Enhanced Recovery After Liver Surgery

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Preface

I, Michael John Hughes, declare that this thesis is original work, composed by myself and has not been submitted for any other degree.

For Katy and Rory.

Acknowledgements

Sincere thanks go to my supervisor, Professor S. J. Wigmore, for providing guidance and expertise during this research period. Mr E.M. Harrison also provided significant statistical, methodological and supervisory support. Thanks also go to Col. Mahoney and Surg. Capt. Midwinter for providing supervision and support. The laboratory based aspects of this thesis were made possible by the cooperation and expertise of the following people: Natalie Horner, Lawrence Rentoul, Ben Stutchfield and Rebecca Aucott. Many thanks also go to Drs C. Beattie and D. McKeown who provided anaesthetic expertise. The running of the trials would not have been possible without the cooperation and flexibility of the medical and nursing staff of wards 115, 116, 106 and 107 at the Royal Infirmary of Edinburgh. The two main funders for the trials, Defence Medical Services Research Steering Committee and the Royal College of Surgeons of Edinburgh are sincerely thanked for the financial assistance granted to me. Finally, the cooperation and professionalism of all those at the Clinical Research Facility are acknowledged and appreciated.

Abstract

Introduction

Liver resection offers curative treatment to a number of malignant conditions. It has traditionally been associated with poor post-operative outcomes. More recently a mortality rate of less than five per cent has become established but morbidity remains high. Enhanced Recovery After Surgery (ERAS) has become established practice in a number of surgical specialties and has shown improvement in post-operative outcomes. ERAS has been introduced for liver resection however practice is less well established and liver surgery has several complexities that need to be accommodated in order to optimise post-operative care. The following thesis aims to identify areas that require clarification and investigate peri-operative care components to establish optimum practice.

Methods

Systematic review and meta-analysis were performed to identify areas that required clarification and were lacking in sufficient evidence to guide practice. A randomised controlled trial was performed to compare established areas of practice. Prospective observational studies were performed when exploratory investigation was required. Retrospective analysis of a prospectively collected database was performed to identify risk factors for post-operative morbidity. Patients included in the above trials underwent liver resection at the Royal Infirmary of Edinburgh, UK, between December 2012 and August 2014.

Results

Post-operative analgesia after liver resection was identified as being an area that was controversial. Continuous wound infiltration was shown to offer improved recovery times when compared to epidural with no significant associated disadvantages. After retrospective review of 603 liver resections, extended resection was observed to be associated with high morbidity rates. It was hypothesised that post-operative nutritional requirements might be higher in these patients. This was not found to be the case but post-operative energy requirements were found to be difficult to predict after liver resection, suggesting the benefits of real-time monitoring of energy expenditure. Finally acetaminophen metabolism was suspected of being altered after major resection. An observational study suggested that despite altered metabolism, glutathione deficiency was not observed after major resection and so liver volume was not a contra-indication to acetaminophen administration.

Summary

Liver resection offers a complex set of conditions on which to base an enhanced recovery protocol. Current ERAS literature does not completely address these issues. This thesis has investigated several aspects of care unique to liver surgery in an attempt to optimise peri-operative care and improve post-operative outcome after liver surgery.

1 Introduction

1.1 The Physiological Response To Surgery

Abdominal surgery results in initiation of a number of physiological and metabolic responses. [1] After the initial surgical incision and for several days afterwards, a stimulation of the inflammatory response occurs. This is a well-orchestrated activation of the sympathetic, endocrine and immunological systems resulting in the release of catecholamine and norepinephrine from the hypothalamus and adrenal medulla respectively. This leads to the characteristic physiological outcome of increased heart rate and a rise in circulatory pressure. [2]

Surgical trauma results in activation of neuronal afferents at the surgical site that travel via the dorsal root to the hypothalamus. The endocrine organs subsequently release a number of hormones via the hypothalamo-pituitary-adrenal (HPA) axis (Figure 1). These include insulin and glucagon, antidiuretic hormone (ADH), cortisol and adrenocorticotropic hormone (ACTH). The net result of this is catabolism of fats, proteins and glycogen and retention of salt and water to satisfy energy requirements and cardiovascular stability. [2]

As a result of injury to tissue and cells, the immune response is also stimulated. This is a complex combination of innate (neutrophils, macrophages and complement) and specific (B cells, T cells and Natural Killer cells) cellular and humoral responses.

This results in chemokines and cytokines being released early on from damaged leukocytes and endothelial cells and they, amongst other factors, stimulate and activate the inflammatory response. [3]

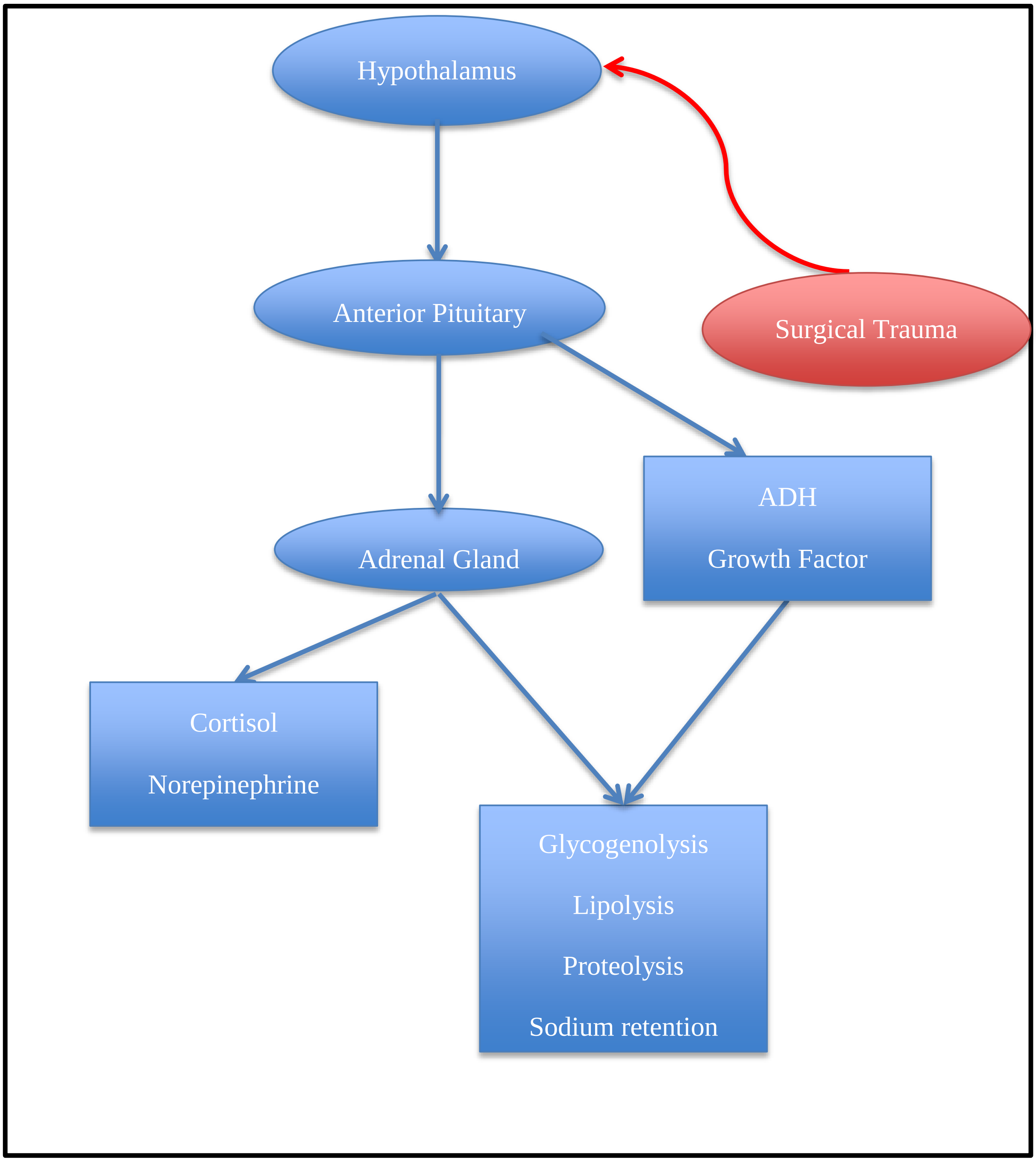

Figure 1. The hypothalamo-pituitary-adrenal axis

The inflammatory response is the result of an interaction between pro-inflammatory and anti-inflammatory mediators (Figure 2). Its magnitude is associated with the extent of the traumatic insult. Inflammatory mediators include the cytokines interleukin 6 (IL6), IL1 and tumour necrosis factor alpha (TNFα). Other factors released from migratory neutrophils include nitric oxide, histamine and phospholipase-A2. [3]

The end physiological result of the immune response is increased blood flow to the affected area, blood vessel dilatation, increased vessel permeability and adhesion and migration of phagocytic cells to the point of injury. Complement cascade and the coagulation pathways are also stimulated as well as growth factors that result in healing, tissue repair and removal of necrotic cells and toxins. [3]

Should the inflammatory response be overwhelming, a systemic inflammatory response syndrome (SIRS) may occur, in which excessive fluid redistribution to the extra vascular space, haemodynamic instability and excessive muscle catabolism can result in multi-organ dysfunction syndrome (MODS). [4] The inflammatory response is normally attenuated by anti-inflammatory mediators, namely IL10, that are released to counterbalance the pro-inflammatory mediators to provide a balanced response capable of optimising healing. [4] Similarly, should excessive anti-inflammatory mediators persist, immunosuppression may occur increasing host susceptibility to infection. [4]

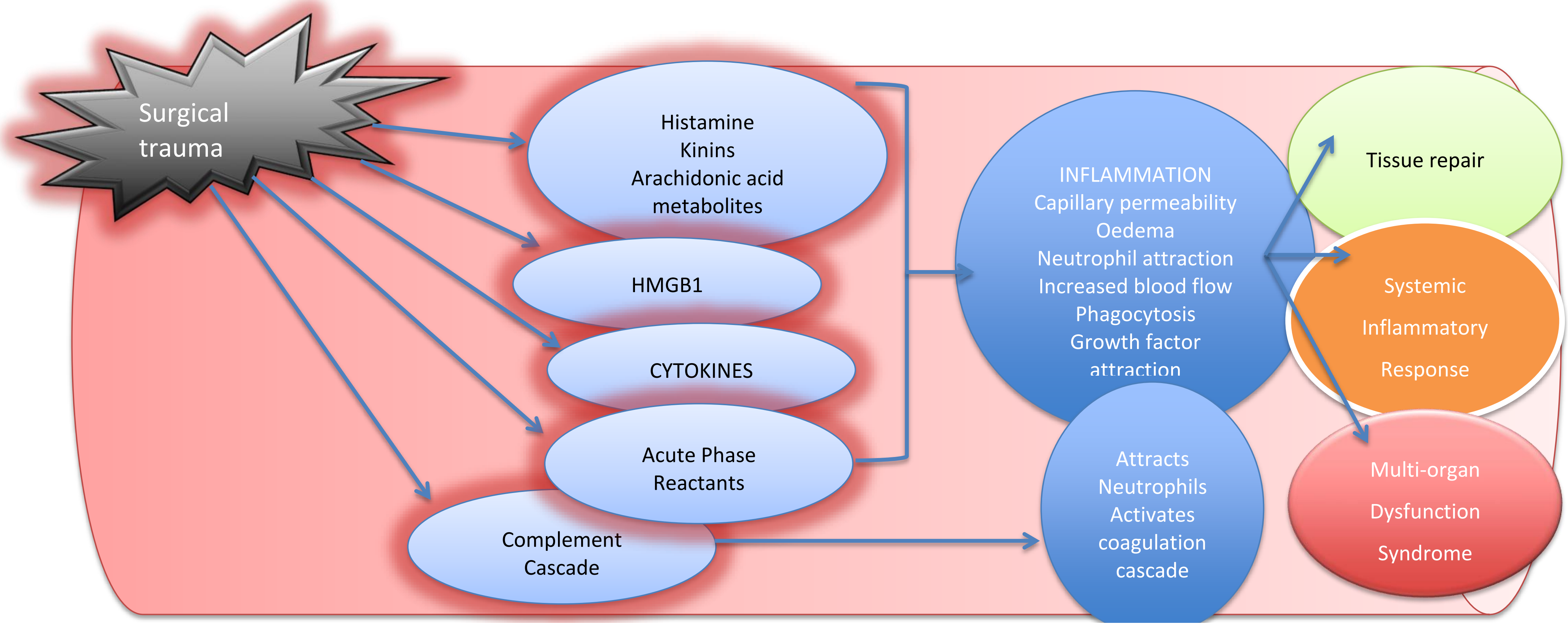

Figure 2. The inflammatory response

1.2 Inflammatory Mediators And Clinical Outcome

The impact of the inflammatory response on patient outcome has been investigated extensively and is well recognised as being associated with clinical course. TNFα is an early mediator of the inflammatory response. It peaks at around 12 hours after surgery and remains elevated for over 72 hours (Figure 3). [5] TNFα is released by T-cells and macrophages that are widely present in peritoneal tissue. [4] TNFα stimulates coagulation, adhesion molecules and glucocorticoids as well as haemodynamic change and muscle catabolism. [4] TNFα at increased levels has been found in patients with anastomotic leakage following colorectal surgery after meta-analysis [6] and a small observational study found low TNFα levels are associated with uncomplicated post-operative recoveries. [7]

IL1 is a pro-inflammatory cytokine. It is released soon after TNFα from macrophages and endothelial cells. There are two subtypes of IL1 – IL1α and IL1β. IL1β is detected in the circulation where its functions include activation of the coagulation cascade, release of adhesion molecules and glucocorticoids. Its release is also associated with haemodynamic instability. [4]

IL6 is released in response to surgical trauma. It is mainly released from endothelial cells and peaks at around 12 hours and remains elevated for several days post-operatively. Its functions include activation of the acute phase response and activation of neutrophils, which can prolong the inflammatory process. [4] Not only has it been found to be associated with the extent and duration of the surgical insult but is also associated with post-operative morbidity. [8] A meta-analysis of five RCTS showed that glucocorticoid administration reduced complications and resulted in correspondingly low IL6 in patients following liver resection. [9]

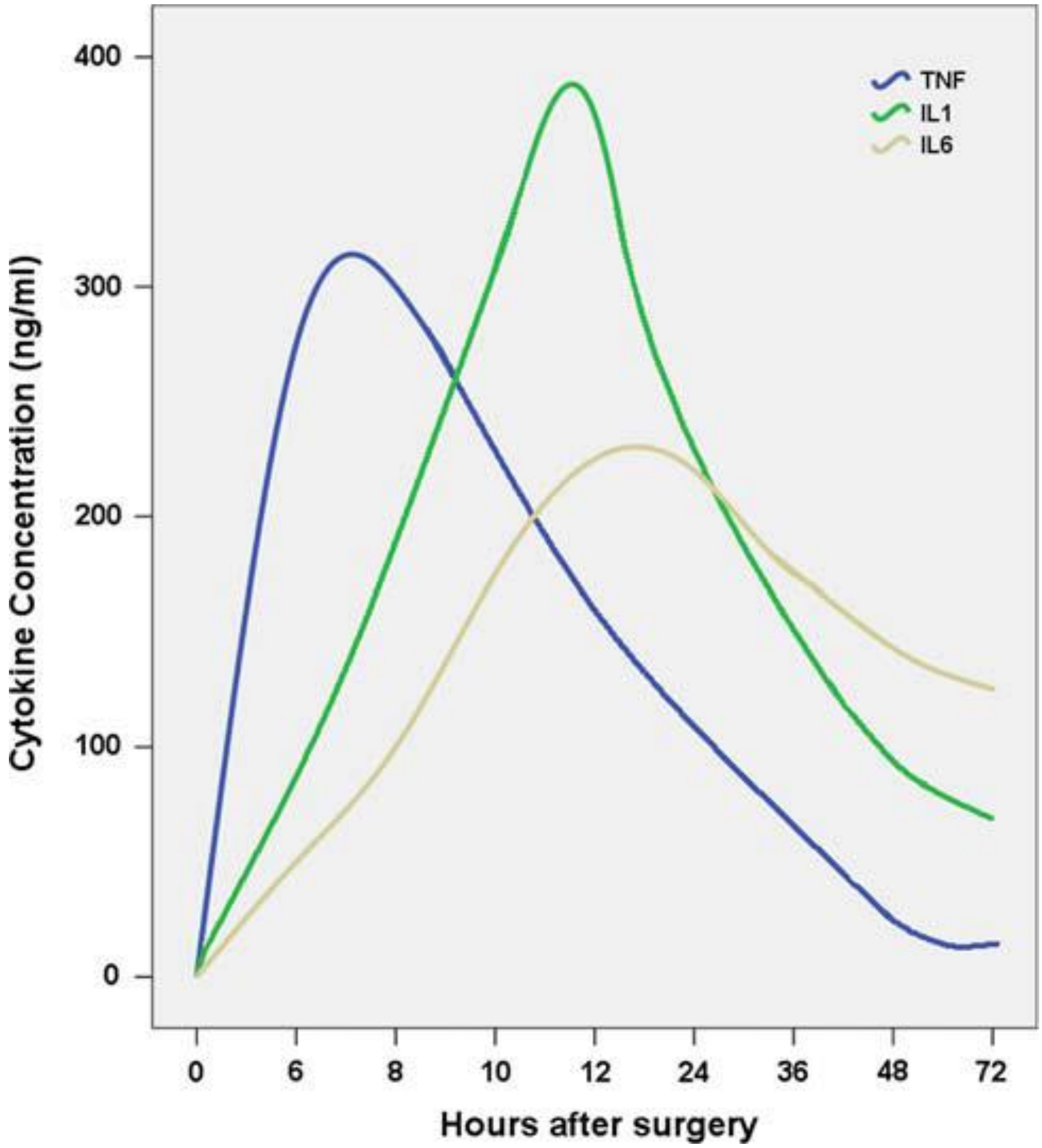

Figure 3. Pro-inflammatory cytokine dynamics

Figure reproduced from Sammour et al [3] with permission from Springer.

IL8 is a pro-inflammatory cytokine and neutrophil activator. [4] It is associated with increased risk of multi-organ failure after trauma [10] and is predictive of poor outcomes in patients with acute pancreatitis. [11] Prospective RCTs have shown that a reduction of IL8 by either methylprednisolone [12] or silvestat [13] resulted in IL8 attenuation and associated improvements in clinical course following major surgery.

In contrast to the above factors, IL10 is described as an anti-inflammatory cytokine. Animal studies have shown increased IL10 levels to reduce mortality [14] and IL10 deficient mice to have increased mortality following peritonitis. [15] Although randomised trials are lacking, low IL10 levels were shown in an observational prospective trial to be associated with post-operative complications following major abdominal surgery. [16] IL10 works in concert with antagonists to TNFα and IL1 to provide a counter to the pro-inflammatory process. [17]

1.3 HMGB1

The Damage Associated Molecular Pattern molecules (DAMPs) are nuclear and cytoplasmic proteins that are released from cells following tissue damage. A subset of DAMPs, the alarmins, has increasingly been shown to play a crucial role in the molecular stimulation of the sterile systemic inflammatory response process. [18]

Numerous alarmins have been identified and studied. Specifically High Mobility Group Box 1 (HMGB1) is increasingly gaining importance as the major stimulant of innate immunity in sterile inflammation. [19]

Once HMGB1 has been released from damaged cells at the point of injury it acts on endothelial cells via the Receptor for Advanced Glycation End Products (RAGE) resulting in release of adhesion molecules (ICAM1, VCAM1), cytokines and tissue plasminogen activator. [20]

Prospective observational studies have shown high levels of HMGB1 to be associated with increased mortality rates following major trauma. [19] After major gastrointestinal surgery HMGB1 is associated with prolonged duration of SIRS and pulmonary dysfunction. [21] HMGB1 has also been reported as associated with increased operative time and blood loss and those with post-operative morbidity after abdominal surgery were found to have higher HMGB1 levels than those without. [22] Patients undergoing oesophagectomy were also found to have higher levels of HMGB1 in those who suffered post-operative morbidity. [23] Anti HMGB1 antibodies when utilised in murine model studies resulted in improved survival following haemorrhagic shock, [24] limb fracture [25] and sepsis. [26] In human studies HMGB1 inhibitors such as sivelstat, a neutrophil elastase inhibitor, have been shown to improve clinical outcomes following major GI surgery in a controlled trial. [23] HMGB1 is released early in the post-operative period (from incision) and peaks at post-operative day (POD) two to three. [22] As described above, high early levels are strongly associated with adverse outcome in the post-operative course and therefore attenuation of this mediator has been recommended by investigators as an area of exploitation in an attempt to improve post-operative outcomes.[27]

1.4 Enhanced Recovery After Surgery

Enhanced Recovery After Surgery (ERAS) is a concept that has increased in popularity over the past decade. It was introduced initially in colorectal surgery and is responsible for improvements in post-operative length of stay and morbidity in this field. [28] Since then its use has extended to multiple surgical specialties including orthopaedic, [29] oesophagogastric [30] and breast surgery. [31]

The underlying principle of ERAS is the application of a multimodal peri-operative protocol to attenuate the inflammatory response and optimise patient rehabilitation following major surgery. [32] This is in an effort to prevent the problems associated with an exaggerated inflammatory reaction to surgery such as poor healing, infective complications and multi-organ dysfunction. [33] This approach, combined with intensive post-operative optimisation of mobility, gut function and analgesia [34] contributes to expediting recovery and minimising morbidity.

ERAS protocols were originally described by Kehlet in 1997 [32] and focused on pre-operative, intraoperative and post-operative factors that could be managed and optimised by a series of multi-disciplinary interventions (Figure 4). Individual protocols vary depending on the procedure and have been altered over time. However the underlying principles of enhanced recovery surgery broadly aim to minimise complications, optimise rehabilitation and reduce the impact of the surgical insult on the patient. This is achieved by suppression of the inflammatory response, targeting and preventing individual complications, promotion of rehabilitation and providing optimum nutrition to achieve a patient-centred recovery. [32]

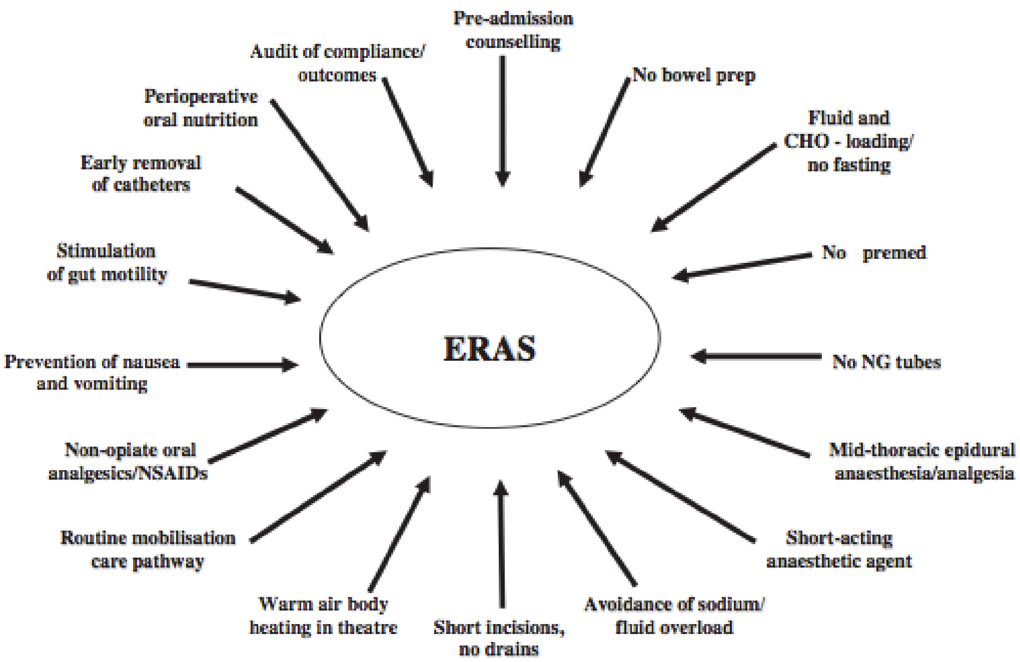

Figure 4 Elements of Enhanced Recovery After Surgery

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1.4.1 ERAS Society Recommendations (Colorectal Surgery)

A significant proportion of investigation of ERAS care has been undertaken in the context of colorectal surgery. The current best evidence assessing individual ERAS care components in the colorectal literature has been reported by the ERAS Society and is summarised below. [36] The level of evidence supporting the recommendations below is high or if not, is strongly recommended by the ERAS Society.

1.4.2 Pre-operative Factors

The ERAS Society [36] advises against the conventional practice of prolonged fasting of patients pre-operatively prior to surgery. Clear fluids up until two hours before induction of anaesthesia is not associated with increased risk of aspiration pneumonia according to a large meta-analysis of 22 RCTs [37] and is therefore recommended to avoid pre-operative dehydration.

Routine bowel preparation is also advocated against in a move away from traditional surgical practice. A large meta-analysis found no benefit in administering bowel preparation [38] in terms of anastomotic leak and, in view of the potential disadvantages with this practice, is not recommended.

Further recommendations by the ERAS Society based on large meta-analyses include avoidance of pre-anaesthetic medication [39] to prevent post-operative sedation and increase speed of rehabilitation and administration of peri-operative prophylactic antibiotics [40] to reduce post-operative wound infections.

Moreover clear fluids containing carbohydrates drunk up to two hours pre-operatively can counter-act the mediation of the inflammatory response by reduced insulin resistance. The evidence supporting this is less conclusive, however a randomised trial showed a reduction in post-operative morbidity after carbohydrate loading and improved recovery times after abdominal surgery. [41]

1.4.3 Intra-operative Factors

Intra-operative care components are centred around the surgical approach and the anaesthetic management of the patient. In order to attenuate the inflammatory response to surgery minimisation of surgical trauma is paramount to ERAS care principles. Laparoscopic surgery has been shown to reduce length of stay (LOS) in two large RCTS [42, 43] and laparoscopic approach is advised when possible and where the expertise is present. [36]

Anaesthetic management is centred around control of pain and fluid management intra-operatively and in the immediate post-operative period. Regional anaesthesia in combination with general anaesthesia is recommended by the ERAS society for open colorectal surgery as it improves post-operative pain, reduces post-operative nausea and vomiting (PONV), increases post-operative mobility and is associated with a reduction in morbidity and modulation of the stress response. [36] These recommendations are made on the basis of large meta-analyses comparing epidural to systemic opiates. [44-46]

Furthermore fluid administration should be delivered according to pre-specified physiological targets, ideally with monitoring of cardiac output to prevent fluid overload. Although a meta-analysis comparing fluid restriction to standard fluid administration failed to show a difference in outcomes, [47] goal directed fluid therapy assessed with oesophageal Doppler was shown after meta-analysis to improve morbidity and length of stay. [48]

1.4.4 Post-operative Factors

ERAS principles advocate a target driven approach to post-operative patient care which is dependent on multi-disciplinary input. Enteral nutrition is advised in the colorectal literature as soon as the patient is able to take oral diet and is supported by a meta-analysis showing a reduction in LOS and septic complications, and was not associated with increased anastomotic leaks when compared to conventional care. [49] Oral nutritional supplementation provided pre- and post-operatively has been shown to improve functional recovery in one RCT. [50] Adequate nutrition prevents muscle catabolism, insulin resistance and allows modulation of the inflammatory response [51] and supplementation is of particular benefit in pre-operatively malnourished patients. [52]

Optimum post-operative analgesia and prevention of ileus and PONV are goals of ERAS protocols and avoidance of excessive morphine administration is seen as central to achieving these goals. With this in mind a multimodal, opiate avoiding analgesic regimen is recommended. [36] This can be achieved by post-operative regional analgesia maintained for up to 72 hours with high level evidence advocating post-operative epidural analgesia being shown to reduce PONV, ileus and opiate use. [45] In addition to this, antiemetics are recommended and are superior to placebo, [53] as is dexamethasone. [54] No benefit is seen after meta-analysis when assessing nasogastric tube placement and this is not recommended. [55]

The avoidance of prolonged bed rest and increased mobilisation is another key component of ERAS care recommended by the ERAS Society. Although no benefits have been shown by RCT for enforced mobilisation, [56] prolonged immobilisation has been shown in a retrospective analysis to be associated with prolonged LOS. [57]

1.4.5 ERAS Outcomes

The aim of ERAS is to minimise the impact of the operation in order to allow the most efficient recovery. As a result a natural marker of success of ERAS has traditionally been the length of time spent in hospital. In the largest meta-analysis of

38 trials of different surgical procedures (predominantly colorectal surgery) Nicolson *et al* showed a significant reduction in LOS in the ERAS group [58]. When looking at individual surgical procedures meta-analyses have been performed assessing oesophagectomy, [30] pancreatic resection, [59] and colorectal surgery. [60] Similar length of stay reduction was reported in these fields of surgery for ERAS care.

An initial concern during initial implementation of ERAS care components was the safety of ERAS protocols and the resultant potential to increase complication rates as a result of alteration of traditional surgical practices. Again this has proven not to be the case on the basis of the current literature. Nicolson *et al* [58] showed significant reductions in morbidity in 22 trials of mixed operation type. Similar significant reductions have also been shown following oesophagectomy [30] colorectal surgery [60] and pancreatic resection. [59] No significant differences have been observed between ERAS protocols and conventional care in terms of mortality.

As a result enhanced recovery principles have become seen as standard of care in certain procedures, most notably colorectal surgery where there is a wealth of supporting literature. However individual care components are not universally agreed upon and not all surgical procedures are as well researched as colorectal surgery, affording areas to optimise.

1.5 Liver Surgery

Liver resection has become a routine procedure worldwide with increasing numbers of resections being performed annually. Liver resection offers the only curative option for a number of primary and secondary liver cancers and long-term cure is becoming increasingly common. [61]

1.5.1 Indication For Resection of the Liver

The liver is commonly affected by malignancy and both primary and secondary tumours can affect the liver. [62] The most common primary liver tumours are hepatocellular carcinoma (HCC) and cholangiocarcinoma. The most common secondary tumour is a metastasis from colorectal cancer.

