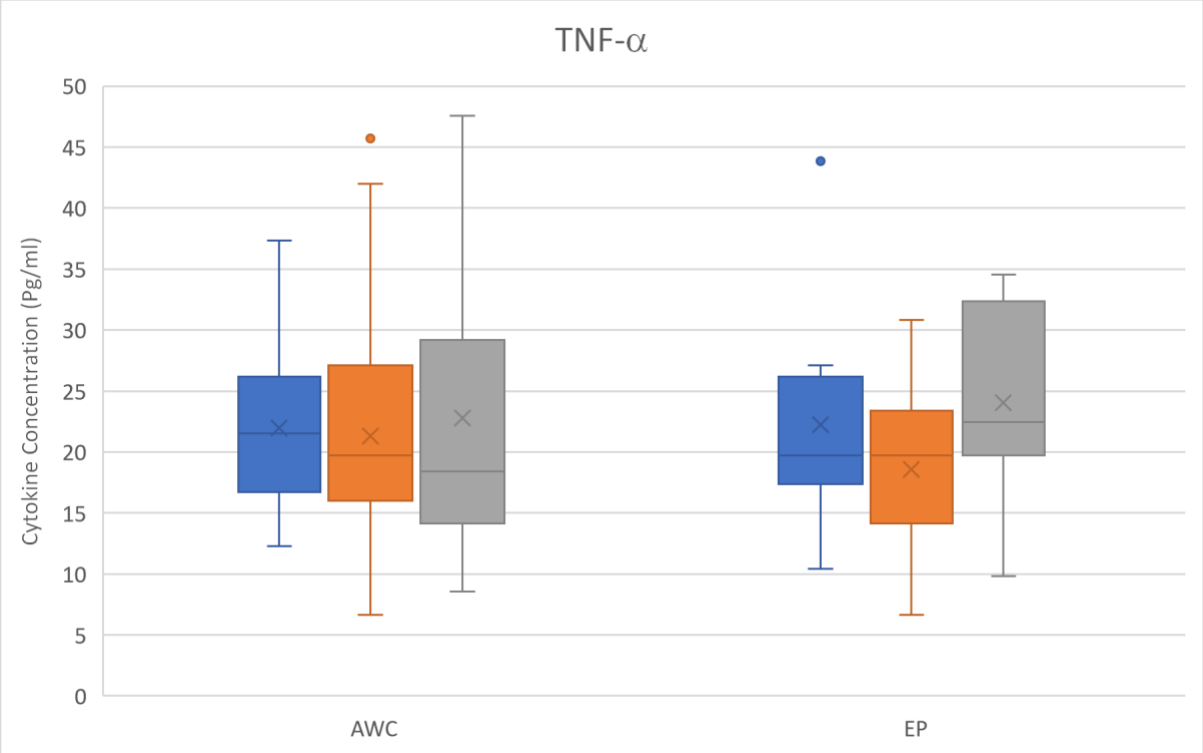

IP-10
Cytokine Concentration (Pg/ml)
200
180
160
140
120
100
80
60
40
20
0
AWC
EP