1.5.1.1 Hepatocellular Carcinoma

HCC is the commonest primary liver tumour and represents 7.9% of all tumours. [63] In northern Europe the incidence is <5 per 100000 people whereas in areas of high incidence such as China and South East Asia HCC is reported in 20 per 100000 people. [63] Its incidence is increasing in the western world but decreasing in areas with traditionally high levels of HCC. [63]

In patients without cirrhosis, liver resection for HCC results in a five year survival rate of 50%. [64] 50% of patients with non-cirrhotic liver will recur within two years. [64] Re-resection is often indicated in these patients with similar long term outcomes to primarily resected patients. [64] Five year survival rates for patients with cirrhosis who undergo resection for HCC is 45% however the recurrence rates has been reported as high as 80%. [64]

1.5.1.2 Cholangiocarcinoma

Cholangiocarcinoma is cancer of the bile ducts and is a relatively rare malignancy accounting for 2% of all malignancies reported worldwide. [65] However it is the second most common primary liver malignancy. [65] Approximately 1500 people a year die in the UK from cholangiocarcinoma. [65]

The only treatment option for a potential cure is surgical resection and often a radical surgical approach is required. However only around one third of patients are found to have resectable disease at presentation [65] and 50% of those who make it to laparotomy are subsequently found to be irresectable at operation. [66]

Cholangiocarcinoma surgery has notoriously poor outcomes. The four year recurrence rate is reported as up to 56%. [67] Complete resection of cholangiocarcinoma is associated with five year survival rates of between 20 and

40% for perihilar cholangiocarcinoma. [68] Intrahepatic cholangiocarcnoma has been associated with five year survival of 61% but the majority of centres again report between 20 and 40%. [68]

1.5.1.3 Colorectal Liver Metastases

The most common tumour encountered in the liver and the most common hepatic secondary tumour is a metastasis from a colorectal primary. Colorectal adenocarcinoma is the third most common newly diagnosed cancer in the UK. Between 2008 and 2010 58 new cases per 100000 men and 37 new cases per 100000 women were diagnosed in the UK. [69] 25% of these patients present with synchronous liver metastases and a further 25% develop metachronous liver metastases over their follow up period after colonic resection. Of these 15% will go on to have resection of the liver metastasis. [70]

1.5.2 Morbidity and Mortality After Liver Resection

Morbidity after liver surgery remains a major consideration. Large retrospective analyses of liver resection cohorts over the past decade have consistently shown mortality rates of under five per cent [71-73]. Mortality rates have decreased from around ten per cent [74] to more acceptable levels mainly as a result of centralisation of liver resection to large volume centres, [75] advancement of techniques to reduce post-operative hepatic failure, [76-78] and reduction in operative blood loss. [79]

Morbidity rates however have consistently been reported at levels between 22 and 45 per cent. [71-73, 80] Common hepatic complications include bleeding, bile leak, liver failure and intra-abdominal sepsis. These complications result in significant compromise to patients' recovery after liver resection and result in increased length of stay, reduced satisfaction and increased risk of mortality. Furthermore general complications such as pneumonia, thromboembolic disease and acute kidney injury (AKI) are also prevalent following liver resection [71-73, 80].

Rates of liver failure have been reported between 2.6 and 5.7 per cent. [71, 81] Liver failure can result in multi-organ dysfunction and is a significant contributor to increased LOS and post-operative mortality. [72] Bile leak is a further significant cause of morbidity and mortality after liver resection. Rates of between 3.6% [82], 3.7 [71] and 4.8% [81] have been reported in large retrospective cohort studies. Bile leak adds to length of stay and is associated with sepsis, liver failure and mortality. [83] Intra-operative and post-operative haemorrhage is a further complication related to resection of the liver parenchyma. Rates of between 0.5 and 6.8 per cent [71, 84, 85] are reported. Not only is bleeding itself a complication associated with poor outcomes and re-laparotomy but peri-operative blood transfusion is associated with other causes of morbidity and mortality. [86] Similarly general complications such as pneumonia, UTI and thromboembolic disease not only increase length of stay but also are associated with reduced disease free and overall survival after resection for malignant disease. [87]

Enhanced recovery protocols have resulted in improved peri-operative complication rates in numerous surgical specialties [30, 58, 59]. With the increasing performance of liver resections at high volume centres and the increasing complexity of liver resectional surgery, the application of ERAS protocols to liver resectional surgery seems a favourable option when attempting to improve outcomes.

Enhanced recovery protocols were initially introduced to liver resectional surgery in 2006. [88] Debate remains regarding the optimal ERAS protocol for liver surgery. Although the basic principles of enhanced recovery surgery can be applied to liver resection surgery, this operation offers several unique facets of complexity that need to be considered when implementing surgical intervention and peri-operative care. These will be discussed below.

1.5.3 Principles of Liver Surgery

1.5.3.1 Anatomy

The liver is a vascular organ and receives inflow of blood from both the portal vein and hepatic artery. The right, middle and left hepatic veins drain blood from the liver into the inferior vena cava (IVC) and back into the heart. As well as this, a system of bile ducts drains bile from the hepatocytes into the duodenum via the biliary tree and common bile duct.

The ability of liver tissue to function is dependent on receiving inflow from the portal vein and hepatic artery and having bile and blood drained away by the biliary tree and hepatic veins respectively. Resectability is defined as the removal of tumour involved liver with R0 resection (surgical resection margin clear of tumour), leaving at least two segments with the corresponding inflow, outflow and biliary drainage. [89]

The liver is divided into segments according to the functional branching of the hepatic inflow and biliary drainage combined in a biliary triad. The standard surgical anatomical description of the liver was first described by Couinaud [90] who defined the segmental anatomy according to the distribution of the portal vein branches. The liver is divided up first of all into two hemilivers: the left and the right. The hemilivers are divided into segments according to the portal vein branches as well as their arterial inflow and biliary drainage. There are eight segments in total. Segments one to four comprise the left hemiliver and segments five to eight make up the right hemiliver. The two hemilivers are divided by the middle hepatic vein. Each hemiliver is further divided into sections. The following description is the Brisbane terminology [91] which is more surgically relevant although does stray from Couinaud's anatomical definition. The right liver is divided into the anterior (segments five and eight) and posterior (segments six and seven) sections. The right hepatic vein divides the right anterior and posterior sections. The left hemiliver is divided into the medial and lateral sections. The left medial section comprises segment four and the left lateral section is made up of segments two and three. These sections are divided by the left hepatic vein. The remaining segment of the left hemiliver is segment one, or the caudate lobe, which lies between the IVC and the portal vein and has its own drainage via short hepatic veins into the IVC.

1.5.3.2 Underlying Liver

As well as the technical resectability of a tumour, the condition of the underlying liver parenchyma is also a consideration when assessing patients prior to liver surgery. Patients with underlying cirrhosis are at potentially increased risks of complications and mortality. Cirrhosis is a particular concern when operating on patients with HCC due to the direct relationship between the two. The Model of End-Stage Liver Disease (MELD) is a strong predictor of outcome following liver resection for patients with cirrhosis and high MELD scores are associated with mortality rates of up to 14% after liver resection. [92]

Chemotherapy-related liver injury (CRLI) is a potential concern prior to liver resection particularly for patients with colorectal liver metastases who might have had either adjuvant chemotherapy following the bowel operation or neoadjuvant chemotherapy for a primarily unresectable or resectable liver tumour. Many of the chemotherapy regimens used can lead to pathological evidence of steatosis, steatohepatitis and sinusoidal obstruction syndrome and can lead to higher rates of post-operative complications. [93]

However peri-operative chemotherapy has been shown in a large RCT to provide a benefit to patients who underwent liver resection for primarily resectable disease in terms of an increased recurrence free survival. [94] Despite no difference being observed in overall survival [95] chemotherapy, namely folinic acid, fluorouracil and oxaliplatin (FOLFOX4), is recommended for primarily resectable disease in view of these data. [70] This is a further facet of care that can contribute to post-operative morbidity following liver resection.

Assessment of liver parenchyma can be made from radiological investigations such as the appearance of the liver on CT or MRI scan as well as by virtue of historical biopsies or laparoscopic assessment. However, often consideration and pre-emption of the possibility of poor functional reserve is factored into the pre-operative work up.

1.5.3.3 Biliary Obstruction

Further consideration should be given to any obstruction of the biliary system prior to resection. Patients with jaundice have been observed to suffer significantly higher morbidity rates following major resection [96] and efforts should be made to relieve obstruction (most commonly secondary to cholangiocarcinoma) prior to surgery in an effort to reduce complications such as abscess formation and bile leak.

1.5.3.4 Resection Extent

Deciding on which operative strategy to take involves consideration of size and location of the tumour. Small peripheral tumours are often amenable to localised non-anatomical resection without disruption to the inflow or drainage of the anatomical segment (referred to as an atypical resection). Larger or more centrally located tumours are not amenable to atypical resection and require formal anatomical resection of the involved segments.

Consideration of the underlying tumour pathology must be made when considering surgical approach. When considering HCC, the performance of an anatomical resection has been shown by meta-analysis to offer superior overall survival and disease free survival than non-anatomical atypical resections. [97] In contrast to this no difference was observed in survival rates when anatomical and non-anatomical resections are compared for colorectal liver metastasis (CLM) resections. [98]

Hilar cholangiocarcinoma resection will often require extended resection and radical excision of the biliary tree. The biliary system then requires to be reconstructed by means of a Roux-en-Y hepatico-jejunosotomy. Such procedures are technically challenging, prolonged and associated with significantly higher post-operative morbidity rates of up to 72 per cent [99] and mortality rates of up to 14.3 per cent. [66] The differences in surgical technique, when resecting hilar cholangiocarcinomas in particular, compared to other resections include the decision to perform a portal vein resection and a recent meta-analysis found this to be related to improved survival rates in patients with portal vein involvement. [100] It is also recommended that the caudate lobe be resected routinely in resection of cholangiocarcinoma as this is associated with better long term results. [101]

The resection margin is an important consideration however the precise margin that is acceptable remains controversial and is often determined by anatomical considerations of the procedure. Incomplete resection (R1) defined as tumour occurring within 1mm of the resection margin is associated with poor long term outcome following resectional liver surgery without neoadjuvant chemotherapy, although no difference between R0 and R1 survival outcome was observed in those who did receive neoadjuvant chemotherapy in a retrospective analysis of 264 patients. [102] However a meta-analyses looking at CLM [103] has shown that resection margins of more than one centimetre are associated with better survival outcome than margins of less than one centimetre although these results were not replicated for HCCs. [104] Therefore underlying liver pathology as well as individual patient factors need to be incorporated into the decision determining the appropriate surgical approach.

Resection of the left or right hemiliver normally leaves adequate remnant liver and often only involves the sacrifice of one hepatic vein and branch of the hepatic artery and portal vein. However, once resection goes beyond the hemiliver and becomes an extended resection, careful consideration of the remaining future liver remnant (FLR) is critical. Twenty-five per cent of the functioning liver is regarded as the minimum predicted FLR. [105] However, this also depends on the functioning of the remaining liver parenchyma. Should the underlying liver be suspected to be sub-optimal, such as in cirrhotic livers or livers affected by chemotherapy, a FLR of 30-40% is indicated [105] and pre-operative interventions to increase the volume of the FLR may need to be employed.

Several options are available should adequate oncological clearance not be perceived to be reached by orthodox resections. Such circumstances might be reached if the resection would leave less than 25 per cent of the liver volume, the functioning parenchyma is suspected to be compromised or the distribution of the tumours involves both lobes and would not be amenable to clearance by resection of a hemiliver.

Possible options for irresectable tumours include conversion chemotherapy, which can downsize tumours into the resectable criteria. This has proven to be an effective approach with improved long-term results and increased number of resectable patients. [106]

Portal vein embolisation (PVE) involves the involved liver being excluded via embolisation of the corresponding branch of the portal vein and hypertrophy of the FLR being induced to increase liver volume. PVE is associated with long term survival outcomes similar to patients undergoing extended resections without PVE. [76] Hypertrophy after PVE takes between four to six weeks.

A further option, either with or without PVE, is termed two-stage resection where bilobar disease is resected first by clearance of one lobe, followed by a staged interval to allow for regeneration and then clearance of the other lobe. This approach, although relatively new in practice has resulted in superior long-term survival compared to chemotherapy alone. [77]

A recent development is known as Associating Liver Partition and Portal Vein Ligation (ALPPS). This technique employs a surgical split of the liver along the falciform ligament in conjunction with a portal vein ligation. This induces the left side of the liver to hypertrophy and the affected right side to atrophy prior to a second stage procedure to remove the affected hemiliver around seven days later. Short-term outcomes are satisfactory [78] and long term outcomes are awaited.

1.5.3.5 Bleeding

Liver resection is notorious for its potential to cause excessive intra-operative bleeding. Much research has focused on minimisation of intra-operative bleeding. Not only is significant bleeding itself intrinsically related to poor outcome and is associated with peri-operative mortality, [107] it is also associated with the development of other peri-operative complications, particularly infective complications. [86]

Central venous pressure (CVP) optimisation during parenchymal resection has been shown to be associated with reduced estimated blood loss (EBL). [108] Methods of CVP reduction are varied. By using anaesthetic methods of intra-venous infusion (IVI) reduction, vasodilators and/or diuretics to maintain a CVP of less than five mmHg then significantly reduced EBLs and length of stay have been observed [109].

Intra-operative use of in-flow occlusion is used to reduce blood loss. The technique involves the clamping of the portal vein and the hepatic artery (the Pringle manoeuvre). This leads to ischaemia of the liver if applied for prolonged periods that can potentially lead to post-operative morbidity. [110, 111] The common protocol for complete inflow occlusion is to apply occlusion for ten minute periods with intermittent five minute intervals of non occlusion during liver transection if required.

Additional surgical techniques to reduce blood loss are total vascular hepatic exclusion (TVHE). This involves clamping of the hepatic veins and the IVC above and below the liver, in combination with a Pringle manoeuvre. Similarly selective vascular hepatic exclusion (SVHE) is also employed and this involves clamping the hepatic veins but the inflow and IVC are still patent. A meta-analysis [112] did not show any benefit of SHVE or THVE in terms of morbidity and mortality compared to Pringle alone, and Pringle was associated with a significantly lower morbidity when compared to THVE.

1.5.4 Inflammatory Mediators and Outcomes After Liver Surgery

Liver resection, in common with other forms of abdominal surgery, results in a similar inflammatory response with mediation from cytokines as well as endocrine and sympathetic responses. Liver resection however has some specific differences that are unique to this type of surgery.

Kupffer cells can result in a highly exaggerated inflammatory response when stimulated due to resection. [113] Liver transection results in disruption and injury to the liver parenchyma resulting in Kupffer cell damage and release of inflammatory mediators.

Portal triad clamping in an attempt to reduce intra-operative blood loss involves the clamping of the hepatic artery and the portal vein. As a result in-flow to the liver is stopped for a period of time. This process can result in an ischaemia/reperfusion injury to the liver whereby hypoxic damage can occur. This results in a further stimulation of the cytokine mediated response. [114]

The liver is also unique in its ability to regenerate following resection. This is a well-orchestrated process that results in cell proliferation and tissue formation. However it is initiated by the cytokine cascade that, in turn, stimulates growth factors and hepatocyte regeneration. [115] Therefore an appropriate inflammatory response is important not only to avoid immunosuppression but also to ensure adequate liver functioning after liver resection.

Attempts to attenuate the inflammatory response after liver resection have been made by several investigators. A meta-analysis of RCTs shows that when perioperative steroids are administered in patients undergoing liver resection a reduction in IL6 and CRP, a raise in IL10 and an improvement in clinical outcomes including morbidity are observed. [116]

1.6 Summary and Required Work

Major surgery results in a stimulation of the inflammatory response in order to preserve function and promote healing. However, as a result of this process, compromises to recovery can occur. Enhanced recovery after surgery is a multifaceted care process that has proven to be effective at reducing post-operative morbidity and expediting recovery. It aims to attenuate the impact of surgery and the inflammatory response to allow recovery to be optimised.

Liver surgery is indicated as a curative option for a number of malignant conditions. Indications for surgery and the numbers of resections being performed are increasing. Due to the complex nature of liver surgery it has several aspects of care that are not encountered in other aspects of abdominal surgery. These unique complexities of liver surgery mandate consideration when attempting to optimise outcome after hepatic resection. For this reason the general ERAS literature is not necessarily translatable to liver resection surgery. Therefore it is crucial to scrutinise the liver ERAS literature in order to establish current practice and determine the areas where improvements are required in order to minimise post-operative morbidity after liver surgery. The following chapter investigates in detail the current evidence assessing enhanced recovery after liver surgery.

1.7 Chapter Publications

Principles of Liver Surgery. Michael J Hughes & Stephen J Wigmore. Surgery 2014;12:643-647

Malignant Liver Tumours. Michael J Hughes & Ewen M Harrison. Surgery 2014;12:655-660

2 Enhanced Recovery Following Liver Surgery: A Systematic Review and Meta-analysis.

2.1 Summary

Enhanced Recovery After Surgery (ERAS) programmes aim to improve post-operative outcomes. They are increasingly being utilised in hepatic surgery. This review aims to evaluate the impact of ERAS on outcomes following liver surgery and identify areas where improvements can be made. EMBASE, Medline, PubMed and the Cochrane database were searched for trials comparing outcomes of patients undergoing liver surgery utilising ERAS principles with conventional care. The primary outcome was post-operative complications within 30 days. Secondary outcomes included length of stay, functional recovery, and adherence to the ERAS protocols. Nine articles were included in the review, of which two were RCTs. The overall complication rate was: ERAS 25% (range 11.5%-46.4%); conventional care: 31% (range 11.8%-46.2%). Significantly reduced overall complication rates following ERAS care were demonstrated by the two RCTs following meta-analysis, (OR 0.49, 95%CI 0.28, 0.84; p=0.01) The median length of stay for ERAS patients reported by the studies was 5 (range 2.5-7) days compared with 7.5 (range 3-11) days for non-ERAS patients. Recovery milestones, where reported, were improved following ERAS care. The adoption of ERAS protocols improves morbidity and length of stay following liver surgery. ERAS programmes need to accommodate the unique properties of liver surgery in order to optimise post-operative outcomes.

2.2 Introduction

ERAS programmes were introduced initially in colorectal surgery, where they have been associated with improvements in post-operative length of stay and morbidity. [28] They have since been adopted by multiple specialties including orthopaedic surgery [29], oesophagogastric surgery [30] and breast surgery. [31]

The underlying principle of ERAS is a multimodal peri-operative protocol to attenuate the inflammatory response and potentiate patient rehabilitation following major surgery. [32] The intention is to prevent the problems associated with an exaggerated inflammatory reaction to surgery such as poor healing, infective complications and organ dysfunction. [33] This approach, incorporating intensive optimisation of mobility, gut function and analgesia [34] contributes to expediting recovery and minimising morbidity.

ERAS programmes have been shown to reduce post-operative morbidity rates following a variety of surgical procedures. [28] Liver resections have traditionally been associated with high mortality and morbidity rates. With current surgical and peri-operative management mortality rates of less than five per cent can be achieved. [71] However, morbidity rates remain high at between 22 and 45 per cent. [71, 73, 81, 117] Adopting ERAS protocols may facilitate further improvement in surgical outcomes in hepatic resection.

Recently a number of publications have examined the application of ERAS programmes to hepatic surgery. This review aims to evaluate the impact of these programmes on morbidity and recovery rates following liver surgery and identify areas of protocol optimisation.

2.3 Methods

This study was conducted according to the PRISMA guidelines for meta-analysis. [118] A literature search was performed independently by two researchers of EMBASE, Medline, PubMed and the Cochrane databases in May 2013.

The databases were searched from 1966-2013 with the following key terms: "enhanced recovery", "fast track", "ERAS" and "liver", "hepatobiliary", "hpb". All abstracts were reviewed for relevance. Relevant full text articles were subsequently reviewed.

All trials assessing enhanced recovery following liver surgery were included. It was required that the protocol be clearly stated and that it contain at least four items of care considered to be contributory to an enhanced recovery programme. [119] Exclusion criteria included: children aged 16 years and below; non-standardised care pathway and comparison of ERAS protocols in both arms of the study.

All studies included in the final analysis were assessed by two independent reviewers. Study quality and bias was assessed independently using the Downs and Black score. [120] Data was extracted directly from the papers as directed by data extraction forms.

Primary outcome was the occurrence of any complication occurring within 30 days post-operatively. The following markers were assessed as secondary outcomes: length of stay (LOS); time to the achievement of functional recovery; readmission rate and adherence to ERAS protocol.

The meta-analysis was performed using Review Manager (RevMan ver 5.2. The Nordic Cochrane Centre, Copenhagen). Dichotomous data were analysed by fixed effects odds ratio. Heterogeneity was assessed by using I^2 and X^2 and adjudged to be significant if I^2 >50 per cent and/or $p<0.05$. Statistical significance was set at $p<0.05$. When continuous quantitative data were not distributed normally, meta-analysis was not performed and a qualitative assessment was utilised.

2.4 Results

2.4.1 Study Characteristics

257 papers were identified. The PRISMA diagram is shown in Figure 5. Nine studies were included for review. [88, 121-128]

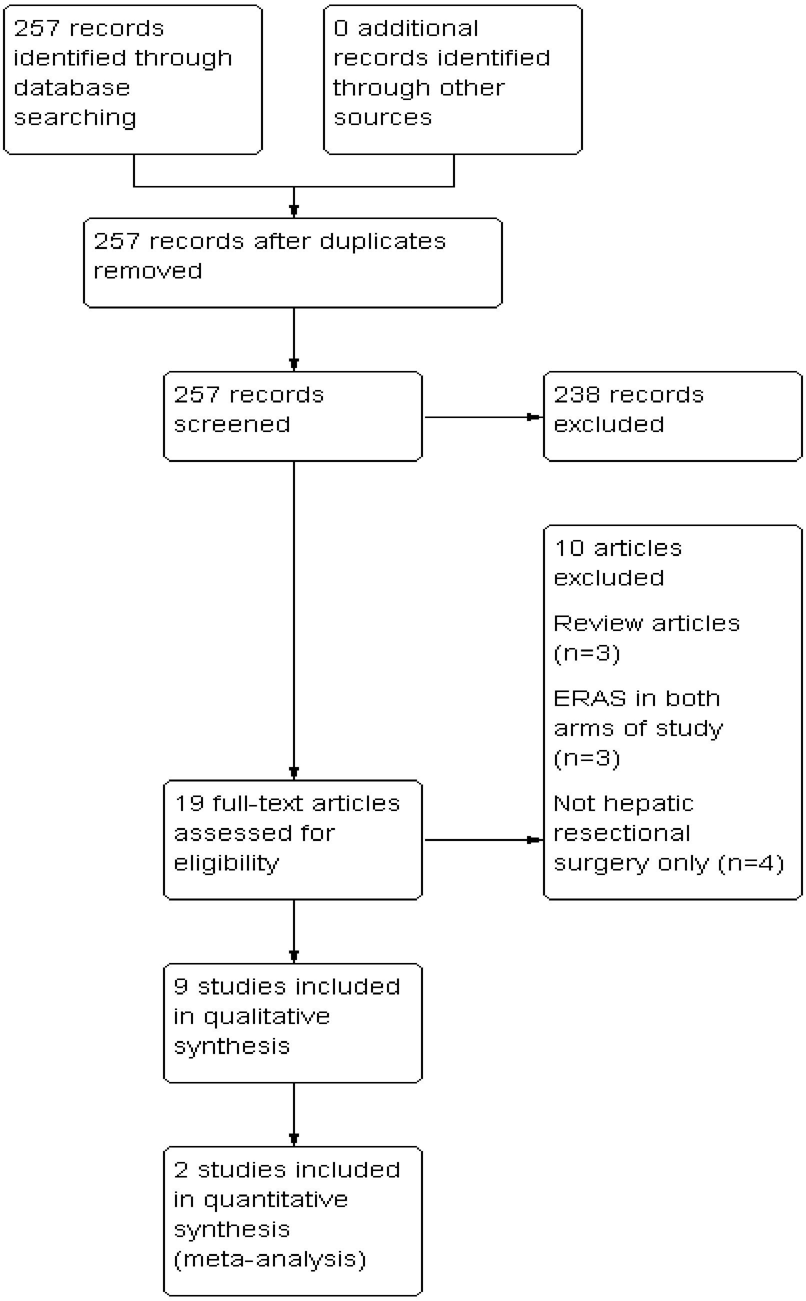


Figure 5. PRISMA diagram

In open hepatic surgery there were two RCTs [122, 124], two prospective [123, 126] and one retrospective [121] cohort studies, and two case control papers. [88, 128]

Two case control trials compared laparoscopic ERAS protocols with laparoscopic conventional care. [125, 127]

The trials included spanned the period 2008 to 2013. A total of 522 patients underwent liver resection with an ERAS protocol and 316 followed a conventional care pathway following liver resection. Patient age was reported between the groups as ERAS: median 60 years (range 48.4 – 64) and conventional care: median 53.8 years (range 45-67). The majority of the operations were for colorectal liver metastases or hepatocellular carcinoma. Details of participant characteristics are shown in Table 1. All studies explicitly described an ERAS protocol. A median of 11 ERAS items were utilised (range 8 - 19). The individual components utilised in the protocol are displayed in Table 2.

	Van Dam *et al* [88]		**Sanchez Perez *et al* [125]**		**Stoot *et al* [127]**		**Jones *et al* [122]**	
	ERAS	**C**	**ERAS**	**C**	**ERAS**	**C**	**ERAS**	**C**
Number	61	100	26	17	13	13	46	45
Age (years)	62 (24-82)	60 (20-81)	58 (29-77)	52 (29-84)	55 (34-82)	45 (26-70)	64 (27-83)	67 (27-84)
ASA n(%)								
I	11(18.0)	14(14.0)	0(0)	0(0)	3(23.1)	6(46.2)	0(0)	2(4.4)
II	42(68.8)	64(64.0)	13(50.0)	8(47.1)	9(69.2)	6(46.2)	43(93.5)	38(84.4)
III	8(13.1)	22(22.0)	13(50.0)	9(52.9)	1(7.7)	1(7.7)	3(6.5)	5(11.1)
IV	-		-	-	-	-	-	-
Resections n(%)								
≥3 segments	34(55.7)	61 (61.0)	0(0)	0(0)	0(0)	0 (0)	21(45.7)	12(26.7)
<3 segments	27(44.3)	39 (39.0)	26(100.0)	17(100.0)	13(100.0)	13(100.0)	25(54.3)§	33(73.3)
Pathology n(%)								
CLM	51(83.6)	72(72.0)	-	**-**	Malignant		**35(76.1)**	**26(57.8)**
HCC	4(6.6)	9(9.0)	3(11.5)	3(17.6)	5(38.5)	2(15.4)	-	**-**
Cholangiocarcinoma	-	-	1(3.8)	0(0)			-	**-**
Benign	4(6.6)	14 (14.0)	14(53.8)	14(82.4)	Benign		1(2.2)	9(20.0)
Other malgnancy	2(3.3)	4 (4.0)	**8(30.8)**	**0(0)**	8(61.6)	11(84.6)	10(21.7)	10(22.2)
Male	35(57.3)	51(51.0)	15(57.7)	10(58.8)	3(23.1)	2(15.4)	31(67)	23(51.1)
Quality	20/32		18/32		19/32		31/32	

ERAS = Enhanced Recovery After Surgery; C = Conventional Care; NA=Not assessed. Statistically significant results ($p<0.05$) are highlighted in bold. § = POSSUM scores significantly greater in ERAS group, *mean±sd. Data are presented as n(%) or median (range).

Table 1. Patient characteristics

	Mackay [123]	Schultz *et al* [126]	Lin *et al* [128]		Connor *et al* [121]	Ni *et al* [124]	
	ERAS	**ERAS**	**ERAS**	**C**	**ERAS**	**ERAS**	**C**
Number	12	100	56	61	128	80	80
Age (years)	60 (43-74)	64 (16-91)	57(23-73)	55 (22-81)	63 (35-82)	48.4 ±15.6*	50.1 ±21.8*
ASA n(%)							
I	4 (33.3)	29 (29.0)	(I+II) 43(76.8)	50(82.0)	I+II 104(81.2)	76(95.0)	78(97.5)
II	7 (58.3)	46(46.0)			-	4(5.0)	2(2.5)
III	1(8.3)	25(25.0)	11(19.6)	10(16.4)	24(18.8)	-	
IV	-	-	2(3.6)	1(1.6)	-	-	
Resections n(%)							
≥3 segments	3(25.0)	32(32.0)	19(33.9)	21(34.4)	64(50.0)	73(91.2)	69(86.2)
<3 segments	9(75.0)	68(68.0)	37(66.1)	40(65.6)	64(50.0)	7(8.8)	11(13.8)
Pathology n(%)							
CLM	12(100.0)	77(77.0)	NA		84(65.1)	-	-
HCC	-	12(12.0)			9(7.0)	71(88.8)	76(95.0)
Cholangiocarcinoma	-	-			11(8.5)	9(11.2)	4(5.0)
Benign	-	-			10(7.8)	-	-
Other malignancy	-	11(11.0)			15(11.6)§§	-	-
Male n (%)	8(66.7)	63(63.0)	31(55.4)	34(55.7)	NA	66(82.5)	59(73.8)
Quality	18/32	22/32	21/32		21/32	27/32	

ERAS = Enhanced Recovery After Surgery; C = Conventional Care; NA=Not assessed. Statistically significant results ($p<0.05$) are highlighted in bold; §§n=129, *mean±sd. Data are presented as n(%) or median (range).

Table 1 contd. Patient characteristics

Care Component	Van Dam *et al* [88]	Sanchez Perez *et al* [125]	Stoot *et al* [127]	Jones *et al* [122]	Ni *et al* [124]	Mackay [123]	Schultz *et al* [126]	Lin *et al* [128]	Connor *et al* [121]
Pre-operative counselling			X	X	X	X	X	X	X
Avoid bowel prep				X	X			X	X
Carb. drinks up to two hours pre-op	X		X	X	X	X		X	X
Avoid anaesthetic pre-med	X		X	X	X			X	X
DVT prophylaxis				X					X
Antibiotic prophylaxis				X		X			X
Standard anaesthetic protocol	X		X	X					X
Ileus avoidance	X		X	X	X		X		
NGT avoidance	X	X	X	X	X		X	X	
Intra-op warming	X			X					X
Minimisation of pre-op fluids	X	X	X	X	X	X	X	X	X
Avoid routine drains	X	X	X	X	X		X	X	X
Early removal of IDC	X	X	X	X	X	X	X	X	X
Multimodal analgesic	X	X	X	X	X	X	X	X	X
Early feeding	X	X	X	X	X	X	X	X	X
Early mobilisation	X	X	X	X	X	X	X	X	X

X=component included, NGT = nasogastric tube, IDC = indwelling catheter, DVT= Deep vein thrombosis.

Table 2. ERAS components present in protocol

2.4.2 Complications

All nine studies assessed complication rates (Table 3). [88, 121-128] The overall morbidity rate was: ERAS 25% (range 11.5% - 46.4%); conventional care: 31% (range 11.8%-46.2%). Ni *et al* [124] observed a significantly reduced overall complication rate in the ERAS group (Figure 6) and meta-analysis of the two RCTs assessing overall complication rates shows significantly fewer complications following ERAS surgery (I^2 0%; OR 0.49, 95% CI 0.28, 0.84; p=0.01). Both Jones *et al* [122] and Ni *et al* [124] reported significantly fewer non-surgical complications in the ERAS arm (Jones *et al*: ERAS 7% versus conventional care 27% p=0.02; Ni *et al*: ERAS 12.5% versus conventional care 25%; p=0.04) but showed no statistically significant difference in liver specific complications (Jones *et al*: ERAS 15% versus conventional care 11%, p=0.612; Ni *et al*: ERAS 17.5% versus conventional care 21%, p=0.55).

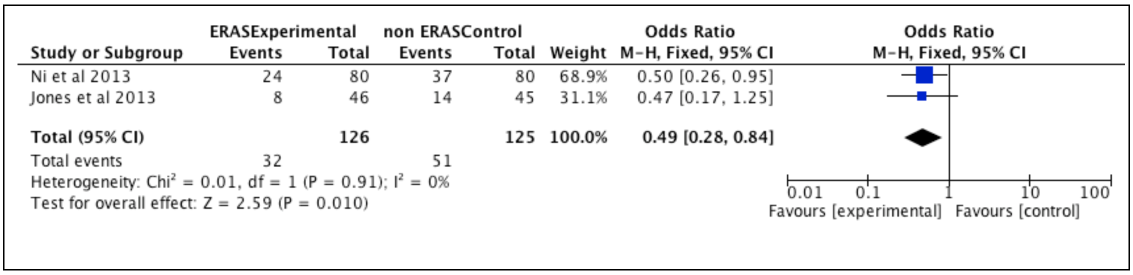


Figure 6. Morbidity rates for ERAS versus conventional care.

Author	Design	n		LOS (Days) Median (IQR) or mean±sd		Functional Recovery (Days) Median (IQR) or mean±sd		Readmission n (%)		Morbidity n (%)	
		ERAS	C	ERAS	C	ERAS	C	ERAS	C	ERAS	C
Van Dam *et al* [88]	Case control	61	100	**6 (3-82)**	**8 (4-68)**	NA	NA	8(13.0)	10(10.0)	25(41.0)	31(31.0)
Sanchez-Perez *et al* [125]	Case control	26	17	2.5 (1-39)	3(1-22)	NA	NA	1(3.8)	1(5.8)	3(11.5)	2(11.8)
Stoot *et al* [127]	Case control	13	13	5 (3-10)	7 (3-12)	**3 (1-7)**	**5 (2-8)**	0 (0)	0 (0)	2 (15.4)	2(15.4)
Jones *et al* [122]	RCT	46	45	**4 (3-5)**	**7 (6-8)**	**3 (3-4)**	**6 (6-7)**	2 (4.3)	0 (0)	8 (17.4)	14 (31.1)
Ni *et al* [124]	RCT	80	80	**6.9 (±.8)**	**8.0 (± 3.7)**	**5.2 (±2.3)**	**6.7 (±2.9)**	NA	NA	**24(30.0)**	**37(46.2)**
Mackay [123]	Prospective cohort	12	-	4 (2-7)	-	NA	-	NA	-	3(25.0)	-
Schultz *et al* [126]	Prospective cohort	100	-	5 (minor) 6 (major)	-	NA	-	6(6.0)	-	25(25.0)	-
Lin *et al* [128]	Case control	56	61	**7 (3-26)**	**11 (4-37)**	NA	NA	4 (7.1)	2(3.3)	26(46.4)	27 (44.3)
Conner *et al* [121]	Retrospective review	128	-	4 (2-111)		NA	-	14(10.9)	-	34 (26.6)	-

ERAS – Enhanced Recovery After Surgery; C – Conventional Care; LOS – Length of Stay; IQR – Interquartile Range; RCT – Randomised Controlled Trial; NA – Not Assessed. Statistically significant results ($p<0.05$) are highlighted in bold.

Table 3. Study outcomes

2.4.3 Length of Stay

The median length of stay for ERAS patients reported by the studies was 5 (range 2.5-7) days compared with 7.5 (range 3-11) days for non-ERAS patients. The three cohort studies reported median LOS of 4 [121, 123] and 5 [126] days. All four studies comparing ERAS open liver surgery to conventional open liver surgery showed a significantly reduced LOS in the ERAS groups. [88, 122, 124, 126] Neither of the two laparoscopic studies [125, 127] identified a reduced LOS. However, Stoot *et al* [127] reported reduced time to achieve functional recovery. Functional recovery was only reported by three studies [122, 124, 127] which all showed reduced time to recovery following ERAS care. Five [88, 122, 125, 126, 128] of the nine trials reported on readmission rates with no significant differences being observed (Table 3).

2.4.4 Adherence

Three of the studies reported rates on adherence to the protocol. [88, 122, 123] Jones *et al* [122] reported a 100% adherence in all 19 ERAS categories except early removal of IDC. Mackay & O'Dwyer [123] reported prolonged use of IV fluid administration beyond the first post-operative day in 25% of patients. Van Dam *et al* [88] reported on abdominal drain insertion (n=1), nasogastric tube insertion (n=3) and epidural analgesia (95%).

2.5 Discussion

This review investigated the effects of ERAS protocols on recovery following liver resection. Three previous reviews [119, 129, 130] have been performed in this area, which concluded that safety and feasibility were satisfactory with reduced length of stay not resulting in increased morbidity or mortality. However these reviews included studies other than purely ERAS versus conventional care, did not report any RCTs and reviewed only two studies comparing open ERAS versus open conventional care. Since these reviews five studies have been published including two RCTs. Therefore in light of this new evidence it is important to review the current recommendations.

This review was limited as a result of the small number of RCTS, preventing meaningful meta-analysis. The majority of studies were observational thus reducing the power of the review and preventing optimal quantitative comparison. However all trials were procedure specific and compared ERAS with conventional recoveries and this review represents the current best available evidence.

In concordance with the previous reviews on this subject, [119, 129, 130] the current review observed that length of stay can be reduced by ERAS programmes, a result that was seen in all of the comparative studies in open liver resection. However, in contrast to the previous reviews, and in line with previous ERAS literature [28] it has also demonstrated that complication rates in hepatic surgery can also be reduced by

ERAS protocols, with meta-analysis of both published RCTs showing a significant reduction in overall complication rates.

This reduction was not repeated in the non-RCT studies. This may be related to study design and power. Also, morbidity as an outcome measure has its limitations, with reporter bias and inconsistent complication classifications potentially contributing to morbidity rate variation. However it is of note that Ni *et al* [124] had the youngest population of all the studies and both RCTs had relatively fitter populations. Advanced age and ASA level are both independent predictors of morbidity following abdominal surgery [131] and it is possible that younger and fitter populations of these studies progressed better in an enhanced recovery protocol. Furthermore, Jones *et al* [122] employed an ERAS programme incorporating 19 components – more than any other trial, and the protocol compliance was exceptionally high, a key consideration in the conduction of ERAS programmes. [132]

Adherence was poorly reported with only three trials commenting on this. The main areas of reported poor compliance were IV fluid restriction, IDC removal and early mobility. Within the colorectal ERAS literature compliance is often not recorded or may be as low as 5% for some elements. [132] Higher rates of compliance are associated with reduced length of stay. [132] Compliance is an area that has potential for improvement in ERAS protocols following liver surgery.

Although the rates of general complications were observed to have been reduced in the two randomised trials, no difference in liver specific surgical complications was observed. Liver resection offers a unique set of post-operative circumstances due to the process of liver regeneration, anatomical complexity of biliary drainage and intra-operative vascular inflow control and transient impairment of liver function following resection. When scrutinising the included ERAS protocols, such components were not consistently addressed and so it is not surprising that the ERAS approach did not reduce surgical complications in these patients.

Whilst the majority of the ERAS protocols focussed on pre- and post-operative considerations, opportunities exist where intra-operative care can be optimised. Minimising blood loss can help to reduce post-operative complications. [71, 73, 117] Raised CVP has been shown to be associated with intra-operative blood loss during liver resection [109]. In this review only two trials [88, 121] commented on titration of IV fluid according to CVP. Jones *et al* [122] used goal directed fluid therapy guided by cardiac output monitoring to prevent fluid overload although this was done in the early post-operative period. It would appear in liver surgery that ERAS protocols should incorporate both intra-operative and post-operative components to maximise their gains.

Areas that were not explored by the included studies included the use of thoracic epidural. Although recommended in colorectal ERAS literature [36] its use has been questioned in liver surgery [133] as it is associated with fluid overload and increased red cell transfusion. There is evidence suggesting that epidurals may impair recovery in liver surgery, and that alternate analgesic methods should be considered. [134, 135] However, the evidence base is not clear or conclusive and controversy regarding this facet of care remains.

Analgesia after liver resection is also complicated by a potentially small liver remnant that may be a contra-indication to administering acetaminophen. [136] Acetaminophen is routinely utilised as the backbone of ERAS analgesic regimens but in major hepatic resections it is often withheld for fear of inducing liver damage, increasing opiate requirements. Evidence addressing this issue is limited to a small observational study. [136] Further evaluation of analgesia for liver surgery within the context of an ERAS programme is required to establish optimum practice.

This review has highlighted the benefits of the application of enhanced recovery principles following liver surgery. However, the evidence supporting these principles stems from the colorectal literature. Resectional liver surgery comes with its own set of unique conditions that must be acknowledged when attempting to optimise the outcomes of patients following liver surgery. In order to maximize the potential benefit of such programmes future research should aim to establish peri-operative care plans specific to liver surgery and accommodate the unique requirements of this operation.

Length of stay is not an ideal outcome to judge the success of an ERAS programme due to the multifactorial aspects of patients being able to leave hospital. [137] Functional recovery was infrequently assessed in the included studies. When this was reported, ERAS protocols resulted in either parity or improvement of these outcomes. Functional recovery has been suggested as more meaningful than simple LOS in assessing the success of an enhanced recovery protocol [119] and should form the measurement of success in future programmes.

In summary the evidence investigating ERAS following liver surgery is limited with only two RCTS. However, postoperative length of stay is reduced when compared to conventional care. Overall and general complication rates seem to be reduced although surgical morbidity remains high and as yet is not affected by ERAS protocols following liver surgery. Future research should concentrate on peri-operative care components specific to liver surgery, such as optimal analgesic regimens and intra-operative manipulations to reduce blood loss, rather than simply transferring components from the colorectal literature. The following two chapters will investigate the literature assessing these two aspects of care during liver surgery.

2.6 Chapter Publication

Enhanced Recovery Following Liver Surgery: a systematic review and meta-analysis. Hughes MJ, McNally S, Wigmore SJ. HPB (Oxford). 2014;16:699-706.

3 Analgesia After Liver Surgery: A Systematic Review of the Literature

3.1 Summary

Post-operative analgesia following liver resection remains controversial. The traditional standard of care of thoracic epidural is increasingly questioned due to perceived associated complications and delays to recovery. Evidence supporting alternative analgesic techniques is emerging however best practice is not yet established. This review aimed to evaluate the literature to assess the optimum analgesic technique following liver resection. A systematic review was conducted of trials evaluating analgesic methods in open liver surgery. Primary outcome was the post-operative complication rate. Secondary outcomes were length of stay and pain scores. Fourteen trials matching the inclusion criteria were analysed. No difference was observed in systemic complication rates between analgesic modalities. Epidural was associated with prolonged length of stay when compared with continuous wound infiltration and intrathecal morphine. Epidural offered equivalent or superior pain scores when compared to alternative techniques. In summary, current evidence suggests alternative analgesic modalities may provide favourable recovery outcomes following liver surgery compared to epidurals but consistent evidence is limited. Epidurals provide superior pain relief to alternatives but this does not translate into reduced length of stay or complication rate following liver surgery.

3.2 Introduction

Liver surgery is commonly performed worldwide and its indications have increased in recent years. Overall mortality has now been reported at levels of less than five per cent [81], when performed in high volume centres. However complication rates remain high at levels reported between 22 and 45%. [71, 73, 117]

Efforts to improve complication rates have focussed on optimising post-operative care. Enhanced Recovery After Surgery (ERAS) programmes, by way of initiating early mobilisation, early feeding and a multi-disciplinary goal directed care package have contributed to improved post-operative morbidity rates. [28] Pain control is a vital component of the post-operative care of these patients and crucial when attempting to achieve ERAS recovery milestones. [36] Traditionally an epidural has been advocated as the routine, optimal choice of analgesic modality following liver surgery, [88, 138] although in recent years this has been questioned. [139]

Criticisms of epidurals cite the associations with hypotension, post-operative intravenous fluid overload [140] and increased rates of blood transfusion. [141] Furthermore high failure rates, [142] risks of urinary retention [143] and epidural haematoma [144] and infection [145] contribute to delays to post-operative recovery. When compared to other abdominal procedures, liver surgery patients have reported post-operative coagulopathy rates of over 50% making epidural haematoma an even greater consideration. [146] Furthermore, liver resection is ideally performed under hypovolemic conditions and increased intra-operative IV fluid administration associated with neuraxial blockade can further complicate post-operative recovery. [147] Therefore choice of analgesic technique is particularly pertinent following liver surgery and can have significant effects on outcome.

In the absence of superior alternatives such negative side effects have been tolerated in favour of the excellent pain relieving components in an effort to optimise post-operative recovery outcomes. [36] However, new analgesic techniques are being developed and used in open abdominal surgery and liver surgery and support for such techniques is growing. [148]

ERAS following liver surgery has grown in popularity. [119] Therefore the effect of analgesic modality on surgical outcomes is coming under scrutiny. Debate continues as to the optimal analgesic modality following liver surgery in terms of overall post-operative outcome. [133] Therefore this review aims to systematically evaluate the literature comparing all analgesic modalities following liver surgery and assess the effects on outcome.

3.3 Methods

This review was conducted in accordance with the PRISMA guidelines. [118] A literature search of Medline, EmBase, OVID and PubMed from November 1966 to September 2013 was performed independently by two reviewers. The following search terms were used: “liver resection” or “hepatic resection” or “hepatectomy” and “epidural” or “opiate” or “opioid” or “spinal” or “intrathecal” or “wound catheter” or “continuous infiltration” or “local infiltration” or “transversus abdominis plane” or “TAP block” or “patient controlled analgesia” or “on-q”.

Two researchers independently performed the literature search and all articles were scrutinised and irrelevant publications excluded. All relevant publications were reviewed and compared with the pre-determined inclusion criteria independently. Each paper was then assessed for quality by the two reviewers using the Downs and Black score. [120]

The following data were extracted directly from the papers: patient demographic details, type of operation, analgesic regimen details, complication rates, length of stay (LOS), pain scores at rest and on movement at 24 hours post-operatively and in hospital mortality rates. If specific data were not presented, statistical or non-statistical differences were extracted where reported.

3.3.1 Inclusion and Exclusion Criteria

Papers assessing any analgesic modality in open liver surgery were included. Papers examining analgesia in other hepatic procedures were excluded (laparoscopic resections, liver transplant recipients, hepatic ablations). Papers examining the effect of epidural on fluid balance and coagulopathy were also excluded. Papers comparing different configurations of the same analgesic technique in both study arms were also excluded. Non-English language papers were excluded due to lack of a reliable translation service.

3.3.2 Outcomes

The primary outcome was overall systemic complication rate within 30 post-operative days. All complications, medical and surgical, were included in a composite manner. Local complications were also examined. Secondary outcomes were LOS and pain scores at 24 hours at rest and on movement.

3.3.3 Analysis

A qualitative descriptive analysis was performed to compare outcomes of the included trials. In order to allow for appropriate comparison of analgesic techniques, studies that compared similar techniques were reviewed together. Statistically significant differences in outcomes were sought. A difference was considered significant if the quoted p value was <0.05.

3.4 Results

Fourteen studies were included in the review [134, 135, 149-160] as shown in the PRISMA diagram (Figure 7) and Tables 4 and 5. Nine of the trials were RCTs, [135, 150, 152-156, 158, 159] four were retrospective studies [134, 151, 157, 160] and one was a prospective non-controlled study. [149] The selected articles reached a high scientific level with a median Down's and Black score of 26 (range 16-30).

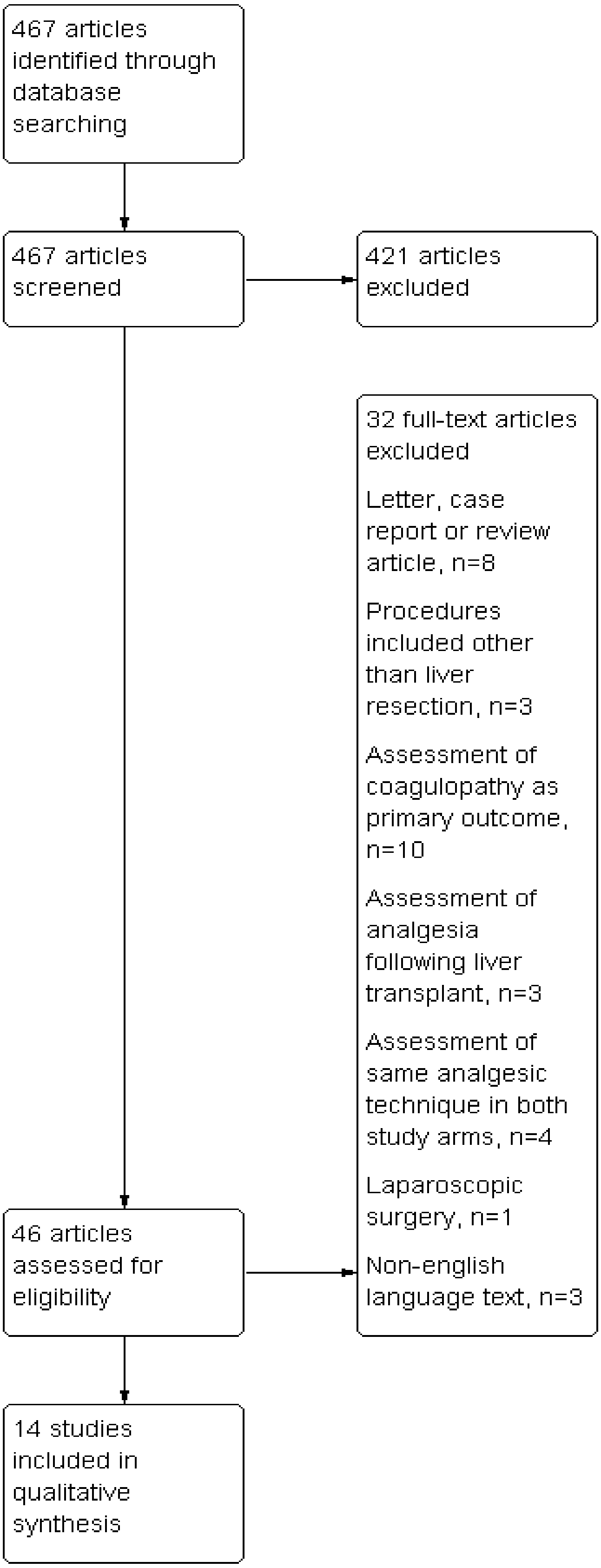


Figure 7. PRISMA diagram

Study	Design	Operation	Modality 1	Regimen 1	Modality 2	Regimen 2	Downs and Black
Page *et al* [157]	Retrospective case control	Liver resection	Epidural	T10-T12 0.1% bupivacaine and 0.1% meperidine until pain suitable for conversion to oral analgesia	IV PCA morphine	Demand pump with IV morphine.	24/32
Clarke *et al* [151]	Retrospective case control	Living donor hepatectomy	Patient controlled epidural	T7-T10 placement, postoperative infusion of 0.1% bupivacaine and 0.015mg/ml hydromorphone at 5ml/hr (with 3ml bolus, 20 minute lockout and a 4hr maximum of 50ml)	IV PCA morphine	Hydromorphone 0.4mg/ml bolus at 0.2-0.4mg with 5min lockout and 4hr max of 10mg. Or morphine 1mg/ml bolus of 1-2mg with 5 min lockout and 4 hour max of 40mg.	23/32
Yong *et al* [160]	Retrospective case control	Living donor hepatectomy	Epidural	0.0625% bupivacaine + 3.3microg/ml fentanyl	IV opiates	IV PCA morphine and IV morphine	16/32
Revie *et al* [135]	RCT	Liver resection	Epidural	T7-8 0.1% bupivacaine and 2mcg/ml fentanyl at 7-10ml/hr	CWI	20ml bolus of 0.25% bupivacaine; Dual Catheter 0.375% levobupivacaine at 4mls/hr in musculofascial layer for 48hrs	30/32

CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block

Table 4. Study analgesia regimens

Study	Design	Operation	Modality 1	Regimen 1	Modality 2	Regimen 2	Downs and Black
Chan *et al* [150]	RCT	Liver resection	Placebo	Dual limb catheter to musculofascial layer, 20ml 0.9% saline to musculofascial layer prior to closure; then 4ml/h for 68h	CWI	Dual limb catheter to musculofascial layer, 20ml 0.25% ropivacaine to musculofascial layer prior to closure; then 4ml/h for 68h	30/32
Basu *et al* [149]	Prospective non-controlled trial	Liver resection	CWI	Dual limb wound catheter. 1 limb in TA plane, 2nd limb posterior to rectus muscle. 10 ml bolus of 0.25% bupivacaine then 0.25% bupivacaine at 3ml/hour for 72h	-	-	21/32
Lee *et al* [154]	RCT	Living donor hepatectomy	Intrathecal morphine + IV fentanyl	Dural puncture of L3-4/L4-5 and injection of 400 microg of morphine sulphate. At end of operation 1500microg of fentanyl in 100ml normal saline commenced at 1ml/hr plus 15microg bolus fentanyl PCA with 15min lockout.	CWI	Dual limb catheter. 1st limb to TA plane and 2nd limb to preperitoneal space in midline. Bolus of 10mls 0.75% ropivacaine given then 300ml of 0.5% ropivacaine delivered at 4ml/hr for 72hrs.	29/32

CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block

Table 4 contd. Study analgesic regimens.

Study	Design	Operation	Modality 1	Regimen 1	Modality 2	Regimen 2	Downs and Black
Koea *et al* [134]	Retrospective case control	Liver resection	Epidural	0.125% bupivacaine and fentanyl 2mcg/ml 0.1ml/kg/hr weaned after 72 hrs	ITM	300microg morphine and oral gabapentin (1200mg pre-op and 400mg bd post-op)	25/32
De Pietri *et al* [152]	RCT	Liver resection	Epidural	T9-T11 ropivacaine 0.2% 6-8 ml and morphine 2mg pre-op; post-op infusion of ropivacaine 0.2% 5-7ml/h	ITM	Dural puncture at L3-L5; morphine 0.2mg in 0.9% saline (2.5ml)	24/32
Mondor *et al* [155]	RCT	Liver resection	Epidural plus ITM	Intraoperative epidural infusion of 0.5% bupivacaine at 3ml/hr plus preoperative intrathecal injection of 0.5mg morphine.	ITM (plus sham epidural)	Preoperative intrathecal injection of 0.5mg morphine plus sham intra-operative epidural	30/32
Roy *et al* [158]	RCT	Liver resection	IV PCA morphine (plus placebo)	Sham intrathecal injection (skin punctured but not advanced beyond subcutaneous tissue). PCA morphine - 0.05mg/kg at 7min intervals if pain >60mm on VAS; then 1.5mg at 7min	Intrathecal morphine and fentanyl	L2/3 or L3-4 lumbar puncture and injection of morphine 0.5mg and 15mcg fentanyl	27/32

CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block

Table 4 contd. Study analgesic regimens.

Study	Design	Operation	Modality 1	Regimen 1	Modality 2	Regimen 2	Downs and Black
Ko *et al* [153]	RCT	Living donor hepatectomy	ITM + IV PCA fentanyl	Dural puncture of L3-4/L4-5, 400microg morphine sulphate in 4ml 0.9% saline injected + IV PCA fentanyl 15microg/l, 1ml bolus, lockout time of 15mins and baseline rate of 1ml/hour	IV PCA fentanyl	IV PCA fentanyl 15microg/l, 1ml bolus, lockout time of 15mins and baseline rate of 1ml/hour	28/32
Weinberg *et al* [159]	RCT	Liver resection	ITP	Levobupivacaine 0.125% at 12.5mg/hr via catheter in interpleural space	IV PCA morphine	Morphine 1mg bolus with 5 min lockout and max dose of 12mg/h	29/32
Moussa [156]	RCT	Living donor hepatectomy	PVB	Pre-operative bilateral thoracic paravertebral injection at T7-8 of 25mls bupivacaine 0.25% with epinephrine 1:200000	Placebo	Pre-operative bilateral thoracic paravertebral injection at T7-8 of 25mls 0.9% NaCl	25/32

CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block

Table 4 contd. Study analgesic regimens.

	Page *et al* [157]	**Clarke *et al* [151]**	**Yong *et al* [160]**	**Revie *et al* [135]**	**Chan *et al* [150]**	**Basu *et al* [149]**
	Epidural/PCA	Epidural/PCA	Epidural/ PCA	Epidural/CWI	CWI/Placebo	CWI
Number	256/111	68/158	6/31	31/33	22/22	10
Age (mean±sd)	54.0±14.0/50.0±16.0	36.2±11.1/36.4±11.5	36(18-51)*	60(23-85)/60(39-84)*	51.8±7.8/52.1±8.3	NA
ASA n(%)						
I	**4(1.6)/15(13.5)**	NA	NA	5(16.1)/2(6.1)	NA	NA
II	**95(37.1)/44(39.6)**			20(64.5)/20(60.5)		
III	**147(57.4)/42(37.8)**			6(19.4)/11(33.3)		
IV	**10(3.9)/10(9.0)**			-		
Resections n(%)						
≥3 segments	154(60.2)/66(59.5)	68(100.0)/158(100.0)	6(100.0)/31(100.0)	**13(41.9)/24(72.7)**	17(77.3)/16(72.7)	NA
<3 segments	102(39.8)/45(40.5)	0(0)/0(0)	0(0)/0(0)	**20(58.1)/9(27.3)**	5(22.7)/6(27.3)	
Pathology n(%)						
CLM	**63(24.6)/58(52.3) "malignant"**	Living Donors	Living donors	17(54.8)/19(57.6)	NA	NA
HCC				3(9.7)/2(6.1)		
Cholangiocarcinoma				5(16.1)/4(12.1)		
Benign	**193(74.6)/53(47.7) "benign"**			3(9.7)/6(18.2)		
Other malignancy				3(9.7)/2(6.1)		
Male n (%)	**140(54.7)/37(33.3)**	28(41.2)/76(48.1)	NA	19(61.3)/17(51.5)	17(77.3)/19(86.4)	NA

NA=Not assessed, CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, HCC = Hepatocellular carcinoma, CLM= Colorectal Liver Metastasis. Statistically significant differences are highlighted in bold. Data are presented as n(%) unless stated otherwise.*median (range)

Table 5. Demographic and pathological characteristics of included studies

	Lee *et al* [154]	**Koea *et al* [134]**	**De Pietri *et al* [152]**	**Mondor *et al* [155]**
	ITM/CWI	Epidural/ITM	Epidural/ITM	Epidural+ITM/ITM
Number	21/19	50/50	25/25	22/22
Age (mean±sd)	35.6±11.0/30.5±8.7	61(28-83)/60(23-79)*	NA	61.0±8.0/58.0±11.0
ASA				
I	I and II 21(100.0)/19(100.0)	13(26.0)/11(22.0)	NA	2(9.1)/4(18.2)
II		31(62.0)/32(64.0)		12(54.5)/13(59.1)
III		6(12.0)/7(14.0)		8(36.4)/5(22.7)
IV		-		-
Resections				
≥3 segments	21(100.0)/19(100.0)	21(42.0)/20(40.0)§	NA	22(100.0)/22(100.0)§§
<3 segments		29(58.0)/30(60.0)		
Pathology				
CLM	Living donors	32(64.0)/31(62.0)	NA	14(63.6)/13(59.1)
HCC		3(6.0)/2(4.0)		4(18.2)/3(13.6)
Cholangiocacinoma		1(2.0)/3(6.0)		0(0)/0(0)
Benign		9(18.0)/8(16.0)		3(13.6)/5(22.7)
Other malignancy		5(10.0)/6(12.0)		1(4.5)/0(0)
Male n(%)	15(71.4)/12(63.2)	27(54.0)/24(48.0)	NA	15(68.2)/14(63.6)

NA=Not reported, CWI = Continuous Wound Infiltration, ITM= Intrathecal Morphine, Statistically significant differences are highlighted in bold. §(≥/<4 segments) §§(≥/<2 segments). Data are presented as n (%) unless stated otherwise, *median (range).

Table 5 contd. Demographic and pathological characteristics of included studies.

	Roy *et al* [158]	**Ko *et al* [153]**	**Weinberg *et al* [159]**	**Moussa [156]**
	ITM/placebo	ITM/PCA	ITP/PCA	PVB/Placebo
Number	10/10	20/20	25/25	12/12
Age (mean±sd)	60.0±8.0/58.0±9.0	31.6±10.4/26.7±6.8	56(19-84)/58(23-77)*	32.8±9.3/34.3±8.2
ASA				
I	NA	I and II 19(95.0)/20(100.0)	1(4.0)/2(8.0)	3(25.0)/4(33.3)
II			21(84.0)/20(80.0)	9(75.0)/8(66.6)
III			3(12.0)/3(12.0)	
IV			-	
Resections				
≥ 3 segments	NA	20(100.0)/20(100.0)	Hepatic resection weight:	12(100.0)/12(100.0)
<3 segments		0(0)/0(0)	ITP 337g/PCA 309g	0/0
Pathology				
CLM	NA	Living donors	Malignant	Living donors
HCC			22(88.0)/24(96.0)	
Cholangiocarcinoma			Benign	
Benign			3(12.0)/1(4.0)	
Other malignancy				
Male n(%)	5(50.0)/5(50.0)	17(85.0)/13(65.0)	10(40.0)/11(44.0)	9(75.0)/10(83.3)

NA=Not reported, CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block. Statistically significant differences are highlighted in bold. §(≥/<4 segments) §§(≥/<2 segments). Data are presented as n (%) unless stated otherwise, *median (range).

Table 5 contd. Demographic and pathology characteristics of included studies.

3.4.1 Study Characteristics

All studies included adult patients only. Two distinct sections emerged in that nine of the studies assessed liver resection for benign or malignant tumours [134, 135, 149, 150, 152, 155, 157-159] and five trials assessed patients following living donor hepatectomies. [151, 153, 154, 156, 160] The demographic details of the included trials are summarised in Table 5. The main differences between the liver resection patients and the living donors were the age ranges and the ASA levels with the living donors representing a younger, fitter population who had not received chemotherapy. Two of the liver resection studies incorporated an enhanced recovery protocol. [134, 135] Six of the studies excluded patients with pre-existing chronic pain issues or were taking regular opiates. [150, 152-155, 159]

Multiple analgesic methods were assessed in combination. These were epidural, systemic opiates (PCA), continuous local anaesthetic wound infiltration (CWI), intrathecal analgesia (ITM), paravertebral block (PVB) and interpleural analgesia (ITP). (127, 128, 142, 143, 145, 148, 150-152) No more than one RCT per comparison of analgesic technique was available and this prevented meta-analysis. The details of the analgesic regimens assessed are summarised in Table 4 and the outcomes are displayed in Table 6.