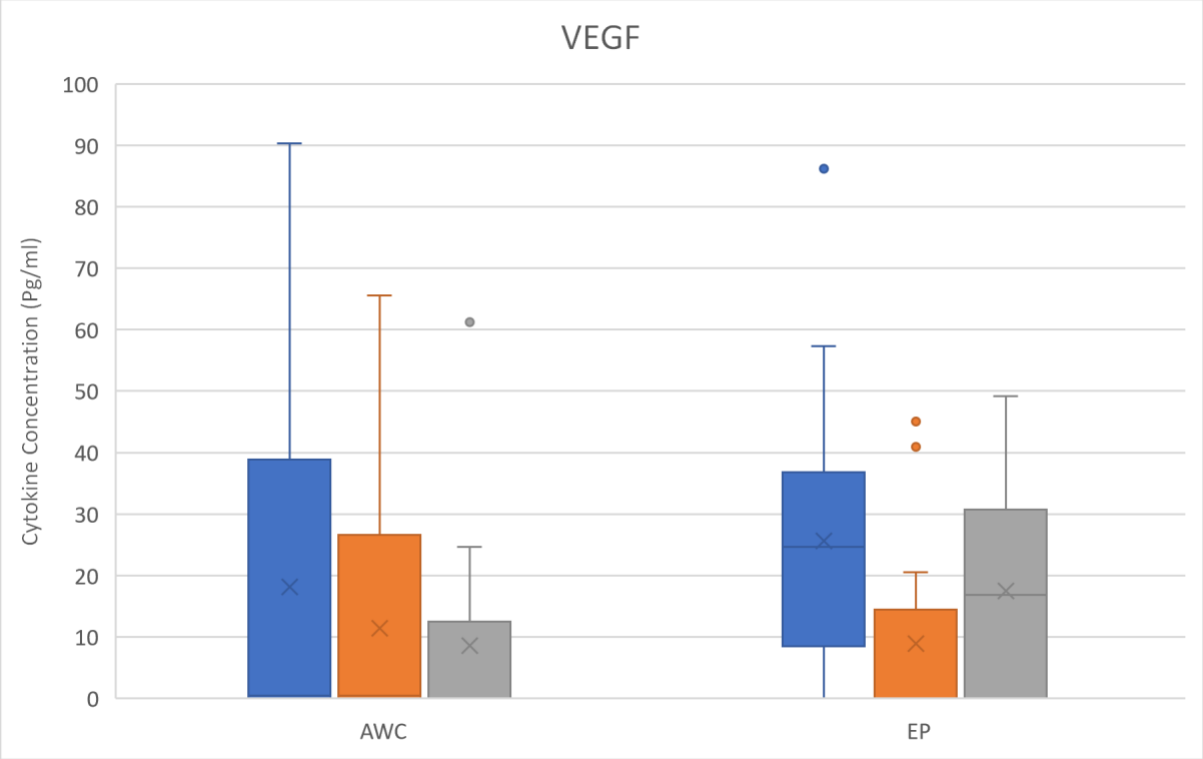

MCP-1
Cytokine Concentration (Pg/ml)
80
70
60
50
40
30
20
10
0
AWC
EP


MIP-1α
Cytokine Concentration (Pg/ml)
2.5
2
1.5
1
0.5
0
AWC
EP


PDGF-bb
Cytokine Concentration (Pg/ml)
1200
1000
800
600
400
200
0
AWC
EP


MIP-1β
Cytokine Concentration (Pg/ml)
80
70
60
50
40
30
20
10
0
AWC
EP


TNF-α
Cytokine Concentration (Pg/ml)
50
45
40
35
30
25
20
15
10
5
0
AWC
EP


VEGF
Cytokine Concentration (Pg/ml)
100
90
80
70
60
50
40
30
20
10
0
AWC
EP

Chapter 5

Discussion

5.1 Discussion

This RCT aimed to compare outcomes after OLR depending on whether EP or AWC-PCA was used within a program of ERAS. Up to commencing this trial EP has been the standard of care in our institution. At the outset of this study only one RCT had been reported comparing AWC with EP following OLR noting a shorter functional recovery but inferior pain control in the first 48 hours [114]. A second study from the same group was published during our study also showing faster functional recovery but with comparable pain relief [159]. We assumed that the use of AWC-PCA would avoid the sympathetic blockade associated with EP thus leading to reduced intravenous fluid infusion, reduced vasopressor support, reduced HDU stay and ultimately faster recovery. Thus, a cohort of 83 patients was recruited and randomized preoperatively and given the nature of the study, no differences in baseline demographics were seen.

This randomised controlled trial has demonstrated that thoracic epidural was not superior to AWC-PCA with regards to length of stay following open liver resection. The use of thoracic epidural following open liver resection was associated with a significantly greater need for vasopressor support up to two days postoperatively than with a multimodal analgesic regimen of local anaesthetic infiltration via abdominal wound catheters in combination with patient-controlled analgesia. As expected for this study design the baseline patient demographics were comparable between the two groups as were the operative factors.

Other findings included a shorter anaesthetic time with AWC-PCA and comparable intravenous fluid requirements, return of bowel function and time to mobilise. In addition, it has also shown that pain control associated with AWC-PCA was worse at all time points up to the morning of postoperative day 2, with the exception of the morning of postoperative day 1 but was comparable thereafter. However, pain scores in both groups were regarded as low at all time points in both groups. This is also demonstrated in the peak flow results taken at the same time points. These differences did not translate into a shorter HDU stay or shorter functional recovery. The rate of complications, severity of complications and 90-day mortality rates were comparable. No differences were seen in return to theatre or readmission within 90 days.

The primary endpoint for this study was the overall length of stay in hospital as a surrogate marker for recovery. Choosing a primary end point for this study was not straightforward. There were several possible options all with their own limitations. We finally elected to choose length of stay for a number of reasons: Firstly, AWC were introduced in our Hepatobiliary and Transplant Surgery Department only a short period of time before commencing this study. This meant it was the only variable we had retrospective data for both groups to enable an accurate sample size calculation. Secondly, if we were to set a target that was a starting point with the length of stay seeming to be the choice in many other ERAS or AWC publications and would allow potential comparisons [114, 159]. In addition, we anticipated that pain control and other outcomes would be largely comparable meaning an unachievable sample size would be needed and not necessarily correlated with recovery. We also aimed to complement length of stay with HDU stay and days to meet 'medically fit for

discharge' data which aimed to eliminate some of the non-medical reasons associated with delayed discharge.

With regards to the primary endpoint, despite AWC-PCA patients requiring less vasopressor support, less need for invasive monitoring and reduced requirement for IV fluids for fewer days, this did not translate into a reduced total length of stay when compared with EP. Although every effort was made to keep HDU admission to the minimal possible with a median of 1 day in each group (mean 1.3 vs. 1.8 in EP), no difference was seen when comparing length of HDU stay. However, it is worth noting that when vasoconstrictors were needed on POD 0 (54% for EP) or POD 1 (22% for EP) then the length of stay in HDU was significantly longer when compared to AWC-PCA (median POD 2.2 ($p=0.004$) and mean 2.6 in EP ($p=<0.001$)). The HDU stay, medically fit for discharge and overall length of stay when comparing the EP group requiring vasopressors on Day 1 was also significantly longer than the AWC-PCA group ($p=<0.001$, 0.006 and 0.012 respectively). It is likely, however, that a much bigger cohort is needed to find a significant difference for the whole group. As other groups have done, we also looked at the functional recovery time in an attempt to eliminate non-medical factors that would impact on overall LOS and again no differences were observed, unlike in previous studies [114, 159]. The reasons for this are perhaps related to the sample size. The patients in this study had a median length of stay of 6 days whereas the dataset used to power this study had a median of 7 days (mean 9 days) this means that more patients are likely to be required to detect a difference. The ERAS protocol itself was introduced in 2015 (immediately prior to this study commencing) and has helped to reduce the length of stay following liver resection from 9.2 (SD 8) days to a mean of 6.6 (SD 4.4) days in our unit (data not published). This is also likely to have impacted on the sample size

calculation. Despite not finding a reduced length of HDU, shorter overall stay or functional recovery with the use of AWC-PCA we were satisfied that recovery was comparable, and importantly not inferior, to those receiving EP.