Author	**Analgesic modality (n)**		**Systemic Complications n(%)**		**Length of Stay (days)**		**Pain Scores at rest at 24hrs**		**Pain Scores on movement at 24hrs**	
	Epidural	**PCA**	**Epidural**	**PCA**	**Epidural**	**PCA**	**Epidural**	**PCA**	**Epidural**	**PCA**
Page et al [157]	256	111	61 (23.8)	19 (17.1)	10.0±7.1	10.0 ±9.3	NA	NA	NA	NA
Clarke et al [151]	68	158	NA	NA	6.6±1.7	6.5 ±1.7	**2.2±0.5**	**2.6± 0.3**	NA	NA
Yong et al [160]	6	31	NS	NS	NA	NA	NS	NS	NS	NS
	ITM	**PCA**	**ITM**	**PCA**	**ITM**	**PCA**	**ITM**	**PCA**	**ITM**	**PCA**
Ko et al [153]	20	20	NA	NA	10.8±2.8	10.7±2.9	**16 (4-36)**	**36 (32-48)**	**40 (21-50)**	**56 (40-70)**
Roy et al [158]	10	10	NA	NA	NA	NA	23 (range 55)	30 (range 75)	48(range 80)	50 (range 50)
	CWI	**Placebo**	**CWI**	**Placebo**	**CWI**	**Placebo**	**CWI**	**Placebo**	**CWI**	**Placebo**
Chan et al [150]	22	22	NA	NA	8.2±3.1	9.7±5.8	**20.0±14.0**	**36.0±14.0**	**30.0±15.0**	**50.0±18.0**
Basu et al [149]	10	-	4(40.0)	-	8 (7-15)	-	NA	-	NA	-
	ITP	**PCA**	**ITP**	**PCA**	**ITP**	**PCA**	**ITP**	**PCA**	**ITP**	**PCA**
Weinberg et al [159]	25	25	5(20.0)	6(24.0)	8.4±3.5	9.0±4.8	22±38	22.0±39.0	42.0 ±7.0	50.0 ±34.0
	PVB	**Placebo**	**PVB**	**Placebo**	**PVB**	**Placebo**	**PVB**	**Placebo**	**PVB**	**Placebo**
Moussa [156]	12	12	NA	NA	NA	NA	Median 1§	Median 4§	NA	NA

NS=non significant, NA=Not assessed, CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block, VAS= Visual Analogue Score. Statistically significant differences are highlighted in bold. LOS data presented as mean±s.d. or median (range) unless otherwise stated. Pain scores presented as VAS 0-100, mean ±s.d. or median (IQR) unless otherwise stated. **§**(VAS1-10)

Table 6. Study outcomes

Author	Analgesic modality (n)		Systemic Complications n(%)		Length of Stay (days)		Pain Scores at rest at 24hrs		Pain Scores on movement at 24hrs	
	Epidural	**CWI**	**Epidural**	**CWI**	**Epidural**	**CWI**	**Epidural**	**CWI**	**Epidural**	**CWI**
Revie *et al* [135]	31	33	18 (58.1)	16(48.5)	**6.0 (3-42)**	**4.5(2.5-64)**	**1.3±1.3§**	**2.6±1.2§**	**3.2±1.9§**	**4.8±1.9§**
	ITM	**CWI**	**ITM**	**CWI**	**ITM**	**CWI**	**ITM**	**CWI**	**ITM**	**CWI**
Lee *et al* [154]	21	19	7 (33.3)	6 (31.6)	15±7.2	17.9 ±11.6	20 (20-32.5)	30 (20-37.5)	40 (30-50)	50 (40-57.5)
	Epidural	**ITM**	**Epidural**	**ITM**	**Epidural**	**ITM**	**Epidural**	**ITM**	**Epidural**	**ITM**
Koea *et al* [134]	50	50	11 (22.0)	8 (16.0)	**6.8±1.2**	**4.7±0.9**	Median 2§	Median 1§	NA	NA
De Pietri *et al* [152]	25	25	NA	NA	NA	NA	19.0±2.0	23.0±4.0	20.5±3.5	24.0±2.0
	Epidural +ITM	**ITM**	**Epidural +ITM**	**ITM**	**Epidural +ITM**	**ITM**	**Epidural +ITM**	**ITM**	**Epidural +ITM**	**ITM**
Mondor *et al* [155]	22	21	NA	NA	8.0±3.2	10.2±6.0	**0 (0-11)**	**12(0-30)**	**16 (6-26)**	**36(24-50)**

NS=non significant, NA=Not assessed, CWI = Continuous Wound Infiltration, PCA= Patient Controlled Analgesia, ITM= Intrathecal Morphine, ITP= Interpleural analgesia, PVB = Paravertebral Block, VAS= Visual Analogue Score. Statistically significant differences are highlighted in bold. LOS data presented as mean±s.d. or median (range) unless otherwise stated. Pain scores presented as VAS 0-100, mean±s.d. or median (IQR) unless otherwise stated. **§**(VAS 1-10).

Table 6 contd. Study outcomes.

3.4.2 Epidural Versus Alternatives

Seven trials compared epidural to an alternative analgesic regimen. Epidural was compared to PCA, [151, 157, 160] CWI, [135] ITM [134, 152] and in one trial was combined with ITM and compared to ITM alone. [155]

Morbidity

Four trials reporting complication rates compared epidural to either systemic opiates, [157, 160] CWI, [135] or ITM. [134] No difference was observed in complication rates between epidural and any of the alternatives.

Pain Scores

Two studies comparing epidural to ITM, [134, 152] and one comparing epidural to PCA [160] showed no superiority of epidural in terms of resting or dynamic pain scores. However improved pain scores were observed in the epidural group comparing epidural to CWI, [135] PCA [151] and when epidural was combined with ITM and compared to ITM alone. [155] None of the trials reported on long term pain outcomes.

Length of Stay

Five trials [134, 135, 155, 157, 160] assessed LOS. Two trials found LOS to be significantly longer in the epidural groups compared to CWI [135] and ITM [134] and two [157, 160] did not find a significant difference between epidural and PCA groups.

Mondor *et al* [155] did not report a significant difference between epidural and ITM versus ITM alone.

3.4.3 CWI Versus Placebo

Chan *et al* [150] compared CWI to placebo and found no difference in complication rate, improved pain scores in the CWI group and no difference in LOS. Basu *et al* [149] assessed 10 patients and found a complication rate of 40% in one of the first studies assessing CWI feasibility.

3.4.4 ITM Versus PCA or Placebo

Two trials assessed ITM with placebo [158] or PCA. [153] Both studies found significantly improved pain scores in the ITM group when compared to placebo [158] or PCA. [153] Of these only Ko *et al* [153] went on to assess complication rate and LOS and found no significant difference between ITM and PCA.

3.4.5 ITP and PVB Versus PCA or Placebo

One study assessed ITP versus PCA [159] and one study assessed PVB versus placebo. [156] Both studies observed improved pain scores in the intervention arm of the study. Weinberg *et al* [159] also assessed LOS and complication rates but did not observe a significant difference between the two groups.

3.4.6 Local Complications

Seven trials commented specifically on complications as a direct result of the pain killing modality i.e. local anaesthetic toxicity or epidural haematoma. [135, 149, 150, 152, 155, 158, 159] None of these trials reported any incidence of these occurring. Of the trials that included wound catheters, no significant difference in wound complication rate was observed in any of the trials. [135, 149, 150, 154]

Five studies assessing ITM [152, 153, 155, 158] and ITP [159] commented specifically on respiratory depression and of these studies only Weinberg *et al* [159] reported a significantly increased rate of respiratory depression following IV PCA compared to interpleural analgesia (PCA morphine n=24%; ITP n=0%, p=0.02).

3.5 Discussion

This review reports that no analgesic method was associated with improved complication rates; epidurals were associated with increased length of stay when compared to ITM and CWI and epidurals demonstrated improved or equivalent pain scores compared to all other techniques. However the large number of different modalities assessed and methodological limitations prevented appropriate meta-analysis or definitive recommendations.

The included trials represent typical patients and conditions facing the surgical and anaesthetic teams involved in major resections for predominantly malignant tumours in patients of ASA grade I-III. The patients undergoing living donor resection were younger and fitter than the patients undergoing liver tumour resection and so would be perceived as being less likely to suffer post-operative morbidity, however similar rates of morbidity and LOS emerged when comparing liver resection to living donor patients and so the recommendations of this review apply to both patient groups.

One previous review [133] assessed the safety and efficacy of epidurals and found that the effects of fluid administration, failure rates and coagulopathy could delay recovery and questioned the routine use of epidurals following liver resection. This present review therefore aimed to systematically assess not only epidurals but also the effect of all analgesic modalities on outcomes following liver resection to establish if a superior modality has emerged. Comparisons between all epidural and non-epidural based analgesic techniques were included to reflect the direction of recent practice and research. The present review primarily focused on the impact of the analgesic modality on patient recovery outcomes after liver resection in an attempt to clarify the role of all analgesic modalities in future ERAS protocols.

Epidurals were shown to provide superior or equivalent pain relief in all the trials that reported on epidurals. Current expert opinion holds that epidural analgesia provides superior post-operative pain relief, both resting and dynamic, when compared with systemic opiates in large meta-analyses. [44, 45] The evidence that we found comparing pain scores between these modalities following liver surgery was much more limited with only two retrospective studies, [151, 160] one of which concurred with the evidence base and reported reduced pain scores for the epidural [151] and a second study that reported equivalent scores for the PCA opiates. [160] However in this study only six patients were included in the epidural group thus reducing the power of the study and potentially introducing a type two error. Therefore the evidence supporting epidural as being superior to opiates is not abundant in this field of surgery and the results are inconclusive.

Continuous wound infiltration has increased in popularity with evidence showing its efficacy compared to placebo in open abdominal surgery, [161] which was the case in this review. It has also been shown in a meta-analysis to be comparable to epidural in terms of analgesic properties in open abdominal surgery. [162] In this review however CWI received higher pain scores compared with epidural in the only RCT comparing these two modalities. [135] The reason for this apparent reduced analgesic efficacy following liver surgery is unclear although the subcostal incision used for liver resection potentially provides a greater challenge for wound catheters compared to laparotomy wounds. Wound catheter position and placement is a factor that can radically alter the efficacy of the technique and variation in placement and configuration can result in variability of observed analgesic effect. More work in this area is required to establish optimum practice.

Therefore when assessing analgesic capabilities of the various analgesic techniques, the current evidence available comparing modalities after liver surgery is heterogeneous, equivocal and lacking in consistent RCTs. Therefore when considering pain scores, the current available evidence is insufficient to guide practice.

A shorter length of stay was demonstrable with the use of ITM [134] and CWI [135] when compared to epidurals. Similarly epidurals did not reduce hospital stay when compared to systemic opiates alone [151, 157] or when used in combination with ITM and compared to ITM alone. [155]

Epidurals have historically been shown to be associated with similar length of stay in other areas of open abdominal surgery when compared to systemic opiate administration. [163] When alternatives to systemic opiates alone are compared to epidurals, i.e. CWI and ITM, equipoise or superiority in terms of duration of hospital stay have been demonstrated following open abdominal surgery, particularly in the setting of an enhanced recovery post-operative protocol. [164-166] Absence of an epidural potentially allows for a speedier recovery. Reduced IV fluid administration, earlier removal of urinary catheter and reduced hypotension, with reduction of systemic opiates, are attractive features of non-epidural based analgesia such as CWI and ITM and this review suggests that these techniques could contribute to reduced length of hospital admission after liver resectional surgery.

However, no difference in LOS was observed in any other trial in this review, [150, 151, 153-155, 157-159] including three further trials [151, 155, 157] comparing epidurals with alternative modalities to systemic opiates. Therefore definitive conclusions cannot be made regarding the effect of epidurals on LOS based on the current evidence and further research is required to clarify this.

The primary outcome of this review, and a critical outcome following major surgery, was morbidity rate. No significant advantage was observed in systemic complication rates when epidural analgesia was compared to systemic opiates, wound catheters or ITM groups.

Epidurals have traditionally been associated with reductions in post-operative complication rates, particularly pulmonary, cardiovascular and gastrointestinal complications when compared to systemic opiates. [167, 168] Minimisation of post-operative pain can result in increased respiratory capacity and ability to mobilise without limitation. Avoidance of systemic opiates reduces rates of ileus and epidural related attenuation of the inflammatory response is associated with improved physiological outcomes. [36]

The often described disadvantages of epidurals such as high failure rate, [142] hypotension, increased IV fluid administration [140] and epidural haematoma risk [146] have often been accepted because of the perceived superiority in terms of analgesia outweighing the disadvantages and leading to a superior recovery and a reduction in post-operative morbidity. [36] However CWI and ITM can potentially avoid such epidural related problems whilst delivering effective opiate sparing pain relief to minimise complications in a similar manner to epidural analgesia. [164-166] This review shows that such evidence in the context of liver surgery is currently limited, but suggests equipoise between epidurals, CWI and ITM in terms of post-operative morbidity thereby offering a realistic alternative to epidurals in this setting.

Of note, however, is that none of the trials reporting complication rates, apart from Koea *et al*, [134] reported the rates of underlying liver disease or neoadjuvant chemotherapy. Such factors are contributory to post-operative complication rates and recovery time following liver resection. [169-171] Moreover, patients suffering from chronic pain conditions were frequently excluded from the included trials, and no assessment of chronic post-operative pain was reported. Therefore in order to determine accurately the effects of a modality on overall recovery and to eliminate potentially confounding factors such as these, accurate reporting is mandated in order to establish the generalisability of the baseline data.

It is also critical to appreciate the importance of a multi-disciplinary enhanced recovery programme complementing the post-operative analgesic technique and achieving optimum recovery outcomes. Enhanced recovery programmes represent optimal post-operative care and contribute to reductions in morbidity rates. [28]

Moreover, implementation of these standards allows for simple comparison and evaluation of the effect of the variable technique. It also allows comparison of outcomes between trials. The trials not commenting specifically on their post-operative recovery pathways make determination of the impact of the analgesic technique on recovery difficult. It is also important to be able to determine if significant suboptimal variations occurred within and between groups as well as between trials to assess the impact of confounding factors on outcome rather than analgesic technique. Therefore, in order to answer the question of optimum analgesic modality after liver surgery, ERAS protocols need to be incorporated into the study design. In this review only two of the studies included such a pathway [134, 135] and so potential systematic variation in the non-ERAS trials makes categorical conclusions inappropriate.

Despite these limitations, the review raises important issues. Wound catheters and intrathecal opiates appear to have the potential to offer faster rehabilitation with no compromise to morbidity rates when compared to epidurals. This raises the possibility of there being a benefit to not using an epidural following liver surgery. When considering other published studies looking at ERAS protocols following liver surgery [88, 122, 126, 128] all have incorporated epidural placement as the analgesic method of choice. In this review the reported LOS for Revie *et al* [135] and Koea *et al* [134] were both less than 5 days - the shortest admission times of all the included trials. Both these trials utilised an ERAS protocol and the short discharge times reflect this practice. Considering these findings this review suggest that epidurals may not be the most appropriate analgesic technique to incorporate into liver resectional ERAS programmes. The evidence suggesting this as yet consists of only two trials

[134, 135] and so this cannot be treated as a definitive recommendation. There is however a clear need to examine this issue further if outcomes are to be optimised and definitive recommendations made. As ERAS programmes have been shown to have procedure specific qualities, it will necessitate RCTs comparing epidurals and alternative analgesic techniques, including combination techniques, within the context of a liver surgery ERAS regimen.

In summary, no analgesic modality resulted in improved complication rates. Epidurals provided equivalent or improved pain scores compared to CWI, ITM and PCA. Epidurals were associated with prolonged length of stay when compared to CWI and ITM, but not PCA. Future research should focus on epidurals versus alternative techniques within an enhanced recovery protocol to establish optimum practice.

3.6 Chapter Publication

Effect of analgesic modality on outcome following open liver surgery: a systematic review of postoperative analgesia. Hughes M, McNally S, McKeown DW, Wigmore S. Minerva Anestesiol. 2015;81:541-56.

4 CVP and Liver Resection: A Systematic Review and Meta-analysis

4.1 Summary

Liver resection under low central venous pressure (CVP) has become standard practice. However the benefits beyond reduction of blood loss are not well documented. Moreover the precise method to achieve CVP reduction is not established. A systematic review and meta-analysis of RCTs was performed to assess the effects of CVP on clinical outcome and to identify the optimum method of CVP reduction. EMBASE, Medline, PubMed and the Cochrane database were searched for trials comparing low CVP surgery with controls. The primary outcome was post-operative complications within 30 days. Secondary outcomes included estimated blood loss, blood transfusion rates and length of stay. Sub-group analysis was performed to assess CVP reduction method on outcome. Eight trials were identified. No difference was observed in morbidity rate between low CVP and control groups (OR=0.96 [95% CI 0.66, 1.40] p=0.84, I^2=0%,). Estimated blood loss (WMD= -308.63mls [95% CI -474.67, -142.58] p=0.0003, I^2=73%) and blood transfusion rates (OR 0.65 [95%CI 0.44, 0.97] p=0.04, I^2=37%) were significantly lower in the low CVP groups. Neither anaesthetic nor surgical methods of bleeding control were associated with reduced post-operative morbidity. In summary, low CVP surgery is associated with reduction in blood loss however this is not translated into an improvement in post-operative morbidity. Optimum method of CVP reduction has not been identified.

4.2 Introduction

Liver resectional surgery is often the only chance of curative treatment for a number of primary and secondary tumours. It is complex surgery although mortality rate in high volume centres should be considered to be less than five per cent. [71] Morbidity rates are reported at up to 45%. [73]

Enhanced recovery protocols after liver surgery have increased in popularity in recent years and several studies have highlighted not only the feasibility and safety of fast track liver protocols [119] but reduction in length of stay and morbidity rates post-operatively. [172] Morbidity rates, however, remain significant and peri-operative protocols require optimisation in order to minimise complications. [172]

It has frequently been reported that blood loss during liver resection is associated with increased post-operative morbidity rates. [73, 86, 117] Endeavours to reduce intra-operative blood loss have included efforts to reduce central venous pressure (CVP) during liver resection. Low CVP parenchymal transection has become an accepted practice during liver surgery. [117] However a review of the initial available data questioned the outcome benefit of low CVP surgery beyond reduction of blood loss. [79] Moreover new techniques are being introduced to reduce CVP, of which the efficacy is not well established. Therefore this review aims to evaluate the current literature to assess the effect of CVP reduction on clinical outcome after liver resection and assess the techniques used to achieve this.

4.3 Methods

This study was conducted according to the PRISMA guidelines for meta-analysis conduct. [118] The protocol was registered prospectively on the PROSPERO database for meta-analyses (registration number CRD42014007651).

A literature search was performed independently by two researchers of EMBASE, Medline, PubMed and the Cochrane databases in December 2013. The databases were searched from 1966 -2013 with the following terms: “central venous pressure” or “CVP” and “liver resection” or “liver surgery” or “hepatic resection” or “hpb”.

All abstracts were reviewed for relevance by two independent investigators. Relevant full text articles were subsequently reviewed and critiqued.

4.3.1 Inclusion Criteria

Studies that fulfilled the eligibility criteria were RCTs that compared significantly different CVPs or compared a low CVP group to a control group and reported on patient outcomes (morbidity, estimated blood loss and length of stay) following open, elective liver resection.

4.3.2 Exclusion Criteria

Non-RCTs were excluded. Trials that did not report significantly different CVPs between groups, did not compare low CVP with a control group or did not report outcomes of EBL and/or morbidity rate were excluded. All reviews were excluded. Irrelevant studies, letters, case reviews, paediatric populations and animal studies were excluded. Non-hepatic surgery and trials including transplant recipients were excluded.

4.3.3 Intervention

The intervention investigated was the reduction of intra-operative CVP. This was defined as either any statistically significantly difference in CVP between groups or a "low CVP" group compared to a control group. Where multiple recordings of CVP have been reported, the CVP during liver parenchymal transection was used.

4.3.4 Comparator

The comparator group comprised the groups where significantly higher intra-operative CVP was reported or the "high CVP" group. The comparator group should either demonstrate a significantly higher CVP (mmHg), regardless of absolute CVP value and regardless of technique used to achieve CVP, or reflect the "uncontrolled CVP" group.

4.3.5 Outcomes

4.3.5.1 Primary Outcome

Primary outcome was a composite end-point of the occurrence of one or more systemic complication within 30 days of liver resection. Derangement of specific blood tests were not included in the overall complication rate.

4.3.5.2 Secondary Outcome

Further comparisons were made between low CVP groups and control groups. The mean CVP (mmHg/cm H_20) during the operation or, if given, during transection was compared between groups. Estimated Blood Loss (EBL) in millilitres was extracted from the data as was length of stay (LOS) which was recorded in days. CVP lowering protocols were also recorded and compared.

4.3.6 Subgroup Analysis

Subgroup analysis was performed according to technique of CVP reduction: anaesthetic methods (IVI restriction, epidural, vasodilators and/or diuretics) and surgical methods (IVC clamping / total or selective vascular hepatic exclusion).

4.3.7 Data Extraction

Abstracts were reviewed for relevance and suitability for inclusion by two independent investigators. Full text articles were reviewed, and data were extracted using pre-designed data extraction forms. If data were not presented in a format conducive for data synthesis, the authors were contacted using the published correspondence details. In the event of no response, an attempt to contact authors was made by repeat email, followed by letter and/or phone call. Where no author response was received medians and ranges were converted to mean/standard deviation using methods described by Hozo *et al*. [173]. The Cochrane bias risk assessment tool was used to assess study quality. [174]

4.3.8 Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan ver 5.2. The Nordic Cochrane Centre, Copenhagen). The following outcomes were treated as dichotomous data and were analysed using pooled odds ratios: major complication rate and intra-operative blood transfusion requirement. The following outcomes were treated as continuous data and were analysed with a weighted mean difference (WMD): estimated blood loss and length of stay. Statistical significance was set at $p<0.05$. Heterogeneity was assessed by using I^2 and X^2 and adjudged to be significant if $I^2 >50\%$ and/or $p<0.05$.

4.4 *Results*

4.4.1 Included Trials

The PRISMA diagram of included trials is shown in Figure 8. Eight RCTs were identified as meeting the inclusion criteria with a total of 339 patients with lower CVP than 342 control patients. [109, 175-181] Patient demographics and indications for hepatic resection are displayed in Table 7. Bias assessment scores for included trials are presented in Table 8.

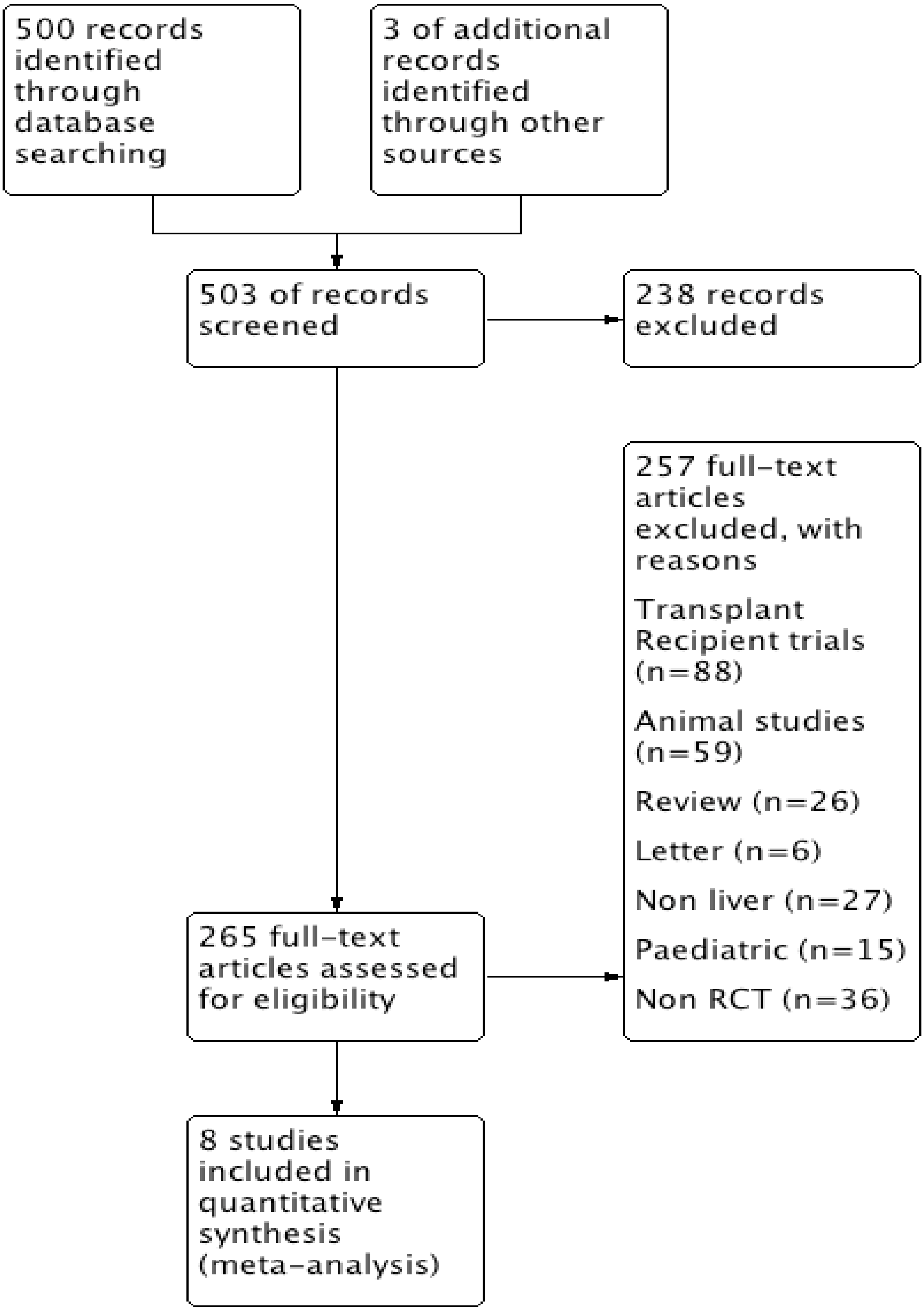


Figure 8. PRISMA diagram

	Wang *et al 2006* [109]		Liu *et al* 2005 [178]		Liu *et al* 2008 [179]		El-Khaboutley *et al* 2004 [175]	
	Ex (n=25)	Con (n=25)	Ex (n=30)	Con (n=30)	Ex (n=23)	Con (n=23)	Ex (n=20)	Con (n=20)
Male	19(76.0)	21(84.0)	NA	NA	14(6.9)	16(69.6)	11(55.0)	12(60.0)
Age (years)	45.3±14.6	46.0±12.1	NA	NA	45.4±13.0	43.0±13.0	49.9±10.4	52.3±7.1
Indication								
CLM	-	-	NA	NA	-	-	-	-
HCC	25(100.0)	25(100.0)			23(100.0)	23(100.0)	19(95.0)	18(90.0)
Cholangiocarcinoma	-	-			-	-	-	-
Other	-	-			-	-	1(5.0)	2(10.0)
Liver pathology								
Cirrhosis	14(56.0)	15(60.0)	NA	NA	NA	NA	20(100.0)	20(100.0)
Steatosis			NA	NA	NA	NA	NA	NA
Resection extent								
≥2 segments	21(84.0)	19(76.0)	NA	NA	NA	NA	13(65.0)§	12(60.0)§
Operating time (mins)	229.6±67.3	246.0±112.4	NA	NA	156.9±38.5	162.8±60.6	**164.0±42.0**	**190.1±24.0**
Transection time (mins)	NA	NA	NA	NA	NA	NA	NA	NA

Ex= experimental group, Con = Control groups, NA = not assessed, NS=no significant difference, CLM=Colorectal Liver Metastasis, HCC= Hepatocellular Carcinoma; § major resection, ** >2 segments, ***>1 segment, ∞ =mean (s.e.m), *median (IQR). Data are otherwise presented as n(%) and mean±s.d. or median (range). Significantly different results (p<0.05) are highlighted in bold.

Table 7. Study characteristics.

	Figueras *et al* 2005 [176]		**Zhu *et al* 2012 [181]**		**Rahbari *et al* 2011 [180]**		**Kato *et al 2008* [177]**	
	Ex (n=41)	Con (n=39)	Ex (n=96)	Con (n=96)	Ex (n=65)	Con (n=63)	Ex (n=43)	Con (n=42)
Male	28(68.3)	31(79.5)	NS		37(56.9)	42(66.7)	NA	
Age (years)	62.0±11.0	61.8±13.0	NS		57.2±10.9	59.2±12.1	65 (28-82)	67 (38-79)
Indication								
CLM	16(39.0)	15(38.5)	NS		35(53.8)	20(31.7)	6(14.0)	7(16.7)
HCC	17(41.5)	16(41.0)			19(29.2)	37(58.7)	35(81.4)	34(81.0)
Cholangiocarcinoma	-	-			-	-	1(2.3)	0(0)
Other	8(19.5)	8(21.5)			11(16.9)	6(9.5)	1(2.3)	1(2.4)
Liver pathology								
Cirrhosis	21(51.2)	18(46)	NS		NA	NA	NA	NA
Steatosis	15.0±19.0§§	21.0±23.0§§			40(61.5)	39(61.9)	NA	NA
Resection extent								
≥2 segments	12(29.3)***	14(35.9)***	NS		38(58.4)**	37(58.7)**	19(44.2)***	18(42.8)***
Operating time (mins)	219.0±45.0	207.0±48.0	161.8(36.1)∞	172.0(46.2)∞	145.0 (111.5-212.5)*	155.0(120.0-221.0)*	NA	NA
Transection time (mins)	65.0±25.0	60.0±26.0	NA	NA	7(4-19)	9(5-19)	55(15-108)	49(7-157)

Ex= experimental group, Con = Control groups, NA = not assessed, NS=no significant difference, CLM = Colorectal Liver Metastasis, HCC = Hepatocellular Carcinoma; §§ steatosis %, ** >2 segments, ***>1 segment. ∞ =mean (s.e.m) *median (IQR), data are otherwise presented as n (%) and mean±s.d. or median (range). Significantly different results ($p<0.05$) are highlighted in bold.

Table 7 contd. Study characteristics

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other Bias
Wang *et al 2006* [109]	+	+	+	-	+	+	+
Liu *et al* 2005 [178]	+	+	-	-	+	?	+
Liu *et al* 2008 [179]	+	+	+	?	+	+	+
El-Khaboutley *et al* 2004 [175]	+	?	?	?	+	+	+
Rahbari *et al* 2011 [180]	+	+	+	-	+	+	+
Zhu *et al* 2012 [181]	+	+	?	?	+	+	+
Kato *et al 2008* [177]	+	?	?	?	+	+	+
Figueras *et al* 2005 [176]	+	?	?	?	+	+	+

+=present; -=absent; ?=unclear

Table 8. Bias assessment table.

Three relevant RCTs were excluded. Ryu *et al* [182] maintained a low CVP in both groups and observed the effect of milrinone on the operative field without reporting EBL or complication rate; Sand *et al* [183] assessed the effect of patient position and positive end expiratory pressure (PEEP) on CVP and did not assess EBL, morbidity or LOS; and Lin *et al* [184] incorporated five randomised groups and assessed EBL as volume per transection area and did not report morbidity or LOS. It was felt that this was not meaningfully comparable to the other included studies and so excluded from the quantitative analysis.

4.4.2 Evaluation of Intervention

Exact CVP was not reported in two trials. [109, 179] In the six trials that did report CVP [175-178, 180, 181], the CVP was significantly reduced in the low CVP group (n=291) compared to the control groups (n=294) (WMD -2.37 mmHg [95%CI -4.11- -0.63] p=0.008, I^2=92%). No difference in in-flow occlusion time was observed in the low CVP group (n=223) compared to the control group (n=227) in the trials that reported using it (WMD 0.21mins [95%CI -1.47 - 1.88] p=0.81, I^2=23%). [109, 176, 180, 181]

Details of the trial protocols used are shown in Table 9. Four trials utilised anaesthetic methods to reduce CVP [109, 175, 178, 179], three trials [177, 180, 181] used IVC clamping to reduce CVP and one trial [176] performed a RCT comparing complete in-flow occlusion with selective in-flow occlusion and observed a significant difference in CVP between the two groups.

	Experimental protocol	In flow occlusion	CVP (mmHg)	Control Protocol	In flow occlusion	CVP (mmHg)
Wang *et al 2006* [109]	IVI, Head tilt, GTN, Furosemide,	Y	2-4	IVI	Y	NA
Liu *et al* 2005 [178]	IVI, head tilt, GTN, isoflurane, fentanyl	N	**3.6±0.4**	IVI	N	**8.9±2.1**
Liu *et al* 2008 [179]	IVI, head tilt, GTN, furosemide, transfusion Hb <80g/L	N	2-4	IVI	N	NA
El-Khaboutley *et al* 2004 [175]	GTN, IVI	Y	**3.0±0.1**	IVI	Y	**6.9±2.8**
Rahbari *et al* 2011[180]	IVC clamp, epidural	Y	**4.0±3.2**	Epidural, IVI, opioids, GTN, furosemide, reduced PEEP, epidural fentanyl	Y	**2.6±1.8**
Zhu *et al* 2012 [181]	IVC clamp	Y	**4.3(0.9)***	GTN, head tilt, furosemide, IVI	Y	**4.7(0.5)***
Kato *et a*l 2008 [177]	IVC clamp, IVI,	N	**4(0-13)**	IVI	N	**6(1-14)**
Figueras *et al* 2005 [176]	NA	Y (Complete occlusion)	**6.4±3**	NA	Y (Selective occlusion)	**7.2 ±3.6**

IVI – Intravenous infusion, GTN – Glycerine trinitrate, PEEP – peak end expiratory pressure. Statistically significant (p<0.05) CVP differences highlighted in bold. *mean (s.e.m.) data otherwise presented as mean±s.d. or median (range)

Table 9. Trial protocol details

4.4.3 Primary Outcome: Morbidity Rate

Five studies [109, 175, 176, 180, 181] with a total of 490 patients (low CVP n=243, control n=247) reported overall systemic complication rates between groups. There was no difference in overall morbidity rate between low and high CVP surgery (OR=0.96 [95% CI 0.66, 1.40] p=0.84, I^2=0%, Figure 9).

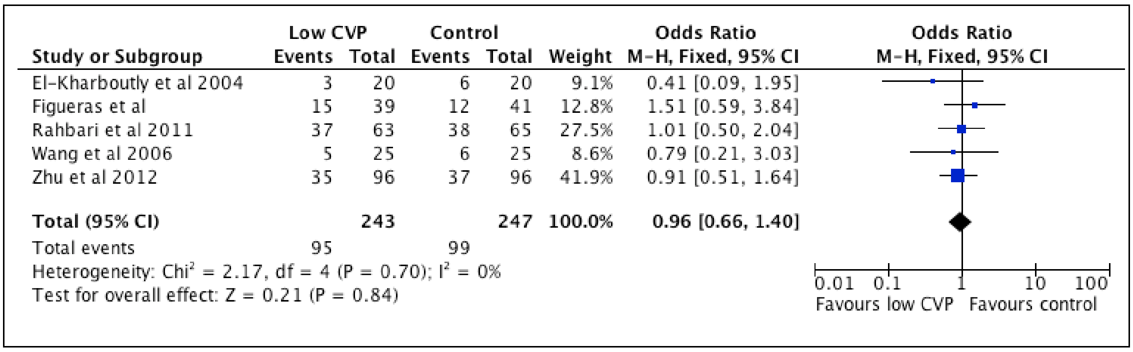


Figure 9. Post-operative morbidity rate

4.4.3.1 Primary Outcome: Subgroup analysis

Subgroup analysis was performed according to the method of CVP reduction (anaesthetic/surgical). Only two trials using anaesthetic methods to reduce CVP [109, 175] reported complication rates and no difference was detected (OR=0.6 [95%CI 0.22, 1.63]; p=0.31, I^2=0%). The two trials [178, 179] not included in the quantitative analysis that did not report complication outcomes did not report any significant differences in post-operative renal functioning between the two groups. Sub-group analysis of the two trials comparing IVC clamping (n=161) versus no IVC clamping (n=159) [180, 181] and reporting complication rates did not report a significant difference in morbidity rate (OR 1.06 [95%CI 0.68, 1.66] p=0.80, I^2=0%).

4.4.4 Secondary Outcomes

4.4.4.1 Estimated Blood Loss

Seven trials [109, 175-179, 181] comprising 553 patients (Low CVP 276, Control 277) reported EBL (Figure 10). There was a significant reduction in EBL in the low CVP group compared with the control group (WMD= -308.63mls [95% CI -474.67, -142.58] p=0.0003, I^2=73%). Subgroup analysis [109, 175, 178, 179] demonstrated that anaesthetic measures to reduce CVP (n=98) led to a significantly reduced EBL compared to control (n=98) (WMD = -406.26mls [95%CI -490.77, -321.76] p=<0.00001, I^2=52). Sub-group analysis of two trials comparing IVC clamping (n=139) with no IVC clamping (n=138) [177, 181] showed no significant difference in EBL between the intervention and control groups (WMD = -88.70mls, [95%CI -268.02, 90.7] p=0.33, I^2=0%).

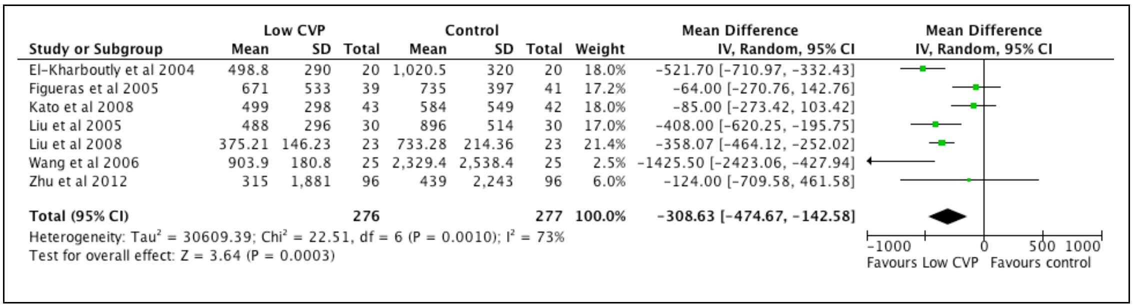


Figure 10. Estimated blood loss

4.4.4.2 Intra-operative Transfusion Requirement

Intra-operative blood transfusion requirements were reported in seven trials [109, 175, 176, 178-181] including 681 patients (low CVP n=339, control n=342). Significantly fewer blood transfusions were required in patients in the low CVP group compared with the control group (OR 0.65 [95% CI 0.44, 0.97] p=0.04, I^2=37%, Figure 11).

Study or Subgroup	Low CVP Events	Low CVP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
El-Kharboutly et al 2004	9	20	11	20	10.3%	0.67 [0.19, 2.33]
Figueras et al 2005	4	39	6	41	8.9%	0.67 [0.17, 2.57]
Kato et al 2008	0	43	0	42		Not estimable
Liu et al 2005	20	30	28	30	15.9%	0.14 [0.03, 0.72]
Liu et al 2008	7	23	13	23	15.4%	0.34 [0.10, 1.13]
Rahbari et al 2011	9	63	6	65	8.6%	1.64 [0.55, 4.91]
Wang et al 2006	8	25	14	25	16.2%	0.37 [0.12, 1.17]
Zhu et al 2012	18	96	18	96	24.8%	1.00 [0.48, 2.06]
Total (95% CI)		**339**		**342**	**100.0%**	**0.65 [0.44, 0.97]**
Total events	75		96			

Heterogeneity: Chi^2 = 9.49, df = 6 (P = 0.15); I^2 = 37%
Test for overall effect: Z = 2.08 (P = 0.04)

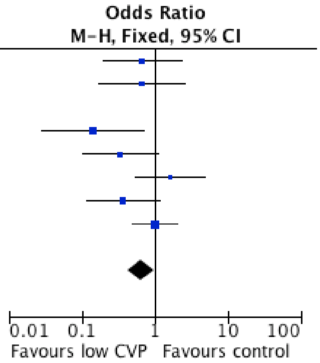


Figure 11. Blood transfusion rates

4.4.4.3 Length of Stay

Length of stay was reported in 4 of the 8 trials [109, 176, 177, 181] with 407 patients (low CVP n=203, control n=204). No significant difference was observed between the low CVP group and control group (WMD -1.75 days [95% CI -5.84, 2.34], p=0.40 I^2=64%, Figure 12).

	Low CVP			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Figueras et al 2005	9.38	4.9	39	8.15	3.8	41	39.6%	1.23 [−0.70, 3.16]
Kato et al 2008	26	18	43	30	16.5	42	18.1%	−4.00 [−11.34, 3.34]
Wang et al 2006	16.3	6.8	25	21.5	8.6	25	29.3%	−5.20 [−9.50, −0.90]
Zhu et al 2012	14	30.4	96	13.9	36.3	96	13.0%	0.10 [−9.37, 9.57]
Total (95% CI)			**203**			**204**	**100.0%**	**−1.75 [−5.84, 2.34]**

Heterogeneity: $Tau^2 = 10.03$; $Chi^2 = 8.32$, df = 3 (P = 0.04); $I^2 = 64\%$
Test for overall effect: Z = 0.84 (P = 0.40)

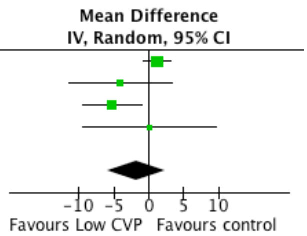


Figure 12. Length of stay

4.5 Discussion

This review provides an assessment of the effect of CVP on outcomes after liver resection and has shown that low CVP surgery reduces EBL. This does not, however, correspond to improved outcomes in terms of morbidity or hospital stay.

Two other reviews have assessed the effect of CVP reduction on EBL. [79, 108] Gurusamy *et al* [79] and Li *et al* [108] analysed three and five studies respectively comparing low CVP with high CVP and found a significant reduction in blood loss during low CVP surgery. This current review includes a further three RCTs assessing high and low CVP, [176, 180, 181] discriminates between anaesthetic and surgical methodology and investigates quantitatively the effect of CVP reduction not only on EBL but also morbidity. This review further demonstrates the beneficial effects of lower CVP during transection when compared to higher CVPs in terms of intra-operative blood loss and blood transfusion rates. This consolidates the data from the previous reviews.

As well as the previous reviews of RCTs, retrospective series exist which have shown low CVP to be safe and associated with satisfactory EBL and outcomes [185-188] and the few comparative studies comparing CVP of greater than five mmHg with CVP of less than five mmHg during liver transection [186, 189, 190] retrospectively concluded that those patients undergoing resection with CVP greater than five mmHg suffered higher EBL. These published series have often guided practice and low CVP surgery is regarded as standard practice.

However controversy does still remain regarding the evidence base for this issue with several trials [191-193] reporting that CVP is not associated with reduced EBL or predictive of EBL following regression analysis. Chibber *et al* [191] performed a sub-group analysis of CVP greater and less than five mmHg from their cohort (all using the same protocol) and did not observe a difference in blood loss in living donor patients.

Moreover, two of the included trials in the current analysis [176, 177] did not show a significant reduction in EBL and Zhu *et al* [181] showed a mean reduction by only 150 mls despite achieving significant reductions in CVP. The reason for the modest reduction in EBL seen in these three included trials is potentially explained by the methodology. The overall difference in CVP between these groups was low. Zhu *et al* [181] and Rahbari *et al* [177] had a “control group” as a low CVP group achieved by standard techniques compared to the IVC clamping group. Therefore the comparisons in the meta-analysis were not all uncontrolled high CVP versus low CVP (although mean CVPs in these groups were statistically significant). When CVP difference was larger a more significant difference in EBL was observed. [175, 178] This finding is suggestive of the importance of well-controlled CVP and does not identify benefits associated with ultra-low CVP.

It is well established that high blood loss intra-operatively has a negative effect on peri-operative complication rates and reduction in EBL leads to improved post-operative outcomes [73, 117]. The overall meta-analysis, however, revealed no significant difference in complication rates between low CVP and control groups.

An explanation for this might be the modest reduction in EBL reported by several of the trials [176, 177, 181] which could have potentially influenced the analysis. The reported difference in EBL in these trials was around 100-200mls less than the control group. This is much less than compared to the other included trials. [109, 175, 180] Intuitively it can be appreciated why a large drop in EBL could contribute to an improved outcome and a modest reduction would not necessarily translate into an enhanced post-operative course.

However it is also important to consider the methodology of the techniques used to reduce CVP and their impact on outcome. Three of the trials compared IVC clamping to reduce CVP compared with no IVC clamping. The potential hazards of IVC clamping have not been fully investigated. A negative effect on hepatic and renal function has not been routinely observed, [180, 194] however significantly higher rates of thromboembolic events [180] were reported. Such complications could negate the benefit of low CVP and low blood loss surgery. Considering the lack of benefit gained by this technique in terms of EBL and outcome when compared to standard practice, it is therefore reasonable to question the benefit of this technique over standard anaesthetic methods of CVP reduction.

A potential explanation for the negative result from the anaesthetic studies is the small numbers in the included RCTs. Only two of the anaesthetic trials reported systemic complication rates. These both showed non-significant improved outcomes in the low CVP groups, which may have resulted from an under powered analysis of secondary outcomes. Even after meta-analysis, no significant difference was noticed. Although this was trending towards reduced morbidity rates, a potential type two error in this analysis cannot be excluded.

However, the two trials included in the meta-analysis [109, 175] did not report significant differences in complication rates and the two trials excluded [178, 179] that did not report overall complication rates did not report significant differences in renal or hepatic function despite significant reductions in EBL. Therefore a clinical benefit to low CVP surgery is not definitively presented by the evidence.

Another explanation for the similar morbidity rates between groups is the potentially detrimental impact of the individual techniques used to reduce CVP by anaesthetic methods. [109, 175, 178, 179] IV fluid restriction during the transection phase, GTN and furosemide were utilised frequently by the included studies. These simple methods help to maintain a state of hypovolaemia and vasodilation to reduce back pressure on the hepatic veins to reduce venous bleeding during hepatic transection. Although evidence of renal dysfunction in these groups has not been established [187] there is a lack of prospective evidence for the efficacy and safety of each individual component of such CVP lowering protocols.

Only Ryu *et al*, [182] Page *et al* [157] and Sand *et al* [183] have performed assessments of single anaesthetic techniques in low CVP surgery. These studies did not fulfil the criteria for inclusion into the meta-analysis.

Sand *et al* [183] investigated the benefit of positional change with or without PEEP on CVP during liver resection, finding a head up tilt to be successful in reducing CVP. Several studies in this review performed positional change to reduce CVP. [109, 178, 179, 181] Sand *et al* [183] found that the CVP rose in the head down position but fell in the head up position. However when taking into consideration that hepatic vein pressure measured at the time did not change regardless of position and head up tilt is associated with gas embolism and haemodynamic instability, [195] positional change is advised against.

Ryu *et al* [182] assessed the effect of milrinone on CVP and the operative field. Milrinone was suggested as beneficial due to its inotropic as well as vasodilatory effect that would prevent the haemodynamic instability of fluid restriction or vasodilation with nitrates. The results were favourable although the study only assessed living donors and so its effect on patients with significant co-morbidities is not yet established.

Another technique that was utilised sparingly by the included trials was epidural. Neuraxial blockade provides vasodilation and subsequent CVP reduction and its inclusion as part of CVP lowering protocols is often advocated. [186] This was utilised by Rahbari *et al* [180] in the control group, which achieved significantly reduced CVP compared to the IVC clamping group. In the published non-randomised trials this has become a controversial matter with two trials not showing an effect on blood loss when using an epidural in the CVP lowering protocol [157, 191] and several others finding its absence associated with improvements in EBL and morbidity. [189, 190, 196] The advocates of epidural would welcome its inclusion peri-operatively due to the perceived improvement in recovery. [36] However this has become a controversial topic of late due to increased concerns being voiced related to coagulopathy secondary to liver resection affecting epidural removal, [144] increased IV fluids due to epidural related hypotension [157] and increased post-operative transfusions of red cells. [157] Such disadvantages are often accepted due to perceptions of improved overall outcomes and CVP reduction. However this concept is increasingly being challenged as improved alternatives to epidurals are becoming more widespread and enhanced recovery protocols improve speed of recovery often without the need for epidural. [134, 135] Moreover the ability to comment on the specific role of epidural on CVP is limited due to the lack of trials assessing this specifically. This is therefore an area that warrants prospective investigation to clarify the effect of epidural on CVP and outcome following liver resection.

An additional point to consider is the effect of in-flow occlusion. All but Kato *et al* [177] combined IVC clamping with in flow occlusion. This could potentially result in a deleterious effect on outcome due to potential ischaemia associated liver injury. [197] This suspicion is further supported by three RCTs [110, 111, 176] whereby selective in flow occlusion rather than complete in-flow occlusion was associated with significantly reduced post-operative morbidity. All maintained a CVP of less than five mmHg, there was no difference in blood loss but Ni *et al* [111] and Fu *et al* [110] reported a reduction in morbidity in the selective Pringle groups when compared to the Pringle groups. This therefore points to other areas of protocol optimisation to consider when CVP has been optimised below five mmHg.

The main limitation of this review is the heterogeneity of the included studies. The anaesthetic studies assessed a CVP of over five with a CVP of less than five mmHg. The IVC clamping studies, despite significant differences in CVP, assessed a CVP of less than five mmHg in both groups. It is therefore unsurprising that little difference is seen in outcome. However the primary aim of all the included trials was to assess the effect of CVP lowering. Therefore these trials represent the current status of RCTs assessing this concept.

In summary this review and meta-analysis shows that low CVP surgery effectively results in reduced blood loss and transfusion requirement during liver resection. However no improvement in clinical outcomes are associated with this and this may be affected by methodology. IVC clamping does not seem to improve outcome over low CVP surgery achieved by standard CVP lowering techniques. The optimum technique to achieve CVP reduction is not known with controversies existing regarding IVC clamping, correct anaesthetic technique and potential disadvantages of using the Pringle manoeuvre. Prospective, randomized trials are required to establish precise protocol components when attempting to optimise outcomes following liver resection.

4.6 Chapter Publication

Central Venous Pressure and Liver Resection: A Systematic Review and Meta-analysis. Accepted for publication HPB (London) June 2015.

5 Summary of Evidence

Enhanced recovery after liver surgery has shown some improvement in overall morbidity but has not resulted in decreased surgical morbidity. In the published trials comparing ERAS protocols with standard care, the majority of trials have utilised epidural analgesia following resection. However the available evidence assessing analgesia after liver resection has not identified a clear optimum analgesic modality to enhance recovery after liver surgery in terms of morbidity. Moreover it is suggested that epidural might actually delay recovery compared to non-opiate alternatives, namely, continuous wound infiltration. Secondly an argument for the use of epidurals during liver resection is their ability to provide a low CVP during transection in order to minimise blood loss. However low CVP surgery has not shown an improvement in post-operative morbidity, potentially as a result of techniques used to achieve low CVP during transection. The evidence supporting the specific benefit of epidural on this facet of resection is not available. Therefore the following chapter will describe a trial investigating analgesic modalities after liver resection investigating these aspects of care.

6 The Effects of Local Infiltration Versus Epidural Following Liver Resection II (LIVER II)

6.1 Summary

Analgesia after liver surgery remains controversial. A previous randomised trial of continuous wound infiltration versus epidural analgesia after liver surgery showed earlier discharge in the continuous wound infiltration (CWI) group but superior early post-operative pain scores in the thoracic epidural analgesia (TEA) group. This trial aims to determine the efficacy of CWI plus abdominal nerve blocks compared to epidural after liver resection. A randomised controlled trial of 100 patients undergoing open liver resection was performed from December 2012 to June 2014. Patients were randomised to receive either wound catheter and nerve block (CWI) or thoracic epidural analgesia (TEA) for 48 hours post-operatively. Primary outcome measure was functional recovery time. Secondary outcome measures were pain scores, complication rates, inflammatory mediators and CVP during transection. 44 patients received TEA and 49 received CWI. Functional recovery time was 6.5 IQR 5-9.75 days (TEA) versus 5.75 IQR 4-7 (CWI) days (p=0.04). Pain scores were equivalent between the two groups and there were also no differences in morbidity, inflammatory response or CVP during transection. Increased opiate requirements were observed in the CWI group on the day of surgery and post-operative day one. CWI could be considered as first line analgesia after liver surgery. CWI offers a reduction in time to recovery. TEA does not offer an advantage over CWI in terms of attenuation of the inflammatory response or pain scores.

6.2 Introduction

Pain control is a key principle of peri-operative care and a major factor when attempting to enhance recovery after surgery. [36] Thoracic epidural analgesia (TEA) has often been advocated as an optimum component of post-operative analgesia following abdominal surgery, particularly colorectal surgery. [36]

Following introduction of enhanced recovery protocols after liver resectional surgery TEA has been incorporated as part of multi-modal analgesic regimens. [88, 122, 126, 128] However, this has become controversial with opinion regarding the role of TEA after liver surgery being divided. [133, 139] Perceived disadvantages of TEA use include concern regarding increased IV fluid overload, [141] coagulopathy following liver resection increasing epidural haematoma rate, [146] a failure rate of up to 25% [142] and an increase in blood transfusion requirements. [157]

Alternative modalities are becoming more popular with continuous wound infiltration (CWI) being used in an increasing number of centres. [135, 149, 150, 154] High level evidence investigating CWI after liver resection is limited with only one small randomised controlled trial [135] comparing TEA with CWI. Despite this trial showing an improvement in recovery time, consensus agreement has not been reached with limited evidence guiding practice. [198, 199]

Potential reasons for this are the superior analgesic properties of TEA compared to CWI [135] and opiates [45] being shown. TEA is also seen as being able to attenuate the inflammatory response to surgery [200, 201] and this is one of the reasons why it has been recommended to be used as part of an ERAS programme. [36] Also TEA is often advocated during liver surgery to aid in CVP reduction to facilitate hypotensive parenchymal transection. [186]

The aim of this study was to perform a randomised controlled trial comparing TEA with CWI following liver surgery in order to establish if superiority exists between these modalities in terms of recovery after surgery. A RCT [135] was previously conducted by the investigating unit comparing CWI and TEA reporting superior early pain scores in the TEA group compared with CWI. In order to overcome this and prevent a delay in establishing effective analgesia in the CWI group, in this trial a greater volume of local anaesthetic was delivered as a transversus abdominis and rectus sheath nerve block at the same time as the wound infiltration catheters were being placed. Moreover in order to comprehensively assess the influence of the analgesic modality on the response to surgery an evaluation of clinical outcomes, inflammatory response mediators and physiological response (intra-operative CVP) were investigated.

6.3 Methods

6.3.1 Ethics

The trial was approved by the South East Scotland Research Ethics Committee and the trial protocol was published prior to commencement (clinicaltrials.gov, NCT01747122). Recruitment was conducted from December 2012 and follow up was completed by August 2014.

6.3.2 Patients

All patient listed to undergo an open liver resection at the Royal Infirmary of Edinburgh, UK, were approached to discuss participating in the trial. After an initial discussion patients were given written trial information at the pre-admission clinic approximately four weeks prior to admission for resection. Written informed consent was obtained on the day of surgery or sooner if appropriate.

Patients were excluded prior to randomisation if they were to undergo a laparoscopic or combined procedure, had a contra-indication to epidural or wound catheter, deranged liver function tests, were below the age of 18 years of age or did not have capacity to provide informed consent to enter the trial.

6.3.3 Perioperative Care

Patients were admitted on the morning of surgery having fasted for six hours and taken clear fluids up to two hours prior to surgery. After consenting to the trial patients were randomised on the morning of surgery to receive either TEA or continuous wound infiltration combined with abdominal nerve block. Sequential, opaque sealed envelopes were pre-filled by an independent adjudicator and opened after consent had been obtained. Randomisation was stratified according to extent of resection - either major resection (three or more segments) or minor resection (less than three segments). Neither participant nor the trial team were blinded to the randomisation.

Patients randomised to TEA underwent a standardised anaesthetic protocol by the same group of anaesthetists experienced in liver resection surgery. In the anaesthetic room prior to induction of anaesthesia, participants received a thoracic epidural puncture at the level of T8-T9. Four millilitres of 2% lignocaine was administered as a test dose followed by 10mls levobupivacaine with 100mcg fentanyl to establish epidural block. An infusion of 0.1% levobupivacaine with 2mcg/ml fentanyl was then started.

All patients underwent induction of anaesthesia with propofol, atracurium and fentanyl (1-2 mcg/kg). Maintenance of anaesthesia was achieved by desflurane or sevoflurane. At induction patients routinely received a central venous catheter in the right internal jugular vein, radial arterial cannulation and a urethral catheter. Routine monitoring of CVP, invasive continuous blood pressure and mean arterial pressure, end tidal CO_2, heart rate, oxygen saturation and urine output was performed throughout the operation.

The peritoneal cavity was entered via a right subcostal incision that was extended if required superiorly in the midline. A full laparotomy was performed to ensure no contra-indications to resection were evident. Intra-operative ultrasound was performed by the operating surgeon to establish resectability and to formulate a final operative approach. Transection of the liver parenchyma was performed with Cavitron Ultrasonic Aspirator (CUSA, ValleyLab, Boulder, Colorado, USA) and monopolar diathermy. Resection was performed in accordance with the patients' pathological, oncological and physiological requirements to ensure optimum short and long term outcomes.

Peri-operative ERAS principles were adhered to with routine thromboprophylaxis administration and peri-operative antibiotics being administered immediately prior to incision. Intra-operative warming was routinely performed. As small an incision as required was used. Intra-peritoneal drains and nasogastric tubes were not routinely administered and intra-operative fluid management was restricted to 80-100mls/hour of crystalloid.

Patients randomised to receive CWI underwent the same induction and maintenance protocol. At the end of the operation an “on-Q” dual limb 12.5cm Painbuster (BBraun, Sheffield, UK) was inserted into the musculofascial layers of the abdominal wall. The lateral limb was placed between the transversus abdominis and internal oblique muscles and the medial limb was placed in the rectus sheath posterior to the muscle as described by Basu *et al* (2004) and Revie *et al* (2012). [135, 149]

On closure of the wound the nerve block was performed by instilling a total of 40mls of 0.125% levobupivacaine into the transversus abdominis plane and the rectus sheath posteriorly via the wound catheter. The wound catheters were subsequently connected to an elastomeric reservoir containing 0.375% levobupivacaine that instilled at a fixed rate of 4ml/hr. This was kept in situ for 48 hours.

6.3.4 Post-operative Care

Patients were transferred from theatre to the recovery ward where they were extubated and monitored until observations and pain scores were satisfactory according to the unit protocol. They were subsequently transferred to the high dependency ward where they remained until they achieved discharge criteria and could be transferred to the general ward. Patients were managed according to an enhanced recovery protocol (Table 10) utilised in the investigating unit. [135]

Time Point	Recovery Elements
Day before surgery	Normal oral nutrition until midnight
	No preanaesthetic medication
DOS	Short-acting IV anaesthetic agent
	No nasogastric drainage
	Warm IV fluids, and upper and lower body air-warming device
	Prophylactic antibiotics
	Avoidance of excessive IV fluids
	No routine drainage of the peritoneal cavity
	Epidural or CWI analgesia
	Patient mobilises to chair evening of surgery
	Restart oral intake of water/nutrition *ad libitum*
POD 1	Arterial and central lines out
	Patient mobilises around bed
	Patient sits out of bed for 6 hours
	Discontinuation of intravenous fluids if haemodynamically stable and drinks more than 1 litre of fluid
	Normal diet
	Continue morphine PCA +/- wound catheter / TEA
	1000 mg paracetamol every 6 hours
	Transfer to general ward if possible
POD 2	Morphine PCA +/- wound catheter /TEA down
	Continue mobilisation
	Patient to sit out of bed for 8 hours
	1000 mg paracetamol every 6 hours
	Urinary catheter out
	Normal diet
	Oral analgesia
	Transfer to general ward
POD 3	Continue mobilisation
	Normal diet
	Check discharge criteria
POD 4	Check discharge criteria
	Discharge

Table 10. Enhanced Recovery Protocol

6.3.5 Outcomes

6.3.5.1 Primary Outcome

The primary outcome was functional recovery time. Patients were determined to be medically fit for discharge when they fulfilled the unit criteria: independently mobilising, eating and drinking with no requirement for IVI in the previous 24 hours, adequate pain control on oral analgesics, blood tests normal or returning to normal and patient willing to go home. Fulfilment of discharge criteria was determined by the senior clinician responsible for the patient, independent of the study team. This was reported as the time taken from the end of the operation to the time when all the recovery criteria were determined to have been achieved. This was assessed twice daily. Actual length of stay was also recorded but recovery criteria time was deemed a more accurate reflection of recovery time due to logistical difficulties of discharging patients on the day of recovery criteria fulfilment.

6.3.5.2 Secondary Outcomes

Pain Scores

Pain scores were recorded by the nursing staff, independent of the trial and trained in pain score recording. Pain scores were recorded at 2, 6 and12 hours after closure of the incision and on post-operative day (POD) 1, POD 2 and POD 3 at 0900hrs. Pain was recorded at rest and on movement. The score was reported from a scale of between 0-10.

Morbidity

Complications were observed for twice daily. The type of complication was defined according to pre-determined complication criteria [202] and the severity of complication was graded according to the Clavien Dindo criteria. [203] The clinical team co-ordinated the diagnosis and management of complications and the investigating team observed twice daily for occurrence of a complication. Patients were reviewed in the out-patient clinic and morbidity within 30 days of discharge was documented also.

Parameters of Recovery

Patient recovery parameters were prospectively assessed. Time to sitting, mobilising independently, drinking, eating, passing wind and moving bowels was prospectively observed. Independent mobilisation was defined as being able to weight bear and walk outwith the bed space without support from aids or assistants.

The Inflammatory Response to Surgery

Cytokine (IL1β, IL6, IL8, IL10, TNFα) and High Mobility Group Box 1 (HMGB1) levels were all assessed pre-operatively and at 24 hours and 72 hours after the incision was made.

Sample Preparation

Cytokine measurement was obtained via analysis of plasma. Whole blood was collected from the patient by standard venepuncture into an EDTA tube and immediately transferred in ice to the laboratory and centrifuged at 1000 g for 15 minutes at 4 degrees centigrade. The separated plasma was then aliquoted into 1.5 ml polypropylene tubes and immediately frozen and stored at -80 degrees. Sample preparation for HMGB1 analysis was different in that serum was required. Whole blood was extracted and was spun at 1000 g for 15 minutes. Serum aliquots were taken and stored at -80 degrees. Batch analysis was performed once all the samples had been obtained.

Sample Analysis

Cytokine analysis was performed via enzyme linked immunoassay (ELISA) procedure as per the manufactures instructions. The Milliplex human cytokine kit (Millipore Corp, St Charles, Missouri, USA) was used to obtain plasma levels of cytokines. High sensitivity analysis was performed to detect levels from a standard curve ranging from 0.13 pg/mL – 2000 pg/mL. Analysis of wells and microsphere identification and detection was performed via a Luminex 100 instrument (Luminex Corporation, Austin, Texas, USA).

HMGB1 levels were obtained from a further quantitative sandwich ELISA (Shino-Test Corporation, Japan). The standard curve was utilised to detect HMGB1 levels from a range of 0-80 ng/mL.

CVP Assessment

CVP was monitored continuously intra-operatively. Mean CVP during transection was recorded as was highest and lowest CVP during the operation. Minimum MAP was recorded also. IV fluid and blood product administration was prospectively recorded until POD 2.

6.3.6 Statistical Analysis

Statistical analysis was performed with SPSS version 19 (IBM, Armonk, New York, USA). Based on unpublished retrospective data within the unit it was determined that a difference to functional recovery time of 1.5 days (with a standard deviation of 2.5 days) with a significance of 0.05 and a power of 80%, would require 44 patients in each arm of the study to achieve this.

Continuous data were compared with Mann Whitney *U* test or T-test depending on the distribution of the data. Paired data were compared with a paired t-test or Wilcoxon signed-rank analysis. Categorical data were compared with the Chi squared or Fishers exact test. Comparisons of multiple measures were performed with two-way ANOVA with repeated measures.