Importantly, the other outcomes for this study also did not demonstrate any inferiority in clinical outcomes when comparing AWC-PCA use with that of EP. Conversely, perhaps the most significant finding of this study, is the large difference in the proportion of patients requiring vasopressor support between the two groups, finding a large difference in favour of AWC-PCA. Hypotension as a consequence of the sympathetic blockade associated with thoracic epidural has been well described with both systolic and diastolic blood pressure, being reduced in healthy volunteers undergoing thoracic epidural [206]. It has been reported that up to one third of non-obstetric patients receiving a thoracic epidural experience a significant reduction in blood pressure. It is estimated that the use of spinal or epidural analgesia brings about a 39-45% reduction in systolic blood pressure [207]. The development of hypotension in patients with thoracic epidural is multifactorial although is largely related to preganglionic sympathetic blockade. This decrease in sympathetic tone with unopposed parasympathetic tone leads to many of the changes to normal homeostasis and subsequent hypotension seen. The impact of thoracic epidural on the cardiovascular system causing hypotension can be broken down in to the following categories:

1. Loss of cardio accelerator nerve function caused by blockade above the T5 level leads to removal of the chronotropic and inotropic influence of the sympathetic nervous system. Reduced venous return also contributes to bradycardia and subsequent reduced cardiac output causing blood pressure to fall.

2. There is limited evidence suggesting that the reduction in cardiac sympathetic outflow may affect myocardial contractility. However, much of the evidence regarding this is contradictory.
3. The reduction in vasomotor tone associated with thoracic epidural is perhaps the main mechanism by which hypotension ensues. The nerve fibres controlling vasomotor tone arise from T5-L1 with blockade of this level leading to loss of vasoconstrictor sympathetic outflow leading to a 'functional hypovolaemia' due to peripheral vasodilatation. Some compensation can arise through a variety of mechanisms including vasoconstriction in the unblocked area, increased activity in unblocked splanchnic nerve fibres leading to release of catecholamines from the adrenal medulla as well as the renin-angiotensin and vasopressin systems [116, 208].

The temptation with this 'functional hypovolaemia' is for volume loading with intravenous fluid. However, this should be avoided, particularly in hepatic resection. During the hepatic transection phase of liver resection, the central venous pressure is kept to a minimum to reduce intra-operative blood loss, with volume loading only occurring once this phase of surgery has been completed. For this reason, vasopressor support is commonly used intraoperatively to maintain adequate blood pressure. This study clearly showed a significant difference in intraoperative vasopressor requirements between the two groups with a greater proportion of patients being managed without vasopressor support or requiring only metaraminol boluses (rather than noradrenaline infusion) in the AWC-PCA group. This is presumably due to more profound hypotension related to the thoracic epidural. This effect is also seen on postoperative days 1 and 2 when significantly more patients also required infusion of noradrenaline, with this being the main reason the volume of intravenous fluid

was comparable at all time points. This requirement for increased vasopressor support can have several implications. The most obvious consequence is the need for invasive monitoring and at least level 2 (high dependency) care whilst vasopressors are required. This seems likely to impact on critical care length of stay and time to mobilise. In this study, when comparing all groups, no overall differences were noted in length of HDU stay or time to first mobilise although there was a non-significant trend towards a longer HDU stay in the EP group. As described previously, HDU stay was longer in the EP group requiring vasopressor support on day 1 than the AWC-PCA group (2.5 days versus 1 day, p= <0.001). However, it must be noted that this RCT was not powered to detect differences in length of HDU stay as given the small clinical difference between the groups a large, unfeasible, number of patients would have to be recruited. A reduction in critical care stay would have a beneficial effect on cost and also resource utilisation. According to the Welsh Consolidated Costing Return a ward bed costs on average £413 per night, a level 2 (HDU) bed £3857 per night and a level 3 (ICU) bed £1932 per night and with critical care bed occupancy rates running at 80% or higher any reduction in length of stay would be advantageous [209]. Whilst a formal cost analysis was not undertaken as part of this study, it seems likely that epidural would be a more costly method of delivering pain relief. Thoracic epidural is also a labour-intensive method of delivering postoperative analgesia with numerous societies including the Royal College of Anaesthetists and Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines recommending enhanced supervision of patients with thoracic epidural as best practice. It is also recommended that patients with thoracic epidural are monitored by an 'acute pain team' which should include a consultant anaesthetist, clinical nurse specialists and support from pharmacy services. Frequent monitoring of sensory and motor blockade, pain scores and routine haemodynamic parameters are also required of the ward-based nursing staff to

identify adverse events [210]. Patients receiving wound catheters conversely require no additional monitoring although, in this study, still fell under the remit of the acute pain service. With increased use and familiarity, the majority of these patients could be managed solely by the parent team without the additional input from acute pain services. The insertion of a thoracic epidural also mandates the insertion of a urinary catheter to prevent urinary retention. The urinary catheter will need to remain in situ for as long as the epidural does. Conversely, with the use of AWC-PCA, the urinary catheter could be removed earlier as it is a regional technique without the blockade of the external urethral sphincter (S1-3) or detrusor muscle (S2-4). Whilst often underestimated, the insertion of a urinary catheter is associated with a 1-2% risk of infection, with the initial insertion rising to 3-7% for each day it remains in situ [211].

Although pain scores were inferior in the AWC-PCA group on the evening following surgery, the afternoon of day 1 and the morning of day 2, pain scores were comparable at all time points beyond this. Whilst median pain scores were inferior at these time points, they were regarded as low (<4 on an 0-10 analgesic scale) at all time points in both groups and therefore these differences are unlikely to be clinically significant. As such, pain relief could be considered as largely comparable. The reason why there is no difference in pain scores on the morning of day 1 is unclear. It is possible that patients with failed thoracic epidurals were identified at this time and converted onto PCA. This would lead to pain scores being temporarily high in the EP group as those with failed epidural would only receive intravenous paracetamol until the epidural had been removed and opiate based PCA commenced.