6.4 Results

The trial was conducted from December 2012 to June 2014. A total of 100 patients were randomised. The CONSORT diagram is shown in Figure 13. 44 and 49 patients were included in the analysis for the primary outcome and clinical assessments in the TEA and CWI groups respectively. Two patients in the CWI group did not have POD 3 samples taken and so were excluded from inflammatory response analysis. One patient refused POD 3 bloods and another patient died on POD 3. Three patients were excluded after randomisation: one patient in the CWI group developed significant lactic acidosis during the procedure of unknown origin and it was elected to not place a wound catheter. One patient underwent CT scanning after randomisation, was found to have advanced disease and was deemed irresectable. A further patient developed a fever in the anaesthetic room and so an epidural was not sited. Both these patients were excluded at this point. One patient in each of the CWI and TEA groups did not have a functioning central line and so were excluded from the CVP analysis.

Baseline characteristics were broadly similar with no significant differences observed between the two groups other than a significantly greater proportion of patients with normal liver in the TEA group (Table 11). Operative time was significantly longer and anaesthetic time was significantly shorter in the CWI group. No significant difference in EBL was observed (Table 12).

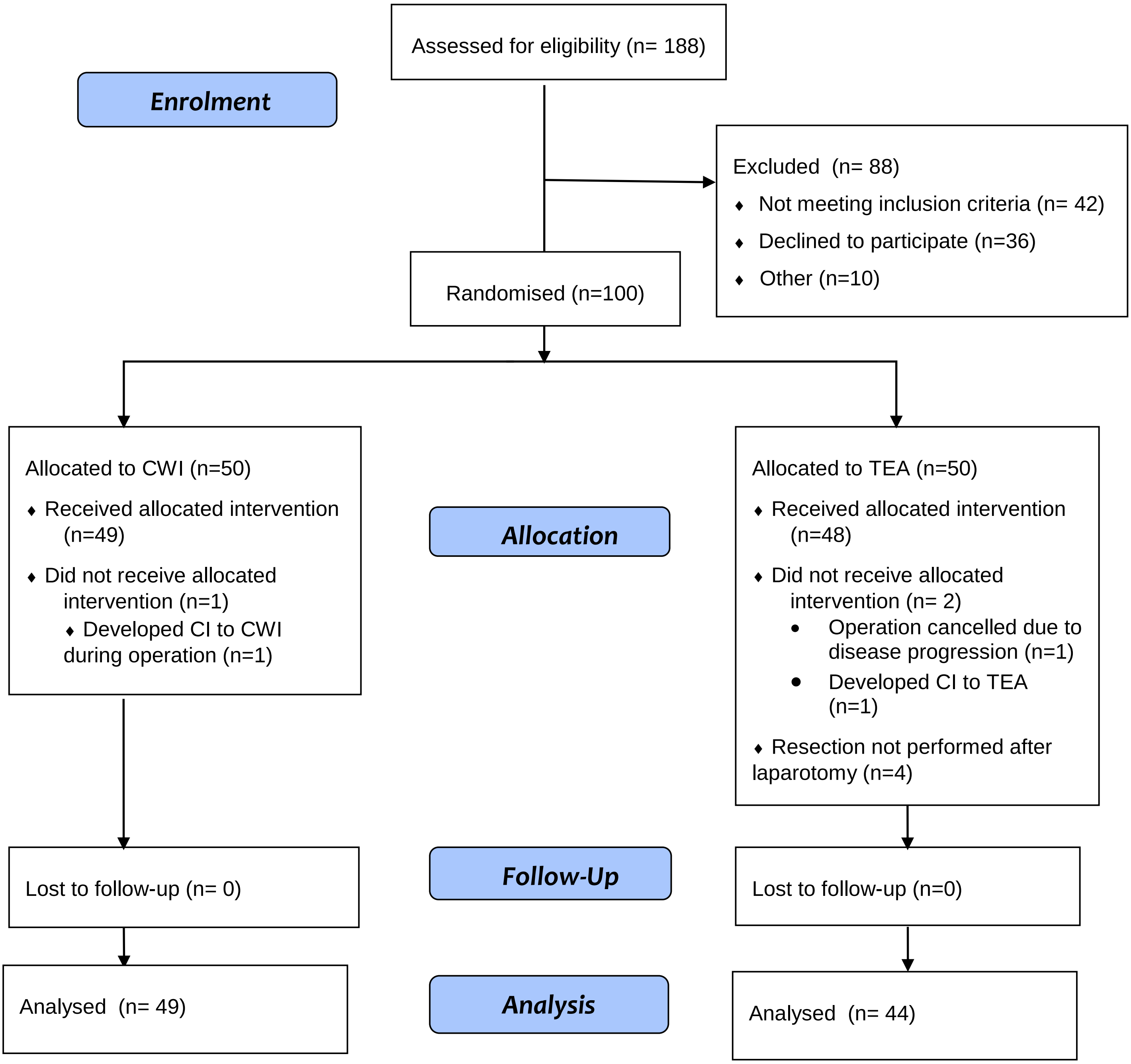


Figure 13. CONSORT diagram

	TEA (n=44)	CWI (n=49)
Age (years)	62.6±11.1	62.8±12.1
Male	29 (65.9)	28 (57.1)
BMI (kg/m^2)	27.7 ± 4.2	28.5±5.0
ASA		
I	3 (6.8)	3 (6.1)
II	32 (72.7)	39 (79.6)
III	9 (20.5)	7 (14.3)
Indication		
CLM	29 (65.9)	34 (69.4)
HCC	6 (13.6)	7 (14.3)
Cholangiocarcinoma	0 (0)	1 (2.0)
Other malignant	2 (4.5)	4 (8.2)
Benign	7 (15.9)	3 (6.1)
Size of tumour (mm)	47.6 ±44.8	45.2±44.0
Number of tumours	1.4±1.2	1.7±1.2
Background liver		
Steatosis	16(36.4)	20(40.8)
Steatohepatitis	2(4.5)	12(24.5)
Sinusoidal dilatation	10(22.7)	11(22.4)
Cirrhosis	3(6.8)	4(8.2)
Normal liver	17(38.6)	2(4.1)
Extent of Resection		
Major resection	27(61.4)	33(67.3)
Minor resection	17(38.6)	16(32.7)
Chemotherapy prior to procedure	23(52.3)	29 (59.2)

BMI = Body Mass Index, ASA = American Society of Anesthesiologists, CLM= Colorectal Liver Metastasis, HCC = Hepatocellular Carcinoma. [a] t-test, [b] χ^2 test, [c]Fishers exact test. Data are presented as n (%) or mean±sd

Table 11. Patient characteristics

	TEA (n=44)	CWI (n=49)	*P* value
Operative time (min)	198 (141-250)	226 (171-306)	0.06[a]
EBL (ml)	675 (452-1313	800 (475-1500)	0.41[a]
Pringle time (min)	12 (0-27)	22 (2-34)	0.07[a]
Transection time (min)	70 (42-100)	75 (48-110)	0.43[a]
Wound size (cm)	31 (28-35)	30 (27-33)	0.25[a]
Anaesthetic time (min)	50 (40-56)	35 (30-37)	<0.0001[a]

EBL = Estimated Blood loss. [a] Mann Whitney *U* test. Data are presented as median (IQR)

Table 12. Operative details

6.4.1 Clinical Outcomes

6.4.1.1 Functional Recovery Time

The primary outcome of functional recovery time was reduced in the CWI group (CWI - 5.75 days, IQR 4-7; TEA – 6.5 days, IQR 5-9.75; p=0.04). As well as this the CWI group spent significantly less time in HDU (42 hours IQR 24-65) compared with TEA (46 hours IQR 42-66; p=0.04). Readmission rates were similar between the two groups (CWI 3 (6.1%), TEA 5 (11.4%); p=0.47). No differences were observed in achievement of recovery milestones (Table 13) or protocol compliance rates (Table 14).

	TEA (n=44)	CWI (n=49)	P value
Recovery parameter			
Passed wind	51 (23-79)	65 (34-78)	0.28[a]
Moved bowels	90 (55-120)	79 (65-101)	0.47[a]
Sitting	22 (20-36.5)	22 (19-24)	0.52[a]
Mobilisation	60 (44-85)	53 (39-72)	0.31[a]
First drink	6(4-14)	7(4-12)	0.68[a]
First meal	20(16-39)	20 (18-24)	0.99[a]

Time to achievement of recovery milestones in hours. Data are presented in median (IQR) hours. [a] Mann Whitney *U* test

Table 13. Post-operative recovery milestones

ERAS compliance	TEA (n=44)	CWI (n=49)	*P* value
Arterial Line out			
POD 1	26 (59.1)	31(63.3)	0.68[a]
POD 2	10(22.7)	14 (28.6)	0.52[a]
POD 3	4(9.1)	1(2.0)	0.19[b]
Later	4(9.1)	3(6.1)	0.70[b]
Central Line out			
POD 1	11 (25.0)	20 (40.8)	0.11[a]
POD 2	20 (45.5)	18 (36.7)	0.39[a]
POD 3	6 (13.6)	4 (8.2)	0.51[b]
Later	7(15.9)	7(14.3)	0.83[a]
Intravenous fluids down			
POD 1	10 (22.7)	5 (10.2)	0.16[b]
POD 2	15 (34.1)	14(28.6)	0.57[a]
POD 3	7(15.9)	11(22.4)	0.43[a]
POD 4	3 (6.8)	7 (14.3)	0.32[b]
Later	9(20.5)	12(24.5)	0.64[a]
Urinary catheter out			
POD 2	9(20.5)	9(18.4)	0.80[a]
POD 3	14(31.8)	15(30.6)	0.90[a]
POD 4	9(20.5)	15(30.6)	0.26[a]
Later	12(27.3)	10(20.4)	0.44[a]

Data are presented as n (%). [a] χ^2 test [b]Fishers exact test.

Table 14. ERAS protocol compliance results

6.4.1.2 Morbidity

A complication rate of 31(70.5%) was observed in the epidural group compared with a rate of 25 (51%) in the CWI group (p=0.06) (Table 15). No difference was observed in severity of morbidity between groups (Table 16). Three deaths occurred in the CWI group. No mortality was observed in the TEA group. Two deaths were as a result of multi organ failure following hepatic insufficiency and one was secondary to multi-organ failure on day 35 as a result of an ischaemic colon. A breakdown of individual complications observed is reported in Table 15.

Individual complication type was recorded. All complications were reported including multiple complications in the same patient. Ten incidences of sustained hypotension related to epidural blockade were observed in the epidural group (p=0.03). Hypotension was defined as the requirement of an infusion of vasopressor to maintain adequate urine output, thus corresponding to a Clavien Dindo classification of two. Three patients in the CWI group required vasopressor support. This was in the context of multi-organ failure and all three of these patients subsequently died. No other differences were observed in specific complication types (Table 15).

	TEA (n=44)	CWI (n=49)	*P* value
Post-operative Outcome			
All complications	31(70.5)	25(51.0)	0.06[a]
Mortality	0 (0)	3 (6.1)	0.24[b]
Complication type			
Bile leak	3 (6.8)	3 (6.1)	1.0[b]
Hematoma	0 (0)	2 (4.1)	0.5[b]
Collection/abscess	3 (6.8)	3 (6.1)	1.0[b]
Perforated DU	0 (0)	1 (2.0)	1.0[b]
Ischemic bowel	0 (0)	1 (2.0)	1.0[b]
Bleeding	1 (2.3)	2 (4.1)	1.0[b]
Wound dehiscence	1 (2.3)	0 (0)	0.47[b]
Wound infection	3 (6.8)	2 (4.1)	0.66[b]
Hepatic Failure	4 (9.1)	4 (8.2)	1.0[b]
Hypotension	10 (22.7)	3 (6.1)	0.03[b]
LRTI	0 (0)	3 (6.1)	0.24[b]
UTI	1 (2.3)	2 (4.1)	1.0[b]
Urinary Retention	5 (11.4)	2 (4.1)	0.25[b]
Septicemia	1 (2.3)	0 (0)	0.47[b]
Ileus	5 (11.4)	4 (8.2)	0.73[b]
AKI	5 (11.4)	3 (6.1)	0.47[b]
Pneumothorax	1 (2.3)	1 (2.0)	1.0[b]
Colo-cutaneous fistula	0 (0)	1 (2.0)	1.0[b]
Arrhythmia	0 (0)	3 (6.1)	0.24[b]

DU – Duodenal ulcer, LRTI – Lower Respiratory Tract Infection, UTI – Urinary Tract Infection, AKI – Acute Kidney Injury. [a] χ^2 test, [b]Fishers exact test. Data are presented as n (%).

Table 15. Post-operative morbidity and mortality

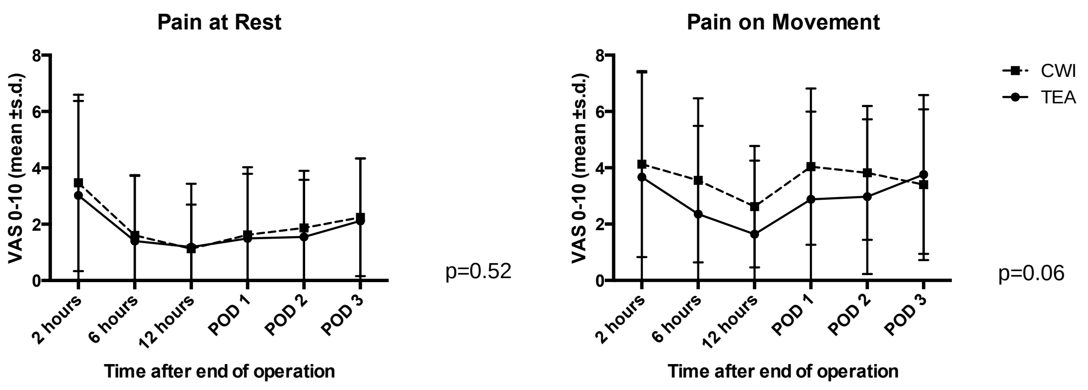
	TEA (n=44)	CWI (n=49)	*P* value
Clavien Dindo Classification			
0	13 (29.5)	21 (42.9)	
1	10 (22.7)	6 (12.2)	
2	15 (34.1)	10 (20.4)	
3a	4 (9.1)	5 (10.2)	
3b	0 (0)	3 (6.1)	
4a	0 (0)	0 (0)	
4b	2 (4.5)	1 (2.0)	
5	0 (0)	3 (6.1)	0.19[a] *

*Clavien Dindo grade ≥ 3 versus <3. If more than one complication observed per patient, highest Clavien Dindo complication reported. Data are presented as n (%).
[a] χ^2 test

Table 16. Morbidity severity

6.4.1.3 Pain Scores

Pain scores were not significantly different between CWI and TEA at rest and on movement (Figure 14). The TEA group reported superior dynamic pain scores although this did not reach statistical significance. Both comparison of individual time points by t-test or comparison of all pain measurements repeated over the first three post operative days (by 2 way RM ANOVA) did not reveal a significant difference between pain scores. Peak dynamic pain scores were recorded immediately post-operatively for both CWI and TEA. Opiate consumption was greater in the CWI group until the first post-operative day. After that the epidural groups received a significantly greater amount of opiates (Table 17).



No significant difference observed after two way repeated measures ANOVA in pain scores at rest and on movement. Scores are recorded as mean±sd.

Figure 14. Pain scores.

	TEA (n=44)	CWI (n=49)	*P* value
Opiate consumption (mg)			
Intra-operative	0 (0-1.9)	24.0 (20.0-38.0)	<0.0001[a]
DOS	0 (0-22.6)	24.0 (14.0-51.0)	<0.0001[a]
POD1	0 (0-34.5)	27.0 (16.0-47.0)	<0.0001[a]
POD 2	18.5 (10.5-27)	12.0 (4.0-20.0)	0.02[a]
POD 3	15.0 (8.0-23.5)	8.0 (3.0-16.0)	0.02[a]

DOS = day of surgery, POD = post-operative day. [a] Mann Whitney *U* test. Data are presented as median (IQR)

Table 17. Post-operative opiate consumption

6.4.2 Inflammatory Response To Surgery

Pro-inflammatory cytokines assessed were IL1β, IL6, IL8 and TNFα. One anti-inflammatory cytokine (IL10) was assessed. HMGB1, a principle mediator of the inflammatory response, was also assessed.

The pro-inflammatory mediators were all raised on POD1 and 3 compared to baseline in both groups except for IL1β (Table 18). All mediators were raised in the CWI group compared with the TEA group on POD 1 but not significantly so (Table 19). The levels then reduced by POD 3 but had not returned to baseline at this point as POD 3 cytokine levels remained significantly raised compared with the pre-operative levels (Table 18). Two way RM ANOVA analysis of all three levels was performed to compare all measurements between groups. No significant difference was observed between any of the mediators assessed (Figure 15).

	TEA (n=44)	*P* value *	CWI (n=47)	*P* value*	*P* value
IL1β pg/mL					
Day 0	0.7±1.0		1.2±4.0		
Day 1	0.8±0.7	0.59[a]	2.7±13.5	0.3[a]	
Day 3	0.9±0.7	0.08[a]	1.0±0.8	0.66[a]	0.37[b]
IL6 pg/mL					
Day 0	2.7±2.5		4.5±7.8		
Day 1	165.6±278.4	0.0003[a]	190.1±219.7	<0.0001[a]	
Day 3	54.2±100.3	0.001[a]	53.7±72.6	<0.0001[a]	0.67[b]
IL8 pg/mL					
Day 0	2.3±2.4		2.8±3.6		
Day 1	12.8±12.0	<0.0001[a]	15.0±13.1	<0.0001[a]	
Day 3	8.0±7.6	<0.0001[a]	10.6±12.2	<0.0001[a]	0.2[b]
TNFα pg/mL					
Day 0	4.0±3.8		3.8±3.8		
Day 1	6.5±6.5	0.003[a]	6.0±6.0	0.0003[a]	
Day 3	6.2±4.2	0.001[a]	5.8±3.6	0.003[a]	0.68[b]
IL10 pg/mL					
Day 0	9.8±10.8		13.8±21.6		
Day 1	96.2±125.0	<0.0001[a]	169.2±599.7	<0.08[a]	
Day 3	31.3±28.1	<0.0001[a]	34.8±27.2	<0.0001[a]	0.4[b]
HMGB1 ng/mL					
Day 0	1.1±1.9		0.6±0.9		
Day 1	6.2±4.1	<0.0001[a]	8.4±10.5	<0.0001[a]	
Day 3	4.6±4.0	<0.0001[a]	3.9±4.0	<0.0001[a]	0.59[b]

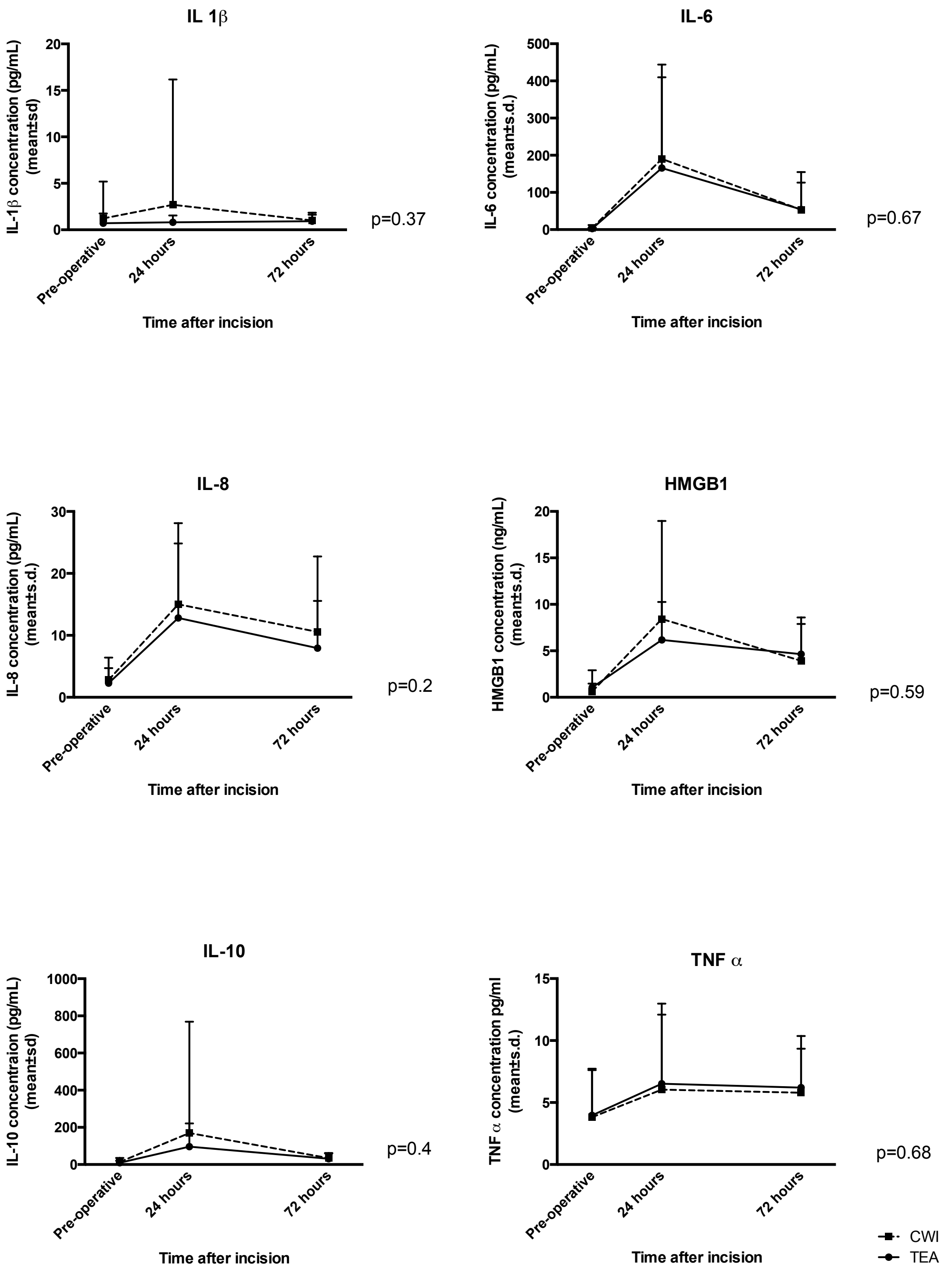
[a] paired t-test, [b] two way repeated measures ANOVA. * versus baseline. Data are presented as mean±s.d.

Table 18. Markers of the inflammatory response

	TEA (n=44)	CWI (n=47)	*P* value
IL10 (pg/mL)	96.2±125.0	169.2±599.7	0.43[a]
IL1β (pg/mL)	0.8±0.7	2.7±13.5	0.36[a]
IL6 (pg/mL)	165.6±278.4	190.1±219.7	0.64[a]
IL8 (pg/mL)	12.8±12.0	15.0±13.1	0.41[a]
TNFα (pg/mL)	6.5±6.5	6.0±6.0	0.72[a]
HMGB1 (ng/mL)	6.2±4.1	8.4±10.5	0.19[a]

[a] unpaired t-test. Data are presented as mean±s.d.

Table 19. Comparison of post-operative day one mediator levels



Mean±sd inflammatory marker levels. No significant difference was observed between groups and levels of inflammatory mediators after testing with two way RM ANOVA.

Figure 15. Pre- and post-operative inflammatory mediators.

6.4.3 Haemodynamic Response

Patients received intra-operative IV crystalloid according to protocol and at the discretion of the anaesthetist. There were no significant differences in patterns of fluid administration other than significantly greater IV crystalloid being administered to the epidural group (1618 mls IQR 1277-1908) compared to CWI (1450 mls IQR 1200-1572) on DOS (p=0.02). Six patients in the TEA group and eight in the CWI group received a blood transfusion (p=0.72). There was a greater volume of crystalloid instilled in the CWI group (1315 mls IQR 320-1825) compared with TEA (779 mls IQR 285-2007) on POD 2 however this did not reach statistical significance (p=0.45) (Table 20).

No difference was observed in CVP change during transection with a mean drop of 6.0±2.7 mmHg and 6.2±3.0 mmHg in the TEA and CWI groups respectively during transection (p=0.65). Minimum mean intra-operative CVP observed was also similar in both groups (TEA 5.7±3.4 mmHg; CWI 5.7±2.7; p=0.99). Minimum MAP was however significantly lower in the TEA group (57.7±5.6 mmHg) compared with the CWI group (61.2 ±7.8 mmHg) (p=0.01) (Table 21).

	TEA (n=44)	CWI (n=49)	*P* value
Intra-operative			
Colloid	850 (0-1500)	1000 (600-2000)	0.55[a]
Crystalloid	1000 (575-2000)	1500 (100-2125)	0.15[a]
RCC transfusion	4 (9.1)	4 (8.2)	1.0[b]
DOS			
Colloid	250 (0-750)	250 (0-750)	0.87[a]
Crystalloid	1618 (1277-1908)	1450 (1200-1572)	0.02[a]
RCC transfusion	4 (9.1)	4 (8.2)	1.0[b]
POD 1			
Colloid	250 (0-500)	0 (0-500)	0.09[a]
Crystalloid	2100 (1380-2637)	1970 (1150-2314)	0.20[a]
RCC transfusion	0 (0)	4 (8.2)	0.12[b]
POD 2			
Colloid	0 (0-0)	0 (0-0)	0.49[a]
Crystalloid	779 (285-2007)	1315 (320-1825)	0.45[a]
RCC transfusion	2 (4.5)	1 (2.0)	0.60[b]

Measurements are in millilitres unless otherwise stated. [a] Mann Whitney *U* test, [b]Fishers exact test. Data are presented as median (IQR) or n (%).

Table 20. Peri-operative fluid administration

	TEA (n=43)	CWI (n=48)	P value
Highest CVP	11.6±4.6	11.9±3.4	0.75[a]
Lowest CVP	5.7±3.4	5.7±2.7	0.99[a]
Minimum MAP	57.7±5.6	61.2 ±7.8	0.01[a]
CVP during transection	7.6±3.7	7.1±3.1	0.53[a]
CVP reduction	6.0±2.7	6.2±3.0	0.65[a]

CVP = central venous pressure, MAP = mean arterial pressure. Units are mmHg,
[a] unpaired t-test. Data are presented as mean±s.d.

Table 21. Intra-operative haemodynamic changes

6.5 Discussion

This trial has shown that CWI offers an advantage in recovery time compared with epidural. No difference in resting or dynamic pain scores was observed. The inflammatory response was not noted to be attenuated to a greater degree in the TEA group and no advantage in terms of CVP reduction or EBL was observed.

Epidurals are often advocated as important for enhanced recovery protocols due to the original perception of their role in improvement in recovery. [36] It has often been considered that a minimisation of pain leads to increased mobility, improved return of bowel function and prevention of complications. However this does not seem to translate to reduced LOS. A large meta-analysis showed no reduction in LOS with epidurals compared to systemic opiates in a heterogeneous sample of recovery protocols. [163] Furthermore a recent meta-analysis looking at abdominal surgery [204] has shown that no difference in LOS was observed when all studies comparing epidural to either systemic opiates or CWI within an enhanced recovery protocol were compared. Moreover, two previous studies have shown epidural to prolong LOS within an enhanced recovery protocol after liver resection when compared with CWI [135] or intrathecal morphine injection. [134] Epidural is often advocated as an optimum analgesic modality following enhanced recovery protocols for liver resection. [88, 122, 126, 128] The current study represents the largest RCT comparing analgesic modalities following liver surgery and adds weight to the evidence that epidurals can actually prolong post-operative recovery time.

What has not been explored previously is why this might be. In this trial no significant differences were observed in recovery milestones and overall complication rates were not significantly different. However, TEA in this study was associated with a significantly increased HDU stay. Also significantly increased levels of hypotension were observed in the epidural group with ten patients requiring vasopressor infusion to maintain their systolic blood pressure above 90mmHg during their HDU admission. This will inevitably slow down post-operative recovery and prevents discharge from a high dependency environment.

Higher rates of opiate consumption were observed in the CWI group on the day of surgery and POD1. However, surprisingly, opiate consumption rates were higher in the epidural group on POD2 (when the epidural was taken down) and POD 3 when both groups were prescribed oral analgesics. This may provide a further explanation as to why recovery time was prolonged in the epidural group. Increased opiate consumption after the epidural has been removed adds an obstacle to recovery and discharge that the CWI group did not have. Highest opiate consumption in the CWI group was on the day of surgery and this dropped thereafter, and as such, once the CWI was removed patients were able to move more seamlessly towards oral analgesics and discharge.

Epidurals have historically been associated with improvements in certain complications such as pulmonary and cardiac complications following surgery. [167, 168] However this evidence base is increasingly out-dated due to the lack of trials including enhanced recovery protocols, comparisons of epidurals and systemic opiates only and heterogeneity of operation specialty and procedure. A more recent meta-analysis [204] compared epidurals versus all other analgesic modalities (PCA and CWI) in patients who all underwent enhanced recovery protocols following open abdominal surgery and no difference in complication rates was observed. This evidence is in agreement with the current trial that did not show a significant difference in overall morbidity rate, the inference being that a well constructed post-operative enhanced recovery protocol should mitigate against preventable complications by providing optimum care to minimise complications and that an epidural is not mandated in order to achieve this.

The overall complication rate of the current study is reasonably high when compared with current reported morbidity rates following liver resection [73] and reflects the prospective nature of the observation and reporting of all minor complications.

Epidurals are traditionally associated with superior pain control however no significant difference was observed in this study. Epidurals have consistently been shown to provide superior pain scores when compared to IV opiates. [45] However when compared to CWI the superiority has been blunted to an extent. A meta-analysis comparing epidurals to CWI showed no significant difference in analgesic benefit following abdominal surgery. [162] This meta-analysis was limited by the heterogeneity of incisions and operations and included mostly lower abdominal or midline laparotomy procedures, the incisions of which do not incorporate a subcostal element. Subcostal incision involves dermatomes up to T6 and require blockade of the transversus abdominis plane as well as the rectus sheath to ensure adequate analgesia. Therefore the results of a review assessing predominantly midline incisions are not directly translatable to a Makuuchi incision. A review of analgesia techniques following specifically liver surgery showed the improved analgesia scores after liver resection of CWI compared to controls [198] however only one previous RCT, also from our group, has compared epidural with CWI follow liver resection [135] and superior scores were noted in the epidural group, in accordance with similar trials comparing epidurals to alternative analgesic regimens [151, 155] after liver resection.

In the first LIVER trial [135] the early pain scores were notably higher in the CWI group compared with the epidural group. In an effort to mitigate against this we incorporated a higher volume TAP and rectus sheath block in an attempt to improve pain scores in the immediate post-operative period. This seemed to have an effect as both early pain scores and overall pain scores were comparable to TEA in the current trial. Dynamic pain scores were observed to be superior in the epidural group although not significantly, however if the two way ANOVA RM was repeated with scores to POD 2 only then a significantly higher pain scores was observed in the CWI group, which suggests a potential for the epidurals to still provide relatively better dynamic analgesia although the mean pain scores were all in the “mild” category and the overall difference is not thought to represent a significant hindrance to clinical recovery as is shown by the equipoise in recovery parameters.

A potential argument for the use of epidurals over alternative analgesic modalities is the increased attenuation of the inflammatory response by epidurals. [36] However a significant rise in inflammatory markers was observed in both groups (except Il1β) thus implying no advantage in this respect in either group. Higher levels were seen in the CWI groups of the individual inflammatory markers on POD1, although this was not significant with either two way RM ANOVA or comparison of the two independent levels.

Both epidural and CWI have been shown to attenuate the inflammatory response when compared to controls in a variety of abdominal surgical settings [200, 201, 205-207] with a meta-analysis showing an association between attenuation of the inflammatory response and clinical outcome [116] and a potential argument for the use of TEA after abdominal surgery is the effect of TEA on the inflammatory response to surgery. [36] We have therefore shown that this is not necessarily the case. It is likely that CWI exhibits its own inflammatory response attenuation via the instillation of local anaesthetic to the afferent nerve fibres.

A multitude of inflammatory mediators have been investigated in the past. More recently HMGB1 has emerged as a principle mediator of the inflammatory response, and moreover has been closely associated with clinical outcome in a variety of settings. [19, 21, 22, 27] Its inhibition by local anaesthetics has also been postulated in an in-vitro study [208] thus making this a particularly interesting mediator to quantify in the two study groups.

The third area of investigation of this trial was the effect of either TEA or CWI on intra-operative transection. No difference was observed in terms of CVP during transection between the CWI and TEA groups. The evidence assessing CVP reduction during liver surgery is lacking large RCTs comparing methods. No trial has assessed the effect of epidural alone on this care component.

Epidural has been included in CVP lowering protocols along with IV fluid restriction, GTN, furosemide and patient positioning. These trials have shown significant improvements in EBL following CVP reduction by these methods [175, 178, 179] when CVP was reduced from over five mmHg to below five mmHg however the impact and importance of TEA in these protocols is not clear due to the multi-modal nature of the intervention. Therefore in light of the findings of our recent trial, epidural may not offer an advantage in terms of CVP reduction and should not be considered mandatory to achieve low CVP.

A retrospective study [141] showed a significantly increased volume of colloid and total fluids administered intra-operatively and post-operatively in patients who received epidurals when compared to those not receiving epidural. Excessive fluid administration is associated with increased complication rates and increased post-operative LOS. [209, 210] One previous large retrospective analysis of TEA versus systemic opiates following liver resection also found increased RCC transfusion rates and increased intra-operative colloid in patients receiving epidural. [157]

The findings of the current study conflict with these previous studies in that we have not shown a significantly deleterious impact of epidural on EBL, transfusion rates or intra-operative fluid administration. In this study, intra-operative MAP was significantly reduced in the TEA group, and vasopressor infusions were required in a significant proportion of patients receiving TEA. This illustrates the effect of epidural on the sympathetic nervous system, which is implied as the mechanism of TEA associated hypotension and fluid overload. However, with the prospective implementation of an appropriately directed protocol in terms of intra-operative and post-operative fluid administration excessive administration of IV fluids and the adverse outcomes associated with IV fluid overload can be prevented.

The results of the trial need to be considered in the context of its limitations. Firstly it was decided to run the trial as unblinded, which could be considered as a potential introduction of bias in the trial. The principle reason for running the trial in this way was to allow a realistic assessment of the advantages and disadvantages of the two analgesic methods. Blinding in this type of trial, as was done in our earlier LIVER study, [135] involves a sham procedure, either epidural or CWI. This is not necessarily effective in providing genuine blinding. Moreover blinding can alter normal usage of the analgesic technique, thus providing an untranslatable picture of each modality. The introduction of purely objective measures such as complication rate, length of stay and cytokine response allows for minimisation of any bias introduction.

Secondly, the timing of the assessment of the inflammatory mediators may potentially be misleading. A true peak is likely immediately post-operatively, and we are unable to categorically exclude a difference in early peaks. However a 24 hour assessment is reasonable and likely to capture a sustained difference in cytokine release. The 24 hour levels are also more important in this trial as the CWI was not inserted until the end of the procedure and so would likely have had no effect on cytokine response by the immediate post-operative time point.

The majority of the secondary outcomes assessed in this trial did not show statistically significant differences. It is appreciated that the opportunity for a type two error is possible in this situation as the original powering of the study was performed to assess a difference in recovery time. However in a study of this size it is reasonable to infer that when no significant difference was observed, no obvious advantage of one modality over the other is evident.

6.6 Summary

TEA did not show an advantage over CWI after liver resection. CWI patients showed improved recovery times with no difference in pain scores or complication rates. No advantage was shown by TEA in terms of the inflammatory response or intra-operative CVP. In the era of enhanced recovery surgery epidurals need no longer be considered mandatory to achieve optimum outcomes when an appropriate post-operative protocol is implemented. CWI could be considered as a first line analgesic method after liver resection.

6.7 Research Requirements Identified

During the conduct of this trial it was observed that adherence to the ERAS protocol was variable and ensuring implementation of the ERAS care components often challenging. This raised questions regarding the obstacles preventing adherence and implementation. The following chapter describes a study investigating these issues.

7 Attitudes Of Patients And Care Providers To Enhanced Recovery After Surgery Programmes Following Major Abdominal Surgery.

7.1 Summary

Enhanced Recovery After Surgery (ERAS) is a well-established pathway of peri-operative care in surgery in an increasing number of specialties. In order to implement protocols and maintain high levels of compliance, continued support from care providers and patients is vital. This survey aimed to assess the perceptions of care providers and patients of the relevance and importance of the ERAS targets and strategies. Pre-operative and post-operative surveys were completed by patients undergoing major hepatic, colorectal or oesophagogastric surgery in three major centres in Scotland, Norway and The Netherlands. Anonymous web-based and paper surveys were also sent to surgeons, anaesthetists and nurses experienced in delivering enhanced recovery protocols. Each questionnaire asked the responder to rate from 0-10 a selection of enhanced recovery targets and strategies in terms of perceived importance. 109 patients and 57 care providers completed the pre-operative survey. Overall both patients and care providers rated the majority of items as important and supported ERAS principles. Freedom from nausea (median 10, IQR 8-10) and pain at rest (median 10, IQR 8-10) were the care components rated highest by both patients and care providers. Early return of bowel function (median 7, IQR 5-8) and avoiding pre-anaesthetic sedation (median 6, IQR 3.75-8) were scored the lowest by care providers. In conclusion, ERAS principles are supported by both

patients and care providers. This is important when attempting to implement and maintain an ERAS programme. Controversies still remain regarding the relative importance of individual ERAS components.

7.2 Introduction

Enhanced Recovery After Surgery (ERAS) protocols have become established practice in patients undergoing major resectional surgery. [148] The original success in colorectal cancer resections has been followed by its application in other fields including surgery for breast [31] and oesophagogastric cancer. [30]

The main measurements of success of enhanced recovery programmes have been the reduced peri-operative morbidity and reduced post-operative length of hospital stay. [58]

However, deviation from ERAS protocols is commonly reported and this is associated with prolonged length of stay. [57] As well as this, barriers to implementing fast track protocols are commonly encountered, [211] with reluctance by care providers to accept care strategies that differ from personally preferred practice being a major factor. [212]

Patient acceptance is vital when attempting to achieve successful results with enhanced recovery approaches. Moreover, care provider support for enhanced recovery care components is critical in order to successfully implement post-operative care pathways relying on multi-disciplinary team input. [212]

It is therefore necessary to explore the views of both patients and care providers regarding their personal priorities pertaining to recovery and the favoured strategies used to achieve these aims. This information is crucial to determine whether enhanced recovery programmes have the correct patient-centred approach to post-operative recovery and the appropriate support of care providers in order to optimise implementation.

This survey of patients and healthcare professionals was performed to investigate these views and provide clarification of patient and clinician care priorities.

7.3 Methods

After satisfying the requirements of the respective institutional review boards a survey was carried out by the investigators across three Northern-European centres – Edinburgh (UK), Tromsø (Norway) and Maastricht (The Netherlands). These institutions are high volume tertiary referral centres experienced in delivering ERAS protocols in hepatic, colorectal and oesophagogastric surgery.

The authors developed a questionnaire for the purpose of this survey. The questionnaire aimed to quantify the responders' perception of the importance of individual enhanced recovery outcomes and strategies.

The questionnaire was divided into two sections. The first assessed individual targets to be achieved during recovery following abdominal surgery (questions 1-8). These incorporated the major domains of ERAS principles [36] – pain control, gut function restitution, mobility, overall function and hospital discharge. These items were identical for questionnaires given to care providers and patients. The second section assessed strategies on how to achieve the recovery targets specified in section one. The items chosen reflected common strategies utilised in enhanced recovery protocols as advocated by the best available evidence. [36] The patients were given four questions and the care providers were given 13 different questions relating to strategy.

The questions were formulated in English and then translated into Dutch and Norwegian. A further separate translation of the questions back into English was performed to ensure accurate translation. The questionnaire was trialled locally to ensure satisfactory comprehension by responders.

Responders in each institution were given a standardised verbal explanation as to what the survey entailed and advice regarding how to complete the survey. They were asked to rate each component from 0-10 on an 11 point Likert scale, depending on how important they believed each component was. The scale used indicator statements of “not important” and “very important” at the relevant extremes of the scale to assist with scoring. An example was performed by the investigator with each responder to ensure comprehension and then the patient was left to complete the questionnaire unaided.

The survey was conducted between November 2012 and November 2013. Consecutive patients scheduled for hepatic, colorectal or oesophagogastric surgery were approached and asked to complete a questionnaire on the morning of their operation or during out-patient work-up prior to surgery. This was repeated following surgery when the patient returned to the out-patient clinic two to four weeks later. Due to the exploratory nature of this survey a sample size calculation was not performed. However, it was determined that each centre would recruit a minimum of 35 patients to complete the questionnaire before and after surgery. The exclusion criteria were an inability to comprehend the survey or unwillingness to participate.

A random sample of senior surgeons, anaesthetists and nurses working in the centres involved in the care of these patient groups were also surveyed. This questionnaire was administered using an internet-based tool (Survey Monkey, Palo Alto, US; for Tromsø: Questback®) or an identical paper-based version depending on convenience.

Results were collated and analysed with Excel 2010 (Microsoft Corp., Seattle, US) and presented as median and interquartile range (IQR). Statistical analysis was performed with R (R Foundation for Statistical Computing, version 2.9.0). Discrete variables were compared with Fishers exact or Chi-square tests where appropriate. Continuous data were assessed with Mann Whitney *U* test. Scores between care-provider specialties were compared with the Kruskal-Wallis test. Statistically significant differences between pre-operative and post-operative patient scores were assessed by the Wilcoxon signed-rank test. Significance tests were adjusted for multiple comparisons using the Bonferroni correction.

As we had devised a novel questionnaire, we undertook validation of the instrument. High internal consistency would be expected if responders scored items within the two sections (outcomes and strategies) similarly. Internal consistency of questionnaire components was determined with Cronbach's alpha including 95%

bootstrapped confidence intervals. Cronbach's alpha increases with greater inter-correlation of questionnaire components and can be interpreted as an overall measure of internal consistency.

Exploratory factor analysis was performed to assess the underlying structure of the questionnaire. The questionnaire had two sections, "attitudes to outcomes" and "attitudes to strategies". It might be expected that answers to questions assessing each of these domains would be correlated. The factor analysis examined whether questions might cluster into alternative groupings representing different underlying concepts. Principal component analysis was performed and eigenvalues generated (representing the proportion of the variance explained by each additional new factor). Eigenvalues were plotted on a scree plot and a cut-off determined. Maximum likelihood factor analysis was then performed with varimax rotation retaining the appropriate number of factors.

7.4 Results

7.4.1 Demographics

One hundred and nine patients scheduled for major abdominal surgery were approached and participated in the pre-operative survey. Patients were included from all three centres – Edinburgh (n=38), Tromsø (n= 36) and Maastricht (n=35). The demographic and clinical characteristics of the patients are shown in table 22 and 23. Eighty-one per cent (88/109) of patients responded to the follow-up survey administered after surgery. The post-operative non-responders had higher ICU admission rates (29% vs 8%, $p<0.05$) and a higher proportion of oesophagogastric resections (24% vs 7% $p<0.05$) performed when compared to the patients who completed the post-operative questionnaire. Sixteen anaesthetists (median age 51, IQR 42-61), 23 nurses (median age 35, IQR 29-38) and 18 surgeons (median age 52, IQR 43-59) were surveyed from across all three sites.

	Tromsø (n=36)	Edinburgh (n=38)	Maastricht (n=35)	Total (n=109)
Age (years)	66 (35-93)	63.5 (32-79)	65 (36-85)	64 (35-93)
Sex				
Male	25 (69.4)	25 (65.8)	20 (57.1)	70 (64.2)
Female	11(30.6)	13 (34.2)	15 (42.9)	39 (35.8)
ASA				
I	2 (5.6)	4 (10.5)	5 (14.3)	11(10.1)
II	25 (69.4)	28 (73.7)	17 (48.6)	70 (64.2)
III	8 (22.2)	6 (15.8)	13 (37.1)	27 (24.8)
IV	1 (2.8)	-	-	1 (0.9)
Previous hospital stay				
Yes	27 (75.0)	32 (84.2)	32 (91.4)	91 (83.5)
No	9 (25.0)	6 (15.8)	3 (8.6)	18 (16.5)
Employment status				
Employed	12 (33.3)	16 (42.1)	7 (20.0)	35 (32.1)
Retired	22 (61.1)	18 (47.4)	22 (62.9)	62 (56.9)
Unemployed	2 (5.6)	4 (10.5)	6 (17.1)	12 (11.0)

Data are presented as median (range) or n (%)

Table 22. Patient characteristics

	Tromsø (n=36)	Edinburgh (n=38)	Maastricht (n=35)	Total (n=109)
Resection performed				
Liver	2 (5.6)	38 (100.0)	20 (57.1)	60 (55.0)
Colorectal/small bowel	19 (52.8)	-	15 (42.9)	34 (31.2)
Oesophagogastric	8 (22.2)	-	-	8 (7.3)
Pancreatic	2 (5.6)	-	-	2 (1.8)
Other	5 (13.9)	-	-	5 (4.6)
Length of Stay (days)	5 (3-96)	7 (4-38)	7 (3-30)	7 (3-96)
Complications				
Yes	11 (30.6)	17 (44.7)	14 (40.0)	42 (38.5)
No	25 (69.4)	21 (55.3)	21 (60.0)	67 (61.5)
ICU admission				
Yes	6 (16.7)	2 (5.3)	2 (5.7)	10 (9.2)
No	30 (83.3)	36 (94.7)	33 (94.3)	99 (90.8)
Readmission				
Yes	7 (19.4)	4 (10.5)	6 (17.1)	17 (15.6)
No	29 (80.6)	34 (89.5)	29 (82.9)	92 (84.4)
Pathology				
CLM	2 (5.6)	25 (65.8)	19 (54.3)	46 (42.2)
Cholangiocarcinoma	-	2 (5.3)	-	2 (1.8)
HCC	-	5 (13.2)	-	5 (4.6)
Other metastasis	4 (11.1)	3 (7.9)	-	7 (6.4)
Primary adenocarcinoma	28 (77.8)	-	16 (45.7)	44 (40.4)
Benign	2 (5.6)	3 (7.9)	-	5 (4.6)

CLM – Colorectal liver metastasis, HCC – Hepatocellular carcinoma. Data are presented as median (range) or n (%)

Table 23. Clinical and pathological outcomes

7.4.2 Questionnaire Validation

The inter-correlation of items within the two parts of the questionnaire was good suggesting internal consistency: care providers outcomes α=0.89 (IQR 0.83-0.93), care providers strategies α=0.83 (IQR 0.75-0.89); patients outcomes α=0.96 (IQR 0.79-1.00) and patient strategies α= 1.00 (IQR 0.34-1.00).

An exploratory factor analysis was performed on the questionnaire components for care providers to assess underlying structure. Three factors were shown to provide an adequate fit. Items relating mainly to enhanced recovery outcomes loaded onto one factor and those relating to individual strategies to a second. Interestingly, four items (two outcomes and two strategies) – "to be completely free from pain at rest", "to be completely free from pain on movement", "using epidural analgesia for 48 hours" and "optimising fluid balance" – loaded onto a third factor, suggesting additional structure not appreciated in the original questionnaire design (Figure 16).

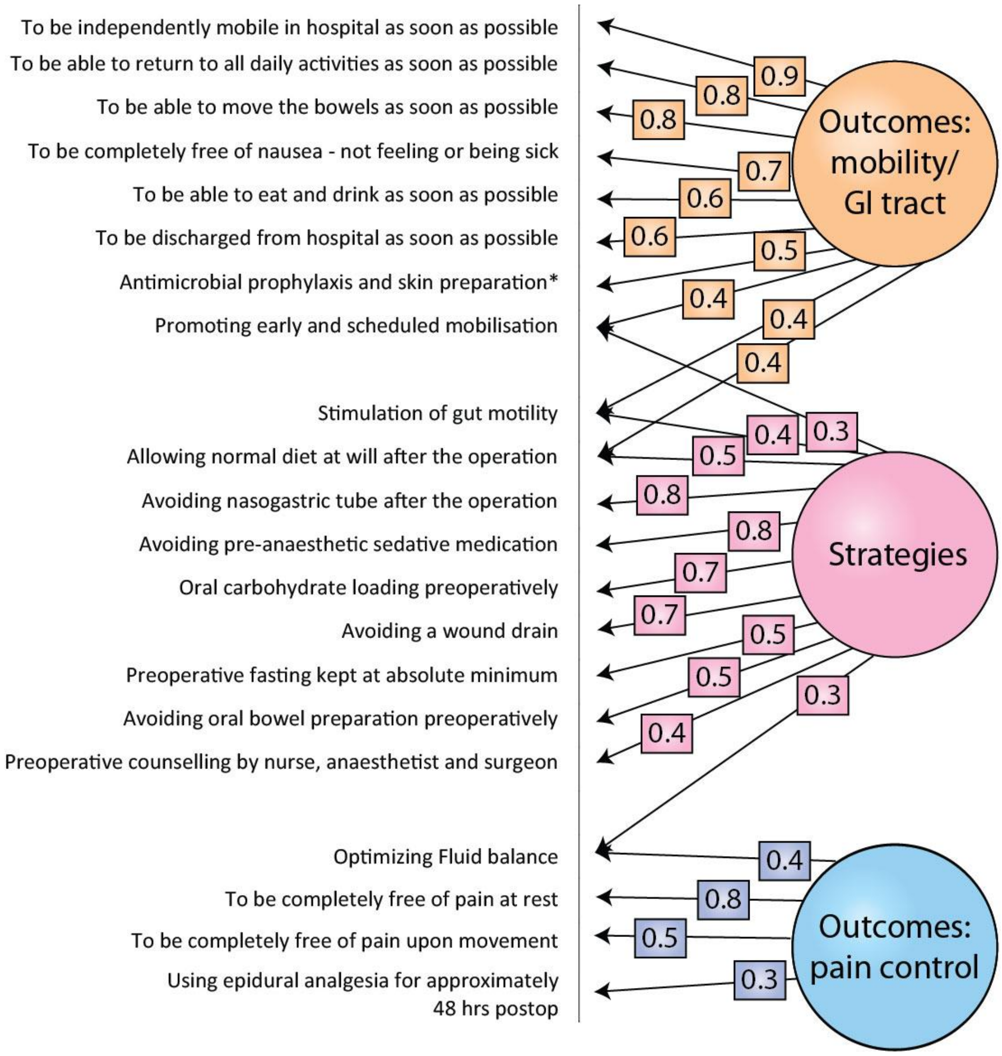


Figure 16. Factor analysis of strategies and outcomes

*Strategy factor

7.4.3 Patient Outcomes

The overall scores were high with the lowest median score being 8/10. The pre-operative impressions of patients awaiting surgery were unchanged by the subsequent surgery, with no significant differences observed between pre- and post-operative scores (i.e $p>0.05$ for each comparison following adjustment for multiple comparisons), as determined by the Wilcoxon signed-rank tests (Figure 17).

Patients scored freedom from nausea (median 10 IQR 8-10) and freedom from pain at rest (median 10 IQR 8-10) as the two most important factors. Achieving independent mobility was also scored highly by patients (median 9, IQR 8-10). Early discharge (median 9, IQR 6.5-10) and early return of bowel movements (median 9, IQR 7.25-10) received the lowest scores when taking the IQR into account (Figure 17).

7.4.4 Patient Strategy

Patients highlighted pre-operative counselling (median 10, IQR 8.75-10) and avoiding infection in hospital (median 10, IQR 9-10) as a priority in achieving recovery (Figure 17).

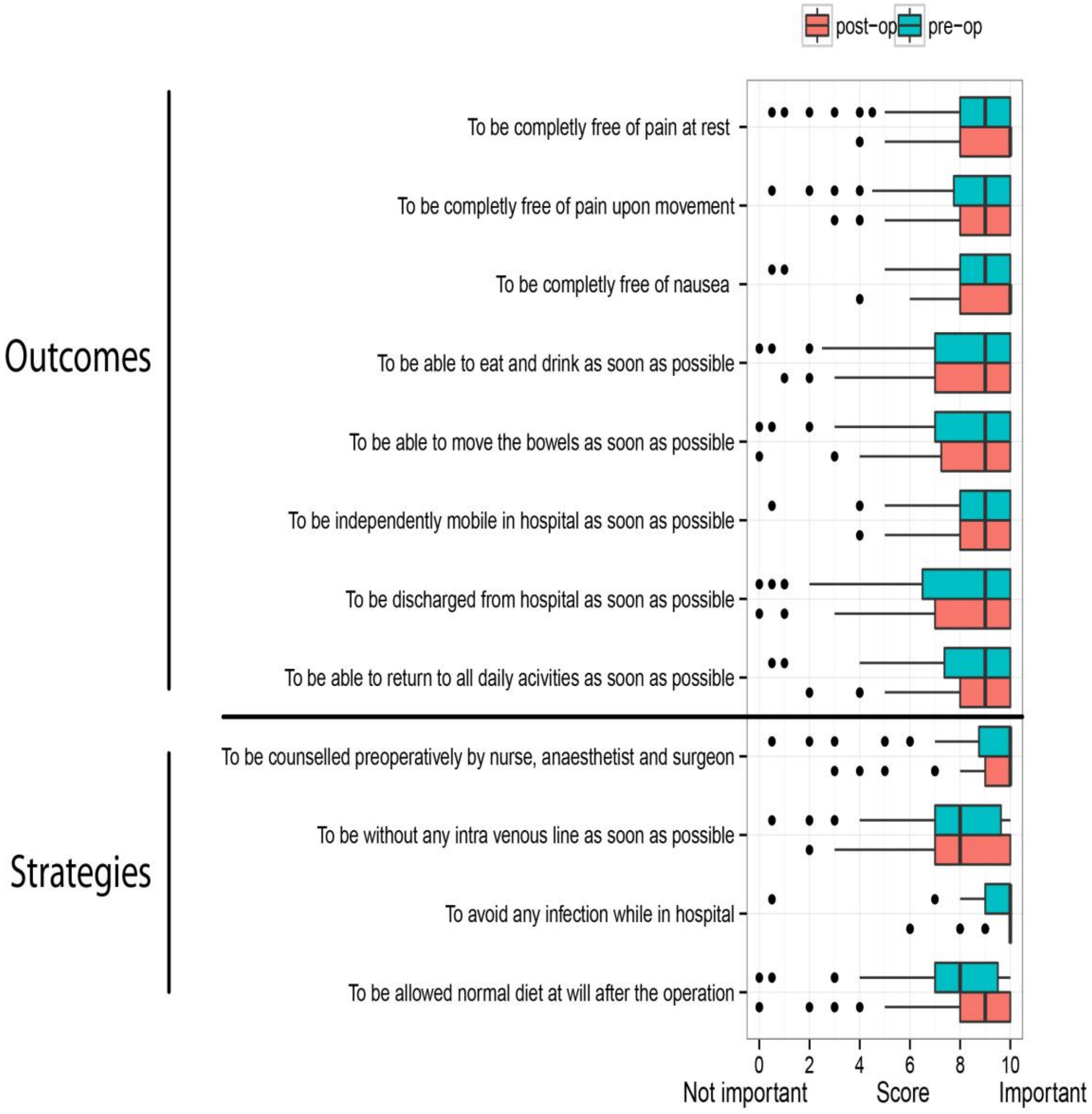


Figure 17. Patient ratings of ERAS outcomes and strategies

7.4.5 Care Provider Outcomes

Outcomes were in general scored highly by the care providers with all items being scored with a median of 7/10 or higher. The outcomes scored as most important by care providers were control of nausea (median 9, IQR 8-10) and being free from pain at rest (median 9, IQR 8-10) (Figure 18).

Being able to move the bowels as soon as possible was scored the lowest (median 7, IQR 5-8) by the care providers. Also being discharged from hospital as soon as possible received lower scores (median 8, IQR 6-9) as did returning to daily activities as soon as possible (median 8, IQR 5.5-9) (Figure 18).

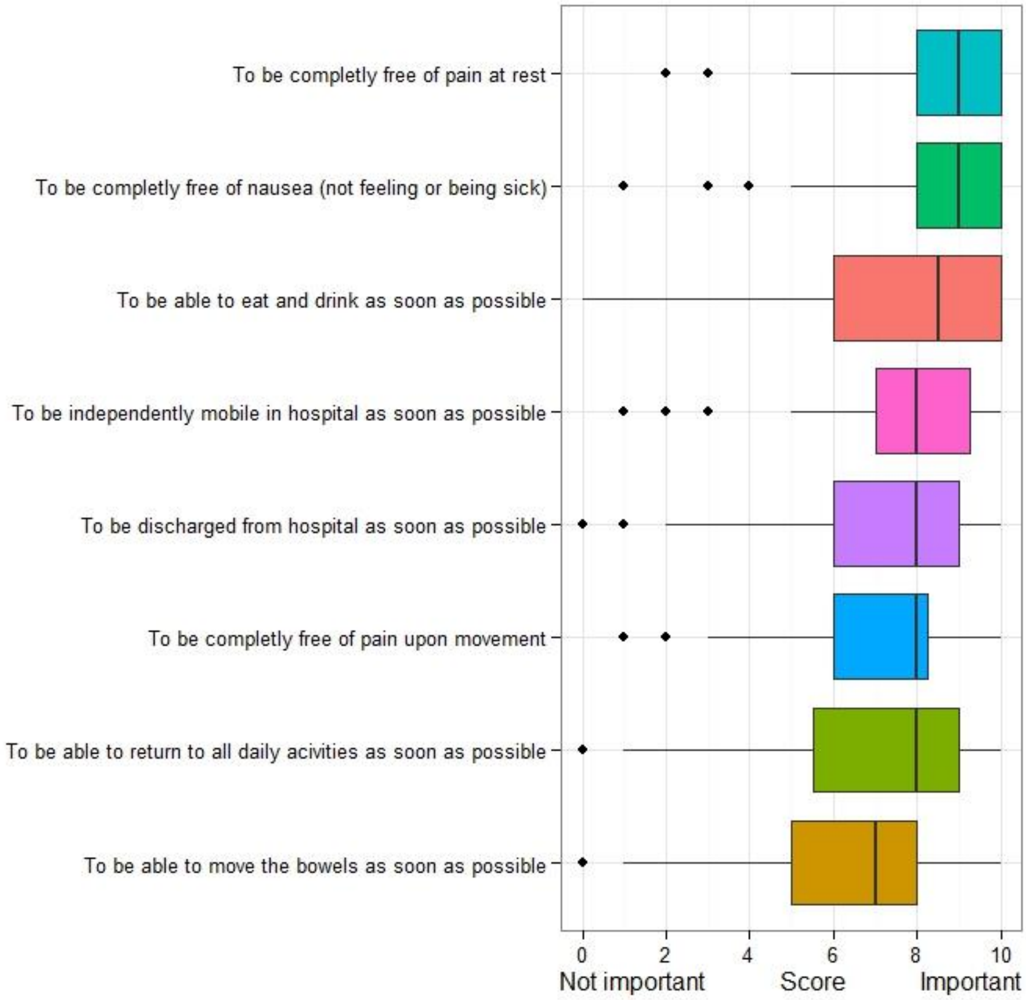


Figure 18. Care provider ratings of ERAS outcomes

7.4.6 Care Provider Strategy

The range of scores was more varied in this area of responses. The highest rated items of care strategy as scored by the care providers were: provision of pre-operative counselling (median 10, IQR 9-10); promotion of early mobilisation (median 9.5, IQR 9-10) and optimisation of IV fluid administration (median 9, IQR 8-10) (Figure 19).

Avoiding wound drains (median 7, IQR 4.5-8.25), avoiding bowel preparation (median 7, IQR 4-8) and avoiding anaesthetic pre-medication (median 6, IQR 3.75-8) were scored the lowest (Figure 19).

Sub-group analyses using the Kruskal Wallis test were performed to compare scores of each item by individual specialties of care providers and between the care provider nationalities. Following adjustment for multiple comparisons no significant differences between care provider specialty nor nationality scores were observed.

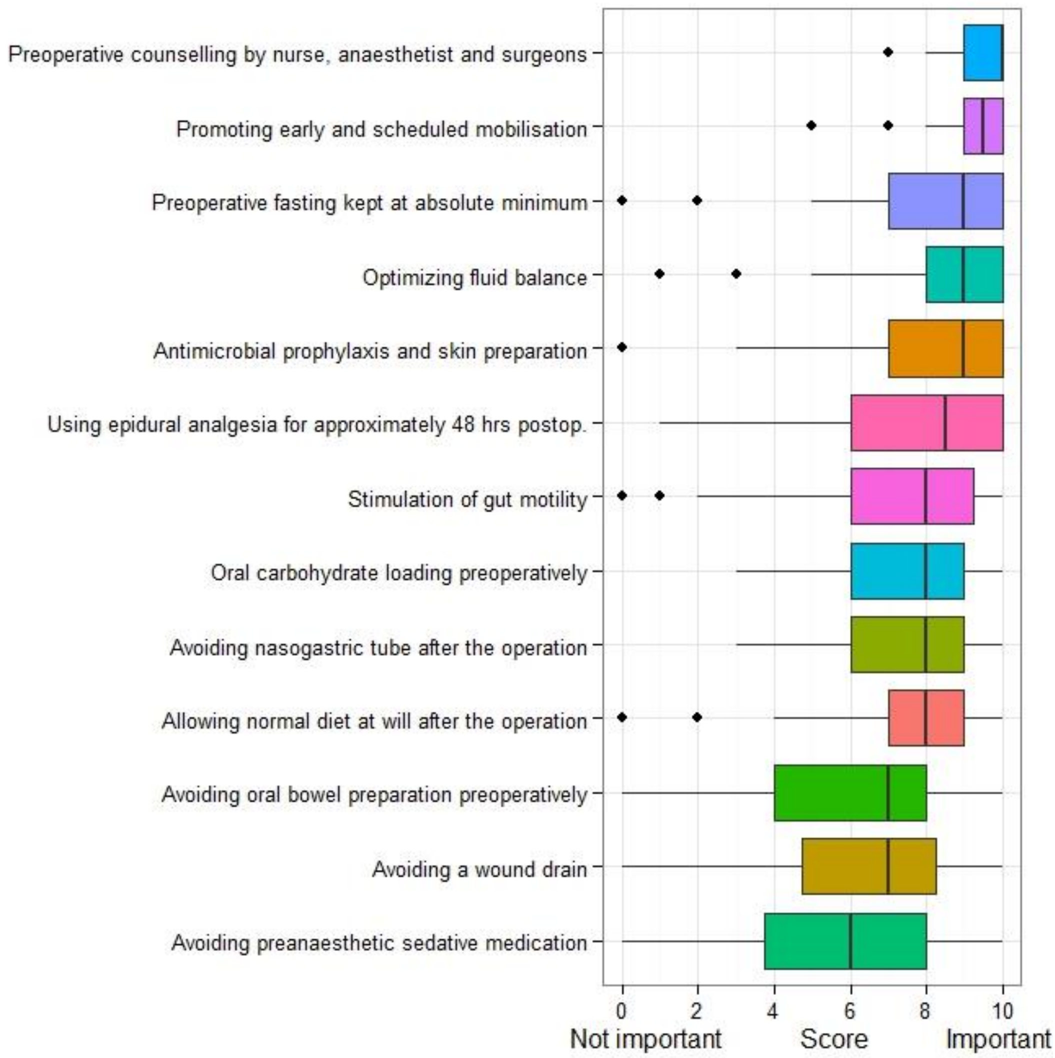


Figure 19. Care provider ratings of ERAS strategies

7.5 Discussion

This study investigated the opinions and perceptions of both providers and receivers of enhanced recovery protocols following major abdominal resectional surgery in three European countries. It is the first study of its kind.