Intravenous opiate based PCA can provide effective post-operative analgesia although in high-doses is associated with nausea, vomiting, constipation, sedation and respiratory

depression [129]. Similarly, epidural is associated with hypotension, the requirement for specialised anaesthetic input, significant failure rates and a small risk of devastating complications such as epidural haematoma or abscess [125, 210]. Although rare, the incidence of permanent disability following epidural abscess/haematoma but also meningitis, nerve injury and cord ischaemia has been reported as 4.2 per 100, 000 [212]. This has led to the development of multi-modal analgesia regimes aimed at avoiding the problems associated with thoracic epidural and also minimising the use of opiates.

Several studies have demonstrated that AWCs have an opioid-sparing effect when used in conjunction with PCA [161, 202, 213]. This was confirmed in our study by comparing the epidural failure group (receiving PCA alone) to the AWC-PCA group. A significant reduction in the volume of IV morphine equivalent use was noted. This may impact on nausea and sedation particularly following liver resection when there is a temporary impairment of liver function as well as impaired opiate metabolism. Reduction in opiates may also be associated with improved return of bowel function with opiates known to have a constipating effect. However, the literature for this is contrasting and dependent on the definition used for 'return of bowel function' [119, 214 - 216]. In addition, epidural has been associated with a decrease in post-operative ileus which is thought to be related to the systemic absorption of local anaesthetic having a stimulating effect on the gastrointestinal tract [217, 218]. Because AWCs also infiltrate local anaesthetic it is possible that this positive effect on return of gastrointestinal function would also be seen in this group. However, in our study, no difference was noted between the two groups when comparing return of gut function.

More recently, there is emerging evidence that some cancers have high levels of *mu* opioid receptor. These when activated by opioid analgesics could lead to tumour growth and spread.

It therefore may become essential that as more is learned about this interaction every effort is made to restrict the quantity of opiates used in postoperative analgesic regimens [140, 219 - 222]. We feel it is feasible that in the future selected patients with a well-functioning AWC would require the PCA for only the initial 24 hours following surgery before this could be discontinued.

In this study, one patient was excluded due to the inability to insert an epidural whereas the insertion of AWC was always an option, even in patients with a high BMI or repeat abdominal surgery. In our experience, the main analgesia related complication experienced when AWC were inserted, was its accidental dislodgement (7% vs 20%, p=0.07). However, this event was far less likely when compared to EP and resulted in PCA only analgesia. Conversely the EP failure rate was 20% in our study, necessitating conversion to PCA, and is in keeping with other published series [114, 125]. There is also concern regarding the use of EP following hepatectomy with the development of a coagulopathy leading to rare but potentially devastating complications such as epidural haematoma. In this series, unsurprisingly, no patients developed such complications. However, the removal of one patient's EP was delayed by one day due to a deranged clotting profile. In addition, some patients may require some form of anticoagulation, such as following major vascular resection/reconstruction, following surgery where the use of EP may be a concern.

In this study, epidural provided marginally better pain control than AWC-PCA but made overall patient management more challenging. In fact, although the difference in pain scores is statistically significant, this is unlikely to be of clinical significance with pain scores in both groups being regarded as low (median <4 on 11-point scale) at all time points [223]. The use of

AWC as part of a multi-modal regime was also effective in reducing the requirement for IV opiates in this study. EP is a more invasive procedure, requires provision of vasopressors more frequently and therefore the need for central venous access, with a higher rate of failure. Ongoing management of patients with epidural is also resource-intensive, requiring involvement of acute pain teams and anaesthetists in the postoperative period [128].

Another aspect of this study was an attempt to characterise and compare the impact, if any, of AWC-PCA and EP on the systemic inflammatory response following open liver resection. This study showed that IL-9 and MIP-1β levels significantly decreased with time in the AWC-PCA group compared to the EP arm. There was no other significant difference in any of the other cytokine levels between the two groups. This would suggest that any impact that the two methods of analgesia have on the SIR is largely comparable and that AWC-PCA is not inferior.

IL-9 levels in both groups fell from baseline level to reach their lowest level on Day 1 before increasing on Day 3. In the AWC-PCA group, the IL-9 level on day 3 did not reach the baseline level although in the EP group it rose significantly above it. IL-9 was first described in the late 1980's initially being described as a T cell and mast cell growth factor and called P40 [224]. However, further studies revealed that it was distinct from other T cell growth factors and it was renamed IL-9 because of its effects on myeloid and lymphoid cells. The major source of IL-9 is from T lymphocytes, with production being regulated by a series of cytokines and transcription factors. In particular, TGF-β and IL-4 have been shown to strongly promote IL-9 production from activated T cells, as has IL-2, whereas IFN-γ inhibits IL-9 production [225, 226]. Studies have shown that IL-9 is produced by several CD4+ T cell groups including Th17 cells,

regulatory T cells and Th9 cells. IL-9 brings about its effects through a receptor complex composed of IL-9Rα and a common γ chain. The receptor IL-9R has been shown to be expressed by several cell types including mast cells, macrophages as well as T cells, B cells and haematopoietic progenitor cells. This wide expression of the IL-9 receptor helps to explain the wide array of activity associated with IL-9, both pro- and anti-inflammatory [224, 227 – 229]. Extensive studies have been done in recent years on the T cell subsets that produce IL-9, a cytokine that was initially thought to be a T cell- derived factor preferentially expressed by Th2 cells [230]. The newly identified Th9 cells that predominantly produce IL-9 and IL-10 changed this conception. However, unlike Th2 cells, the Th9 cells do not exhibit any regulatory properties [231, 232], indicating that IL-9/IL-10-producing T cells are not regulatory T cells but effector T cells that induce tissue inflammation [233].

MIP-1β is a member of the chemokine family. These are regulatory molecules involved in leucocyte maturation, traffic and homing of lymphocytes, as well as the development of lymphoid tissue [234]. This group of cytokines have been shown to possess chemotactic activity for inflammatory and immune effector cells [235]. The sources of MIP-1β have not been as well studied as those of MIP-1α. However, it has been shown that monocytes produce high amounts of MIP-1β when stimulated with IL-7 or lipopolysaccharide. Production of MIP-1β is counteracted by IL-4, which reduces the level of MIP-1β mRNA expression. In addition, activated T cells and B cells that have been stimulated by antigen binding produce MIP-1β as do natural killer (NK) cells. MIP-1β has multiple roles, including augmenting adhesion of T lymphocytes to vascular adhesion molecule – 1 (VCAM-1), a potent chemo-attractor of lymphocytes and NK cells and modulation of cytokines from T lymphocytes [236]. The cytokines

usually associated with a pro-inflammatory response such as IL-1β, IL-6 and TNF-α were all comparable between the two groups.

In this study, the two groups were reasonably well matched although the EP group had a larger number of segments resected on average than the AWC-PCA group (median 4 vs 2, p=0.03) and there was a non-significant trend towards more serious complications (Clavien-Dindo ≥3) in the AWC-PCA group (4 vs 0, p=0.083). It is already known that patients experiencing major post-operative complications have an increased systemic inflammatory response [172 - 174]. As the AWC-PCA group in the cytokine analysis had a tendency towards more serious complications, it would be expected that the systemic inflammatory response in this cohort would be greater. In particular, levels of IL-6 and IL-8 are known to be significantly increased with major complications following surgery. Schwarz et al found a higher mean increase in levels of IL-2, and higher perioperative IL-5 in patients with severe complications following liver resection compared to those that did not [237]. This has been replicated in other surgical specialities, with some suggesting that postoperative levels of cytokines may have a better diagnostic value than the currently used leucocyte count and CRP levels [238].

Overall, there was no major difference in cytokine response between the two groups. This is with the exception of IL-9 and MIP-1β. However, as both of these cytokines have a pleiotropic effect and the major cytokines implicated in the systemic inflammatory response were comparable, it is unlikely that this finding is of clinical significance. It would appear from the findings of this study that there is no significant difference in the impact that either analgesic modality have on the systemic inflammatory response. When comparing the results of this study to the current literature, it would appear that the results are comparable although the levels of cytokines appear to be lower in our study.

There are several limitations to this study. An open label study was designed and thus may be a source of potential response bias. Whilst sham AWC or EP catheters can be employed previous studies have attempted their use with extreme difficulty and have counselled against their use [114]. The use of length of stay as a primary endpoint also has its limitations with discharge from hospital being multifactorial. However, as AWC had only recently been introduced into the unit at the outset of this study it was one of the few variables we had retrospective data for to allow sample size calculation. As we also hypothesized that other outcomes would be largely comparable an unachievable sample size would be needed for these outcomes. In addition, the sample size is insufficient to detect small differences in secondary outcomes between the two groups. Although we have not seen a shorter LOS in hospital, we did not find any justification to advocate the use of EP routinely in our patients and we believe that AWC-PCA provides a comparable alternative and better fits the philosophy of ERAS and should be incorporated into future protocols.

The systemic inflammatory response analysis also has its limitations. This was a 'single run' experiment and therefore it is not possible to comment on the reliability and replicability of the results. However, this does help to eliminate inter-plate variation if multiple plates were being tested. The storage of samples for prolonged periods of time may have led to degradation of samples which could impact on cytokine levels. However, the protocol used for sample storage is well validated and it has been demonstrated that cytokine levels can be stable for up to 4 years in such conditions [239]. The time taken from sample collection to processing and freezing also varied slightly from patient to patient. This could again have impacted on cytokine levels however samples in EDTA are stable at 4°C for up to 4 hours before requiring centrifugation and all samples were collected, centrifuged and frozen within

this time-frame [240]. The samples were also run in singlet only although standards and blanks were run in duplicate to ensure precision of the concentration curve. This unfortunately doesn't allow for calculation of sample variation and therefore no comment can be given about the precision of the assay. Whilst samples were collected and stored in triplicate due to the size of the plate, number of patients recruited and the cost of the materials required for this analysis it wasn't feasible to run this study in duplicate/triplicate. Whilst this aspect of the study is not internally validated it does provide some reassurance that there is no major difference between the two techniques on the systemic inflammatory response.

There are many potential avenues for further work. Further large volume, multicentre randomised controlled trials comparing AWC-PCA as a multimodal regime to thoracic epidural or intrathecal morphine may help to demonstrate reduced length of stay particularly on HDU. It is possible that such studies would also identify further differences in secondary outcomes that this study was not powered to find. In addition, the majority of ERAS pathways are based on low quality evidence. High quality studies are needed to confirm the benefit of ERAS in hepatobiliary surgery and to further develop the individual components of such pathways.

Conclusion

AWC-PCA was comparable to EP with regards to overall length of stay following open liver resection. The use of AWC-PCA was associated with reduced treatment failure and a reduced vasopressor requirement than EP up to two days post-operatively, whilst providing pain relief that was acceptable and comparable morbidity. There was no difference in systemic inflammatory response. Whilst the use of AWC-PCA did not translate into a shorter LOS in this study, it simplified patient management after OLR. We therefore found no reason to routinely incorporate EP into ERAS protocols following OLR and have subsequently abandoned its routine use. AWC-PCA provides an acceptable alternative as part of a multimodal regime and we believe further ERAS protocols should incorporate its use. Further randomized studies should be aimed at developing other aspects of ERAS protocols following liver surgery.

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Appendices

A. – ERAS Protocol

Day 0 - Pre surgery/Surgery

- Admission either morning of surgery or day before
- No routine pre-medication (unless very anxious)
- Anaesthetic
    - Anaesthetic (Appendix C)
    - Epidural Group Only(Appendix D)
    - Pre-op antibiotics
        - 1.2g IV Augmentin
        - Penicillin Allergy: Gentamicin 2mg/kg + Metronidazole 500mg IV
    - Intra-op antiemetic: 8mg dexamethasone
    - Central line
    - Arterial line
    - Urinary catheter
    - Fluid Protocol - during the liver resection phase a low CVP (central venous pressure) of 0-5mmHg will be maintained to minimise venous bleeding. Following liver resection Hartmann's solution will be administered to maintain a CVP of 8-12mmHg
    - Blood losses replaced at 1:1 ratio with volplex
    - Patient warming with 'bear hugger'
- Surgical
    - Incision
    - No routine NG tube. NG sited intra-operatively will be removed at the end of surgery
    - No routine use of drains
    - Wound catheter Group Only (Appendix E)

Day 0 - Post Surgery (evening of surgery)

- All patients will receive regular 1g Paracetamol (unless stated in post op instructions)
- All patients will receive 4mg Ondansetron QDS
- All patients will receive 15ml Lactulose BD
- Routine VTE prophylaxis (Tinzaparin/Enoxaparin (impaired renal function) and TED stockings (unless contraindicated)) as per LTHT protocol
- Oxygen as required to maintain Sats >94%
- Fluid Protocol - In the postoperative period patients would be started on maintenance fluid with Hartmann's solution @ 80ml/hr. Fluid challenges of crystalloid up to 200ml would be used to achieve desired CVP/ urine output (0.5ml/kg/min).
- Epidural/Wound catheter as per protocol
- Patient will be encouraged to sit out for 2hours on the evening following surgery
- Resume free fluids on evening following surgery
- Pain score (rest and on movement) at 2 and 6hr from arriving on HDU
- Sedation score at 2 and 6hr from arriving on HDU
- Nausea score at 2 and 6hr from arriving on HDU
- Peak flow at 6hr from arriving on HDU

Day 1

- Resume normal diet
- Stop IVI if > 1litre oral intake. Maintenance with Hartmann's 40ml/hr if less than 1litre intake
- Initiate oral analgesic regime (1g Paracetamol QDS, 400mg Ibuprofen TDS),
- Arterial line out (if not clinically required)
- Central line out (if not clinically required)
- Continue Epidural and wound catheter/PCA as per protocol
- Sit out in chair for >6hours
- Record pain/sedation/nausea scores, peak flow, bowels opened
- Record total daily volumes of IVI, vasopressors, opioids

- Assess against criteria to discharge from HDU twice daily

Day 2

- Sit out for >8hours
- Initiate oral analgesic regime (1g Paracetamol QDS, 400mg Ibuprofen TDS), Record pain/sedation/nausea scores, peak flow, bowels opened
- Record total daily volumes of IVI, vasopressors, opioids
- Assess against criteria to discharge from HDU twice daily (Appendix B)
- PCA can be removed if not used. The addition of Codeine 30 mg/qds (if not 50-100mg Tramadol QDS) when PCA stopped

Day 3 (60 hours from end of surgery)

- Trial of stopping/Remove epidural (if INR <1.5) and wound catheters
- Remove PCA if still in place.
- Remove urinary catheter if not clinically required.
- 1g Paracetamol QDS and 400mg Ibuprofen TDS
- Codeine 30 mg/qds (if not 50-100mg Tramadol QDS)
- 5-10mg Oral morphine as required for breakthrough pain
- If significant difficulties controlling pain, PCA might be recommenced.
- Increase mobilisation
- Encourage oral intake
- Assess against criteria to discharge from HDU twice daily (Appendix B)
- Record pain/sedation/nausea scores, peak flow, bowels opened
- Record total daily volumes of IVI, vasopressors, opioids

Day 4 onwards

- Assess against criteria to discharge from hospital twice daily (Appendix B)
- Mobilise
- Increase oral intake
- Oral analgesia: Paracetamol 1 gr QDS and Codeine 30 mg/qds (if not 50-100mg Tramadol QDS). Ibuprofen will be stopped.
- Record pain/sedation/nausea scores, peak flow, bowels opened until Day 5

4-6 Weeks Post Discharge

- routine clinical review in OPD
- Patient satisfaction questionnaire

The Leeds Teaching Hospitals NHS
NHS Trust

Centre Number: 1

Study Number: 14/YH/1267

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Epidural versus Wound Catheters following Open Liver Resection

Name of Researcher: Mr E. Hidalgo

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 09/02/2015 (version 1.7) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

4. I understand that sections of my medical notes and data may be looked at by responsible individuals from the NHS Trust or regulatory authorities where it is relevant to my taking part in this research'. I give my permission for these individuals to have access to my records ☐

Name of Participant	Date	Signature

Patient Information Leaflet:

Epidural Analgesia vs Wound Catheters Following Open Liver Resection.
14/YH/1267

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Feel free to discuss the study with family and friends if you wish. Please ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

At present patients undergoing an open liver resection at SJUH mainly receive an epidural for postoperative pain relief. This involves putting a small tube into your back to numb you from your chest to your feet. Whilst the pain relief provided can be good there are a number of side effects that can occur with epidural analgesia. In addition, epidural analgesia does not work well up to 30% of the time. We propose using a new combination of analgesia that has already been shown to be effective following other surgery. This involves placing wound catheters (small tubes placed into the wound during your operation) which continually infuse the wound with local anaesthetic. In addition to this you will have a PCA button (patient controlled analgesia) to give you additional pain killers as and when you require them. We want to investigate how the recovery between these two methods of analgesia varies and in particular if this new method of analgesia leads to a quicker discharge from hospital.

Why have I been invited?

All adults who are scheduled to have an open liver resection at SJUH have been invited to take part.

Do I have to take part?

No. Your participation in this study is entirely voluntary. If you decide that you do not want to take part your care will not be affected in any way.

What will happen if I take part?

You will be approached on the morning of surgery to sign a form confirming you want to take part in the study. You will then be randomly assigned to receive either an epidural or the combination of analgesia. The epidural will be placed whilst you are awake and involves a small plastic tube being placed in your back. Medication is delivered via this to block the nerve signals involved in pain. The combination of analgesia will be placed whilst you are asleep. This involves placing 2 plastic tubes within the muscles that make up the wall of your abdomen. A pump is attached to these which will deliver medication to block pain signals. The PCA will be connected to your drip and gives you additional pain relief when you press the button. **You cannot choose which method you want to receive**.

In the days following surgery both groups will receive exactly the same care. 60 hours following the operation both groups will have either the epidural or combination of analgesia removed. Both groups will then receive the same analgesic regime. At set points during your recovery we will record various scores:

Peak Flow - breathing into a small plastic tube as hard and fast as possible. This will be measured once before your operation and once a day after your operation up to day 5 and gives an indication of how comfortable you are.

Pain Score - you are asked to rate your pain from 1- 10 on a scale. This tells us how effective your pain relief is. This is recorded at 2 and 6 hours post operation, twice a day on postoperative days 1 and 2 and then once a day on post-operative days 3, 4 and 5.

Nausea Score - a scale from 1 - 3 looking at nauseous you feel as some of the side effects of pain killers can cause this. This is recorded twice a day up to day 5.

Sedation Score - A scale from 1 - 3 looking at how drowsy you are as some of the side effects of pain killers can cause this. This is recorded twice a day up to day 5.

These scores are taken more frequently than someone receiving routine care. Following your discharge from hospital you will be seen in your routine outpatient follow up appointment and asked to complete a questionnaire. This usually happens between 4 and 6 weeks after surgery. This will be the end of the study and you will then receive routine follow up.

What are the disadvantages to taking part?

There will be no effect on your surgery. The pain relief with the wound catheters may not be as effective as the epidural although current evidence suggests they are similar.

What are the benefits to taking part?

Your recovery following your surgery may be enhanced. The length of time you stay in hospital may be shorter if you are allocated to the wound catheter group. This study may help to improve care for patients undergoing open liver resection in the future.

Will my taking part be kept confidential?

All information kept as part of the study will be kept in the strictest confidence. Only members of the medical team looking after you will have access to your specific information.

What will happen if I don't want to take part?

It is your decision whether you want to take part or not. If you decide that you do not want to take part then your care will not be affected. If you decide that you do not want to take part you may receive an epidural as part of your care.

What will happen if I decide I want to stop my participation in the study?

You can decide to withdraw from the study at any point. Your care will be unaffected. Information collected up to your withdrawal from the study will be kept. No further information will be kept or stored after your withdrawal. You will continue to receive routine follow-up following your withdrawal from the study.

What will happen to the results of the study?

We will look to publish the results of the study in medical journals or at conferences. You will not be identifiable in this publication. If you would like to know the results, we can send you a report when the study is completed.

Who is organising the study?

The study is being organised by a combination of surgeons and anaesthetists who work at the Leeds Teaching Hospitals. The lead surgeon for this study is Mr Ernest Hidalgo. This study has been reviewed and approved by The Bradford Leeds Research Ethics Committee.

Contact for Complaints or Independent advice:

If you feel like you would like advice from someone independent to the study please contact the patient advice and liaison service (PALS):

Tel: 0113 2066261

Email: patientexperience.leedsth@nhs.net

Contact for further information:

If you would like more information about the study then please contact:

Mr Richard Bell

Clinical Research Fellow

Email: Richard.bell6@nhs.net

Tel: 0113 20668378

RCT comparing epidural analgesia vs. continuous local anaesthetic infiltration via wound catheter and IV opioid PCA in open liver resection

Contact details for Trial personnel

Mr Richard Bell (Clinical Research Fellow)

Mr Razdy Igasan - ERAS-CNS

Mr Ernest Hidalgo (Consultant Surgeon)

Patient Care Pathway

Pre-operation		
-Pre-op drinks x 6		☐
-Patient warming	☐	
Day 0 – Pre-op		
-Consented		☐
-Baseline peak flow		☐
-Randomisation at theatre briefing	☐	

Surgery + Wound Catheter/Epidural Insertion

Day 0 – Post-op		
-Oral Fluids		☐
-Pain, Nausea and Sedation scores	☐	
-Regular IV Ondansetron 4mg TDS	☐	
-Regular paracetamol 1g QDS, 400mg Ibuprofen TDS (unless contraindicated)	☐	
-Omeprazole 20mg OD IV/PO		☐
-Tinzaparin + TEDS (unless specified otherwise)		☐
-Hartmanns 80ml/hr maintenance +/- Volplex (as required)	☐	
-Oxygen as required (to maintain sats >94%)		☐
Day 1		
-Normal diet and fluids		☐
-Fresubin 200ml TDS		☐
-Lactulose 10ml BD		☐
-Omeprazole 20mg OD		☐
-Regular PO Paracetamol 1g QDS, 400mg Ibuprofen TDS (unless contraindicated)		☐
-Mobilize/Sit out for >6 hours		☐
-Pain, nausea and sedation scores (morning and afternoon)	☐	
-Peak flow (morning and afternoon)		☐
-Stop IVI if PO intake >1 litre (maintenance as above if required)		☐
-Hartmanns 80ml/hr if IVI still required		☐
-Arterial line/Central line/Urinary catheter/drain out (if appropriate)	☐	
-Assess if fit for discharge from HDU		☐
-Leave Epidural/Wound Catheters		☐

Day 2

-Normal diet and fluid ☐
-Mobilise out of bed >8 hours ☐
-Pain, nausea and sedation scores (morning and afternoon) ☐
-Peak flow (morning and afternoon) ☐
-Arterial line/Central line/Urinary catheter/Drain out (if appropriate) ☐
-Trial of stopping PCA ☐
-Codeine 30-60mg QDS/Tramadol 50-100mg QDS (if PCA discontinued) ☐
-Oral morphine 10mg 2-4 hrly PRN (if PCA discontinued) ☐
-Leave Epidural/Wound Catheters ☐
-Assess if fit for discharge from HDU ☐

Day 3

-REMOVE WOUND CATHETER/EPIDURAL ☐
-Stop PCA ☐
-Arterial line/Central line/Urinary catheter/Drain out (if appropriate) ☐
-Pain, nausea and sedation scores (morning and afternoon) ☐
-Peak flow (morning and afternoon) ☐
-Codeine 30-60mg QDS/Tramadol 50-100mg QDS (when PCA discontinued) ☐
-Oral morphine 10mg 2-4 hrly PRN (when PCA discontinued) ☐
-Assess if fit for discharge from HDU/Hospital ☐

Day 4

-Pain, nausea and sedation scores (morning and afternoon) ☐
-Lines/Catheter/Drain out (if appropriate) ☐
-Peak flow (morning and afternoon) ☐
-Assess if fit for discharge from HDU/Hospital ☐

Day 5

-Pain, nausea and sedation scores (morning and afternoon) ☐
-Peak flow (morning and afternoon) ☐
-Assess if fit for discharge ☐

Day 6

-Pain, nausea and sedation scores (morning and afternoon) ☐
-Peak flow (morning and afternoon) ☐
-Assess if fit for discharge ☐

Clinic

-Patient satisfaction questionnaire ☐

Data Collection Proforma

Pre-Op

Baseline Peak-flow -

_____

Surgical/Anaesthetic

Date of Birth - _____

Gender – M / F

BMI - _____

ASA – I / II / III / IV

Diagnosis - _____

Previous Abdominal Surgery – Yes / No Previous Liver Surgery - Yes / No

Previous Surgery -

_____

_

Operation -

_____

_____

Other:

Major / Minor (Please circle) Number of segments resected - _____

Date of Operation:_____

Time into Anaesthetic Room: _____:_____

Time at Knife to Skin: _____:_____

Time at Completion of Closure: _____:_____

Wound Length (cm): _____

Wound Shape: Reverse L / Reverse L / Mercedes

Please Document any deviation from the protocol below:

_____

_____

Day 0 – Until 8am

Date: _____

Pain Score (17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score: 0 1 2 3

Sedation Score: 0 1 2 3

Day 1 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Vasopressor Requirement (mg):

_____

Total Opioid Used (mg):

_____

Day 2 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Vasopressor Requirement (mg):

_____

Total Opioid Used (mg):

_____

Please document any deviation from the protocol or complications below:

_____

_____

_____

Day 3 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9 10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9 10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Vasopressor Requirement (mg):

_____

Total Opioid Used (mg):

_____

Please document any deviation from the protocol or complications below:

_____

_____

_____

Day 4 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Opioid Used (mg):

_____

Total Tries/Number Good: _____

/_____

Please document any deviation from the protocol or complications below:

_____

_____

_____

Day 5 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Opioid Used (mg):

_____

Total Tries/Number Good: _____

/_____

Please document any deviation from the protocol or complications below:

_____

_____

_____

_____

Day 6 – 8am – 8am

Date: _____

Pain Score (08:00-09:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (08:00-09:00): 0 1 2 3

Sedation Score (08:00-09:00): 0 1 2 3

Peak Flow (08:00-09:00):

_____

Pain Score (13:00-17:00): 0 1 2 3 4 5 6 7 8 9

10

Nausea Score (13:00-17:00): 0 1 2 3

Sedation Score (13:00-17:00): 0 1 2 3

Peak Flow (13:00-17:00):

_____

Total Volume of IV Fluid (ml):

_____

Total Opioid Used (mg):

_____

Total Tries/Number Good: _____

/_____

Please document any deviation from the protocol or complications below:

_____

_____

_____

Medically Fit for Discharge Date: _____ Time:

_____:_____

Actual Discharge Date: _____

Time:_____:_____

Clinic Review

Wound Complications:

_____

__

Other Complications:

_____

___

_____

_____

HDU Discharge Criteria

- Respiratory
  - Requiring less than 40% Oxygen
  - Respiratory rate <20 >10
  - SpO2 >94%
- Cardiovascular
  - No CVP/invasive BP monitoring required
  - ECG monitoring not required
  - No vasopressor requirements or large boluses of fluid
- Renal
  - Stable renal function on biochemistry
  - Urine output >25ml/hr
- Analgesia
  - Pain control adequate with current method of analgesia
- General
  - Able to mobilise out of bed

Discharge Home Criteria:

- Adequate pain control on oral analgesia.
- Eating and drinking with no requirement for intravenous fluids in previous 24 hours.
- Independently mobile (can mobilise independently to toilet).
- Able to perform activities of daily living (washing, dressing) without help from nursing staff.
- Blood tests returning to normal range.
- Patient willing to go home.

Abstracts/Presentations

1. European – African Hepato-Pancreato-Biliary Association Meeting. Mainz, Germany. 2017. Randomized Clinical Trial of Abdominal Wound Catheters (AWC) versus Epidural Analgesia (EP) following Open Liver Resection (OLR): An Interim Analysis. Richard Bell*, Julie Jeffery, Deesa Ward, Peter Lodge, Ernest Hidalgo.

2. A Systematic Review and Meta-analysis of Epidural versus Local Anaesthetic Infiltration via Wound Catheters in Open Liver Resection. R. Bell*, S. Pandanaboyana, I. Wijetunga, E. Hidalgo, R. Prasad. *BJS* 2015; 102 (S1): 127–301

3. International Hepato-Pancreato-Biliary Association Meeting. Geneva, Switzerland. 2018. Randomized Clinical Trial of Abdominal Wound Catheters versus Epidural Analgesia following Open Liver Resection. Richard Bell*, Julie Jeffery, Deesa Ward, Giles Toogood, Peter Lodge, Krishna Rao, Sharmeen Lotia, Ernest Hidalgo.