The novel questionnaire was designed for the purposes of this study and validated successfully. Good internal consistency was observed and the factor analysis performed revealed a logical separation of items into ERAS outcomes and strategies. This suggests consistent and distinct scoring patterns within these groups of questionnaire items indicating satisfactory validity of the items selected. These results also reflect the consistently high scores throughout the survey and overall support for the outcomes and strategies used in the questionnaire.

The post-operative response rate of eighty-one per cent was satisfactory. The non-responders underwent a greater proportion of oesophagogastric resections and fewer hepatic resections than those who completed the post-operative questionnaire. Although the ICU admission rate was higher in this sub-group, readmission and complication rates remained unchanged. This likely reflects a tendency for oesophagogastric resections to be managed initially in ICU routinely, which was not the case for hepatic resections, and their absence was not thought to adversely influence the post-operative responses observed.

Patients attributed high importance to all of the ERAS aims and strategies asked of them. This represents concordance between patients' beliefs and current recommendations by ERAS experts and this finding should be used to encourage and develop ERAS implementation.

Previous studies have also shown that compliance with ERAS protocols can be compromised resulting in deviation from care plans. [57] However, our results show that patient support for the ERAS process is high and therefore we suggest it is unlikely that lack of patient acceptance is the main cause of deviation from protocols. Moreover, we did not show a difference in patient opinion pre- and post-operatively, suggesting that patient support for such care plans does not change even after having gained experience of the care principles.

A qualitative assessment of patient experience following ERAS surgery [213] found that decreased satisfaction was reported in a subgroup of patients who suffered a complication following discharge. Our survey sample included patients who suffered complications at rates that would be expected from these types of surgery. This did not cause significantly different pre-operative and post-operative patient scoring and so we do not concur with the view that the development of a complication negatively impacts on patients' support for the ERAS principles.

The clinicians also scored highly for the majority of targets and strategies and good inter-specialty agreement was observed, representing streamlined support for ERAS principles. Opinions of different professional groups involved in delivering ERAS programmes has not been assessed before and represents a novel finding of the study and justification for continued implementation.

However, although our scores were high there were some areas of relatively lower scoring. There was a broad range of scores for the importance of epidurals, particularly from surgeons (range 1-10). This reflects the controversy that surrounds routine epidural use. [139] The use of alternative analgesic modalities, such as intrathecal analgesia and continuous wound infiltration, has become increasingly popular. [134, 135] The UK Department of Health’s Enhanced Recovery Partnership Programme (ERPP) consensus opinion [148] has subsequently advocated less routine epidural use and increased alternative analgesic methods.

Fluid balance optimisation was scored highly by care providers. Both inappropriate fluid restriction and excessive fluid administration have been shown to be associated with prolonged hospital stays [209] and increased post-operative morbidity [210] reflecting the importance of accurate fluid balance. Epidural use is associated with vasodilation and hypotension and can be associated with excessive intravenous fluid administration.[140] It may be that these perceived drawbacks associated with epidural use are contributory to its lower rating. Indeed the factor analysis identified epidural use, fluid balance and minimisation of pain as a distinct group separate from ERAS outcomes and strategies, reflecting an independent but uniform scoring pattern for these items by the care providers.

Strategies scored lowest overall by care providers were the avoidance of post-operative abdominal drains, oral bowel preparation and pre-anaesthetic sedatives. There is high-level evidence in colorectal surgery advocating against drain insertion. [214] Similarly, there is good evidence suggesting no benefit of routine bowel preparation prior to abdominal surgery. [215]

The stimulation of gut motility was also scored in the lower half of results, particularly by anaesthetists and, to a lesser degree, surgeons. Liberal laxative use to prevent constipation and achieve restoration of bowel function is often advocated as a preventative measure against post-operative ileus [216] and is a component of many enhanced recovery protocols. However the care provider responses were at odds with this evidence.

These results may be partly due to of the presence of resections other than colorectal in the study population where there is less clear evidence for the benefits of drain avoidance and less relevance of bowel preparation and stimulation. However, the reluctance to abandon previously well-established practice despite evidence to the contrary is recognised in the literature. [137, 211] This is a potential obstacle to the implementation and continued establishment of ERAS principles and is a phenomenon that continues to be observed [217] and requires attention when addressing failing ERAS implementation.

Potential drawbacks to the study are the relatively small sample size and the post-operative response rate. It is also acknowledged that due to the small sample size and the high concordance in the overall scoring it is not possible to determine which items are considered more important relative to each other. However it is possible to determine those items scored highest and lowest and an appropriate qualitative assessment of these items was performed. Additionally, the overall high internal consistency of the results suggests that the sample provides valid results and is an acceptable number for this descriptive analysis.

The survey was performed on patients, for the most part, undergoing major open abdominal surgery for malignant disease processes. This therefore represents a population representative of the majority of ERAS recipients however is not strictly relevant to non-abdominal surgery.

In conclusion, this novel study has shown good patient and multidisciplinary care provider approval for the principles of enhanced recovery care after surgery and supports on going development and implementation of such programmes. It highlights potential areas of concern for care providers, namely epidural use and fluid administration. Lastly, we identified several items scored as low priority by care providers where there is a strong evidence base to the contrary. This highlights a potential barrier to ERAS implementation and is an area that requires consideration and education if continued sustainability and development of ERAS programmes is to be achieved.

7.6 Research Requirements Identified

The establishment of support for ERAS principles in this chapter is an encouraging finding. However, what is of concern is the morbidity burden associated with liver resection. This and the previous chapter reported morbidity rates of 45 per cent and over. The following chapter investigates this finding further and attempts to quantify overall morbidity rate for the investigating unit and identify factors associated with morbidity.

7.7 Chapter Publication

Attitudes of patients and care providers to enhanced recovery after surgery programs after major abdominal surgery. Hughes M, Coolsen MM, Aahlin EK, Harrison EM, McNally SJ, Dejong CH, Lassen K, Wigmore SJ. J Surg Res. 2015;193:102-10.

8 Short Term Outcomes After Liver Resection For Malignant And Benign Disease In The Age Of ERAS.

8.1 Summary

Post-operative morbidity following liver resection remains high and has not reduced significantly over the past decade. Recently Enhanced Recovery After Surgery protocols have been implemented effectively and suggest some benefits in terms of general morbidity. In order to improve the effectiveness of peri-operative care protocols, further investigation is required to identify factors associated with poor outcome after liver resection when enhanced recovery principles are applied. An analysis of a prospectively collated database of patients undergoing liver resection at the Royal Infirmary of Edinburgh, UK between January 2006 and September 2012 was conducted. The primary outcome was morbidity rate. Data were collected on patient demographics, oncological, operative and pathological details and post-operative outcomes including length of stay (LOS) and complication type. Univariate and multivariate analyses were performed to determine independent predictors of morbidity. 603 patients underwent liver resection during the study period. Morbidity and mortality rates were 34.3% and 1.5% respectively. Independent predictors of overall morbidity included age (OR 1.02; 95%CI 1.007-1.037), major resection (OR 1.835; 95% CI 1.224-2.751) and extended resection (OR 2.443; 95% CI 1.475-4.047). The only predictor of major morbidity was extended resection (OR 4.079; 95% CI 2.177-7.642). In summary, age is still associated with adverse outcome after liver resection despite the application of enhanced recovery principles. Extended

resection is associated with both major and overall morbidity and further investigation is required to establish post-operative care components to improve this. When determining optimum peri-operative care, factors associated with adverse outcome must be acknowledged and incorporated into protocols in an effort to minimise morbidity.

8.2 Introduction

Liver resection offers definitive surgery for a number of malignant conditions. Traditionally liver resection has been associated with high post-operative mortality and morbidity rates. [218] With centralisation of services to high volume centres, mortality rate has steadily declined to an accepted rate of less than five per cent. [71] Morbidity rates, however, remain high at up to 45%. [73] Not only is peri-operative morbidity delaying discharge, causing patient suffering and leading to increased risk of mortality, it is also associated with decreased overall long term survival following surgery for malignant disease. [87]

Therefore the minimisation of morbidity is fundamental to improving outcomes. Enhanced Recovery After Surgery (ERAS) programmes have been utilised extensively in colorectal surgery and have been shown to not only reduce hospital admission time but also reduce morbidity rates and are now established as standard of care. [28] In liver resectional surgery there has been increasing interest in ERAS protocols. [172] Not only is ERAS after liver surgery deemed safe and feasible but two recent RCTs [122, 124] have shown reduced general morbidity rates after liver resections.

Predictors of morbidity have been assessed before, [73, 117] however, a recent assessment of predictors of outcome after resection of all tumour types, in a general population undergoing enhanced recovery multi-modal peri-operative care is lacking.

The investigating unit is experienced at providing enhanced recovery care after liver surgery. [88, 135, 219] In order to formulate successful post-operative ERAS protocols and continue to effectively reduce surgical complications it is critical to evaluate the factors associated with post-operative morbidity and determine areas of care that can be optimised after liver resection. The aim of this study was to quantify outcomes and assess the predictors of morbidity after liver surgery when enhanced recovery care principles have been applied.

8.3 Methods

Approval from the NHS Lothian review board was obtained prior to commencing the data collection. All patients who underwent a liver resection between January 2006 and September 2012 within the Royal Infirmary of Edinburgh, UK, were identified from the prospectively collated Lothian Surgical Audit database. The Caldicott Guardian approval was obtained and these principles of data management were adhered to.

8.3.1 Peri-operative Protocol

All patients undergoing liver resection underwent review in a multi-disciplinary team meeting where their radiological investigation was assessed by the surgical and radiological team in an attempt to ascertain resectability. This decision was made in concert with the oncology team and a decision made regarding pre-operative chemotherapy, further staging and suitability for surgery if appropriate.

Peri-operative care at the Royal Infirmary of Edinburgh is based on a protocol first described by van Dam *et al* (2006) [88] and has been utilised in subsequent clinical trials. [135, 219] Patients are routinely admitted to hospital on the day of surgery after having fasted from midnight. Patients are allowed to drink clear fluids up until two hours prior to induction of anaesthesia. Endotracheal intubation is performed in the anaesthetic room. Pre-operative sedative mediation is routinely avoided. Monitoring is performed invasively with a central venous line to assess CVP and an invasive blood pressure monitor via the radial artery. Oxygen saturation levels, end tidal CO_2, heart rate, blood pressure and urine output are monitored continuously throughout the procedure. Patients received peri-operative antibiotic prophylaxis, low molecular weight heparin and pneumatic calf compression as thromboprophylaxis. Warming blankets are applied to the patient for the duration of surgery.

Liver resection is performed from either a bilateral subcostal incision or right subcostal incision, extended to the midline if required. Full laparotomy is performed to establish any contra-indication to resection. Intra-operative ultrasound is performed by the operating surgeon to determine the location and extent of disease and confirm the operative approach. Transection is performed with the Cavitron Ultrasonic Aspirator (CUSA) device, with or without hepatic in-flow occlusion and under hypovolaemic conditions via CVP monitoring. Routine NG tube and peritoneal drainage are avoided.

Post-operatively patients are transferred to the recovery unit where they are extubated and monitored for immediate complications. They are subsequently transferred to the High Dependency Unit and then the general ward after approximately 48 hours. Patients are managed according to unit protocol until medically fit for discharge and capable of self care. Pain control is routinely managed with a thoracic epidural and then oral analgesia as coordinated by a specialist pain team. Patients are encouraged to eat and drink from the first post-operative day and mobilised daily from post-operative day one. Venous and arterial cannulae and urinary catheters are removed from post-operative day one.

The patients are routinely reviewed in the out-patient clinic approximately four weeks post discharge and discussed in the MDT meeting where pathological analysis of the specimen was reported and follow up and adjuvant chemotherapy decided upon.

8.3.2 Data Collection

Demographic details, namely age, gender and comorbidities were collected from the patient case files. Presence of co-morbidity was determined as positive when at least one co-morbidity was described in the pre-operative clinic assessment.

Pre-operative oncological data were obtained from the transcription of the Multi-Disciplinary Team (MDT) meeting prior to resection. From this report performance of portal vein embolization (PVE) and neoadjuvant chemotherapy data were obtained. Confirmation of PVE was obtained from the CT report. Neoadjuvant chemotherapy was also confirmed from the MDT report and deemed to be positive if chemotherapy was commenced prior to resection. Pre-operative blood tests were obtained from the laboratory investigations contained within the electronic case records.

The extent of the procedure and use of in-flow occlusion were determined with major resection being defined as resection of three or more segments. Extended resection was defined as resection of five or more segments as per the Brisbane criteria. [91]

Intra-operative and post-operative blood transfusion information was obtained from the Blood Transfusion Service database of prospectively collected data. Day of operation from the operation note and admission dates were linked with the dates of transfusion of blood and reported as receiving transfusion accordingly.

Admission data were gained from the patient case records and clinical course, complications and length of stay were documented. Post-operative complications were also gathered from the patent records, namely the discharge letter from the discharging surgeon. Complication type was recorded as it was reported in the case documentation.

Pathology data were gained from the original pathology report. Underlying tumour pathology, size and number were recorded. Underlying liver parenchyma was also confirmed from the pathology report as was resection margin with a R1 resection being confirmed if the tumour edge was within 1 mm of the resection margin.

Peri-operative mortality was confirmed if patients were reported to have died in hospital or within thirty days after operation. Thirty and ninety day mortality was confirmed by data from the Information and Statistics Department (Scotland).

8.3.3 Statistical Analysis

Continuous data were expressed as median and interquartile range (IQR) and compared using the Mann Whitney *U* test when not normally distributed. If normal distribution was observed a mean and standard deviation were presented and unpaired t-tests performed to determine differences in means. Categorical data were assessed with Chi squared test or Fishers exact test where appropriate. Multivariable logistic regression analysis was performed to assess for independent predictors of morbidity. Factors were entered into the multivariable analysis if they were clinically relevant or achieved significance at the 10% level. P values were two-tailed and considered statistically significant if less than 0.05.

8.4 Results

During the study period 603 patients underwent liver resection for malignant (n=540) and benign (n=63) disease (Table 24).

The mean age of the cohort was 60.5±13.4 years with 41.8% having at least one co-morbidity. The main malignant indications for resection were Colorectal Liver Metastasis (CLM) (n=381), Hepatocellular Carcinoma (HCC) (n=75) and cholangiocarcinoma (n=50).

As the majority of patients had resection for CLM, data were gathered on neoadjuvant chemotherapy and chemotherapy related liver injury. 168 (27.9%) patients received neoadjuvant chemotherapy. The precise chemotherapeutic regimen was not available on all patients and so only the presence or absence of chemotherapy administration recorded in the patients records was reported.

55.7% of patients underwent a major resection, defined as resection of greater than or equal to three segments with patients undergoing resection for cholangiocarcinoma having predominantly major resections (92.0%). Cholangiocarcinoma resections were also associated with a greater number of patients receiving intra-operative blood transfusions (Table 25).

	All (n=603)	Cholangiocarcinoma (n=50)	HCC (n=75)	CLM (n=381)	Other malignant (n=34)	Benign (n=63)
Age (years)	60.5±13.4	60.1±11.8	63.0±15.0	62.4±11.8	66.0±12.0	48.8±15.6
Female	253(42.0)	21(42)	20(26.7)	150(39.4)	19(55.9)	43(68.3)
Comorbidities	252 (41.8)	18(36)	64(85.3)	139 (36.5)	12 (35.3)	19(30.2)
Baseline bloods						
WCC ($x10^9$/L)	7.3±2.3	8.4±2.8	6.9±2.3	7.1±2.1	7.3±2.6	8.3±2.4
Haemoglobin (g/L)	132±17	128±16	135±17	133±17	129±15	134±15
Platelets ($x10^9$/L)	252±92	310±100	225±109	244±83	281±128	271±70
Creatinine (μmol/L)	79±32	76±49	81±23	81±33	79±24	71±19
Albumin (g/L)	41±4	39±5	41±5	42±4	41±4	42±5
Bilirubin (μmol/L)	15±27	57±77	12±7	10±5	12±8	15±18
ALT (U/L)	41±59	84±68	50±44	30±29	29±24	68±144
Prothrombin Time (secs)	11±2	11±2	12±2	11±2	10±2	11±2
Neoadjuvant chemotherapy	168 (27.9)	0 (0)	0 (0)	158(41.5)	9(26.5)	1(1.6)
PVE	41(6.8)	6(12)	4(5.3)	28(7.3)	2(5.9)	1(1.6)

WCC – White Cell Count, PVE – Portal Vein Embolisation, ALT – Alanine Transaminase. CLM – Colorectal Liver Metastasis, HCC Hepatocellular Carcinoma. Data presented as mean±sd or n (%).

Table 24. Patient characteristics

	Total (n=603)	Cholangiocarcinoma (n=50)	HCC (n=75)	CLM (n=381)	Other malignant (n=34)	Benign (n=63)
Procedure						
Major resection	336(55.7)	46(92.0)	25(33.3)	209(54.9)	17(50.0)	39(61.9)
Minor resection	267(44.3)	4(8.0)	50(66.7)	172(45.1)	17(50.0)	24(38.1)
Pringle	157(26.0)	5 (10.0)	20(26.7)	110(28.9)	8(23.5)	14(22.2)
Blood transfusion						
Intra-operative	88(14.6)	9(18.0)	15(20.0)	49(12.9)	6(17.6)	9(14.3)
No. of units	2(2-4)	2 (2-4)	2(1-4)	2(2-5)	2(1-10)	2(2-5)
Rest of admission	74(12.3)	10 (20.0)	12(16.0)	37(9.7)	4(11.8)	11(17.5)
No. of units	1(1-2)	1(1-2)	2(1-3)	1(1-2)	1(1-2)	1(1-2)
Redo procedure	41(6.8)	2(4.0)	3(4.0)	34(8.9)	1(2.9)	1(1.6)
Laparoscopic resection	33(5.5)	0(0)	12(16.0)	17(4.5)	1(2.9)	3(4.8)

CLM – Colorectal Liver Metastasis, HCC Hepatocellular Carcinoma. Data are presented as n(%) or median (IQR)

Table 25. Operative details

Pathological analysis of the resected specimen revealed that resection was carried out for two or fewer tumours in 81.9% of patients and the mean diameter of the largest tumour was 40.9±33.6 mm. Cirrhosis was predominantly confined to patients undergoing resection for HCC (38.7%). CRLI was mainly manifested as steatosis, which, although greatest in the CLM group, was evident across all sub-groups. Perineural and vascular invasion was predominantly evident in the cholangiocarcinoma and HCC groups (Table 26).

	Total (n=603)	Cholangiocarcinoma (n=50)	HCC (n=75)	CLM (n=381)	Other malignant (n=34)	Benign (n=63)
Number of tumours						
0	33 (5.5)	0(0)	0(0)	9(2.4)	8(23.5)	16(25.4)
1	362 (60.0)	47(94.0)	58(77.3)	204(53.5)	13(38.2)	40(63.5)
2	99 (16.4)	1(2.0)	14(18.7)	75(19.7)	6(17.6)	3(4.8)
3	46(7.6)	0(0)	3(4.0)	40(10.5)	2(5.9)	1(1.6)
4	32(5.3)	0(0)	0(0)	30(7.9)	1(2.9)	1(1.6)
5	10(1.7)	0(0)	0(0)	9(2.4)	1(2.9)	0(0)
>5	21 (3.5)	2(4.0)	0(0)	14(3.7)	3(8.8)	2(3.2)
Size of largest tumour (mm)	40.9±33.6	34.9±19.9	53.7±41.8	36.9±27.3	46.9±45.6	51.4±50.5
Cirrhosis	34(5.6)	1(2.0)	29(38.7)	1(0.3)	1(2.9)	2(3.2)
Steatosis	252(41.8)	6(12.0)	22(29.3)	200(52.5)	12(35.3)	12(19.0)
Steatohepatitis	43(7.1)	1(2.0)	16(21.3)	22(5.8)	2(5.9)	2(3.2)
Sinusoidal obstruction syndrome	67(11.1)	1(2.0)	4(5.3)	55(14.4)	1(2.9)	6(9.5)
Microvascular invasion	83(13.8)	16(32.0)	24(32.0)	37(9.7)	6(17.6)	0(0)
Perineural invasion	35(5.8)	25(50.0)	1(1.3)	9(2.4)	0(0)	0(0)
R1 resection	95(15.8)	15(30.0)	7(9.3)	71(18.6)	2(5.9)	0(0)

Data are presented as n(%) or mean±s.d.

Table 26. Pathology of resected specimen

Nine patients died in hospital over the review period. This equated to a mortality rate of 1.5%. All nine patients died in the intensive care unit having suffered a major post-operative complication. Six of these patients died of multi-organ failure secondary to hepatic failure, one died after complications following significant post-operative bleeding and two died following prolonged respiratory failure. Two further patients died within 90 days or surgery, resulting in a ninety day mortality of 1.8% (n=11). Due to the small numbers of patients in this group, mortality as an individual outcome was not able to be meaningfully assessed and so these patients were included in the "major morbidity" group. Major morbidity was assessed separately from all morbidity in an effort to differentiate between severity of post-operative morbidity.

Overall morbidity rate (inclusive of patients who died within 30 days) following a complication) was analysed and the composite all cause rate is reported as 34.3%. Cholangiocarinoma had the highest morbidity rate of 54.0% whereas those patients undergoing resection for benign pathology had the lowest morbidity rate of all the subgroups at 25.4%. Patients having resection for cholangiocarcinoma also had the highest major morbidity rates (26.0%) as defined as morbidity relating to a Clavien Dindo classification of three and above (Table 27).

Individual morbidity types were also reported. The morbidity corresponding to the highest Clavien Dindo classification was reported and only this morbidity was reported in patients who had more than one morbidity. Bile leak (5.0%) and intra-abdominal abscess (5.1%) were the two most frequent intra-abdominal morbidities. (Table 28). LRTI (4.5%) was the most frequently reported non-abdominal morbidity (Table 29). Cholangiocarcinoma resection was associated with higher rates of liver failure (10.0%) and intra-abdominal abscess (14.0%).

	Total (n=603)	Cholangiocarcinoma (n=50)	HCC (n=75)	CLM (n=381)	Other malignant (n=34)	Benign (n=63)
Overall Complications	207(34.3)	27(54.0)	28(37.3)	124(32.5)	12(35.3)	16(25.4)
Major complication	72(11.9)	13(26.0)	9(12.0)	42(11.0)	1(2.9)	7(11.1)
Minor complication	135(22.4)	14(28.0)	19(25.3)	82(21.5)	11(32.4)	9(14.3)
Clavien Dindo Classification						
V	9(1.5)	3 (6.0)	2(2.7)	4(1.0)	0(0)	0(0)
IVa	2(0.3)	1(2.0)	0(0)	1(0.3)	0(0)	0(0)
IVb	6(1.0)	0(0)	1(1.3)	4(1.0)	0(0)	1(1.6)
IIIb	19(3.2)	3(6.0)	3(4.0)	11(2.9)	0(0)	2(3.2)
IIIa	36(6.0)	6(12.0)	3(4.0)	22(5.8)	1(2.9)	4(6.3)
II	57(9.5)	7(14.0)	11(14.7)	32(8.4)	6(17.6)	1(1.6)
I	78(12.9)	7(14.0)	8(10.7)	50(13.1)	5(14.7)	8(12.7)
Length of stay (days)	7 (5-10)	12 (7-21)	7 (5-9)	7(5-10)	7(6-9)	7 (5-9)
Readmission	45(7.5)	8(16.0)	2(2.7)	26(6.8)	4(11.8)	5(7.9)
30 day mortality	9 (1.5)	3(6.0)	2(2.7)	4(1.0)	0(0)	0(0)

Overall and major complications are inclusive of nine patients who suffered mortality. Data are presented as n (%) or median (IQR).

Table 27. Post-operative outcomes

	Total (n=603)	**Cholangiocarcinoma (n=50)**	**HCC (n=75)**	**CLM (n=381)**	**Other malignant (n=34)**	**Benign (n=63)**
Bile leak	30(5.0)	3(6.0)	1(1.3)	19(5.0)	2(5.9)	5(7.9)
Liver failure	15(2.5)	5(10.0)	2(2.7)	6(1.6)	1(2.9)	1(1.6)
Bleeding	11(1.8)	0(0)	3(4.0)	8(2.1)	0(0)	0(0)
IAA	31(5.1)	7(14.0)	3(4.0)	16(4.2)	3(8.8)	2(3.2)
Wound infection	24(4.0)	3(6.0)	2(2.7)	16(4.2)	2(5.9)	1(1.6)
MOF	6(1.0)	3(6.0)	1(1.3)	2(0.5)	0(0)	0(0)
Bowel ischaemia	2(0.3)	0(0)	1(1.3)	1(0.3)	0(0)	0(0)
Anastomotic leak	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	0(0)
Other hepatic	3(0.5)	1(2.0)	1(1.3)	1(0.3)	0(0)	0(0)
Ileus	13(2.2)	0(0)	2(2.7)	11(2.9)	0(0)	0(0)

IAA – Intra-abdominal abscess, MOF – Multi-organ failure. Data are presented as n(%).

Table 28. Surgical morbidity

	Total (n =603)	Cholangiocarcinoma (n=50)	HCC (n=75)	CLM (n=381)	Other malignant (n=34)	Benign (n=63)
AKI	8(1.3)	0(0)	1(1.3)	6(1.6)	1(2.9)	0(0)
Thromboembolism	5(0.8)	1(2.0)	1(1.3)	3(0.8)	0(0)	0(0)
LRTI	27(4.5)	2(4.0)	5(6.7)	16(4.2)	2(5.9)	2(3.2)
ARDS	4(0.7)	0(0)	0(0)	4(1.0)	0(0)	0(0)
Atelectasis	5(0.8)	0(0)	1(1.3)	1(0.3)	0(0)	3(4.8)
Confusion	4(0.7)	1(2.0)	0(0)	2(0.5)	0(0)	1(1.6)
Cardiac	8(1.3)	0(0)	3(4.0)	4(1.0)	0(0)	1(1.6)
UTI	1(0.2)	0(0)	1(1.3)	0(0)	0(0)	0(0)
Pleural effusion	3(0.5)	0(0)	0(0)	2(0.5)	1(2.9)	0(0)
Pneumothorax	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	0(0)
Electrolyte derangement	2(0.3)	0(0)	0(0)	2(0.5)	0(0)	0(0)
Diarrhoea	3(0.5)	1(2.0)	0(0)	2(0.5)	0(0)	0(0)

AKI – Acute Kidney Injury; LRTI – Lower Respiratory Tract Infection; ARDS – Adult Respiratory Distress Syndrome; UTI – Urinary tract Infection. Data are presented as n(%).

Table 29. General morbidity

After these data were gathered, univariate analyses were performed to identify significant independent factors associated with morbidity. These are highlighted in Table 30.

Predictors of all adverse outcomes, including death, were identified. After multivariate analysis age, major and extended resection and pre-operative thrombocytopenia, hypoalbuminaemia and hyperbilirubinaemia were significantly predictive of adverse outcome (Table 30).

Total (n=603)	CD I-V (n=207)	Univariate analysis *P* value	OR	95%CI	Multivariate analysis *P* value
Age - 60.5±13.4	**62.7(±12.9)**	**0.004[a]**	**1.022**	**1.007-1.037**	**0.03**
Female (n=253)	77 (30.4)	0.09[b]	1.203	0.83-1.746	0.329
Re-do procedure (n=41)	12(29.3)	0.48[b]			
Neoadjuvant chemotherapy (n=168)	62(36.9)	0.41[b]			
EHD (n=61)	19 (31.1)	0.58[b]			
Co-morbidities (n=252)	99 (39.3)	0.03[b]	1.421	0.974-2.072	0.068
Major resection (n=336)	**139(41.4)**	**<0.0001[b]**	**1.835**	**1.224-2.751**	**0.003**
Extended resection (n=96)	**54(56.2)**	**<0.0001[b]**	**2.443**	**1.475-4.047**	**0.001**
Steatosis (n=252)	86(34.1)	0.93[b]			
Steatohepatitis (n=43)	17(39.5)	0.46[b]			
Sinusoidal dilatation (n=67)	21(31.3)	0.59[b]			
Cirrhosis (n=34)	15(44.1)	0.22[b]			
Blood transfusion (n=88)	31(35.2)	0.85[b]			
Albumin < 35 g/L(n=31)	**18(58.1)**	**0.004[b]**	**2.224**	**1.009-4.901**	**0.047**
Platelets < 150 $x10^9$/L (n=51)	**25(49.0)**	**0.02[b]**	**2.289**	**1.233-4.249**	**0.009**
Bilirubin ≥ 20 µmol/L (n=63)	**32(50.8)**	**0.004[b]**	**1.781**	**1.016-3.119**	**0.044**

EHD – Extra hepatic disease. [a] Unpaired t-test, [b] χ^2 test. Data are presented as n(%) or mean ±sd.

Table 30. Univariate and multivariate analysis of factors associated with overall morbidity (CD grade I-V)

A further analysis was performed to identify independent predictors of major morbidity. This was specified as Clavien Dindo grade of three and above including death (Table 31). Extended resection was the only factor independently predictive of major adverse outcome. A further analysis of complication types following extended resection was performed and significantly higher levels of liver failure, intra-abdominal abscess and mortality were observed (Table 32).

Total (n=603)	**CD III-V (n=72)**	**Univariate analysis *P* value**	**OR**	**95%CI**	**Multivariate analysis *P* value**
Age - 60.5±13.4	62.6±14.0	0.15[a]			
Female (n= 253)	26(10.3)	0.28[b]			
Re-do (n= 41)	5(12.2)	1.0[c]			
Primarily resectable (n=512)	61(11.9)	0.96[b]			
Neoadjuvant chemo (n=168)	20(11.9)	0.99[b]			
EHD (n=61)	6(9.8)	0.59[b]			
Co-morbidities (n=252)	30(11.9)	0.98[b]			
Major resection (n=336)	51(15.2)	0.006[b]	1.122	0.597-2.109	0.720
Extended resection (n=96)	**30(31.2)**	**<0.0001[b]**	**4.079**	**2.177-7.642**	**0.000**
Steatosis (n=252)	24(9.5)	0.12[b]			
Steatohepatitis (n=43)	5(11.6)	1.0[c]			
Sinusoidal dilatation (n=67)	4(6.0)	0.16[c]			
Cirrhosis (n=34)	4(11.8)	1.0[c]			
Blood transfusion (n=88)	10(11.4)	0.86[b]			
Albumin ≤ 30g/L (n=31)	8(25.8)	0.01[b]	2.420	0.989-5.922	0.053
Platelets ≤ 150 x10^9/L (n=51)	8(15.7)	0.39[b]			
Bilirubin ≥ 20 μmol/L (n=63)	15(23.8)	0.002[b]	1.850	0.931-3.676	0.079

EHD – Extra hepatic disease. [a] Unpaired t-test, [b] χ^2 test, [c] Fisher's exact test. Data are presented as n (%) or mean ±sd

Table 31. Univariate and multivariate analysis of factors associated with major morbidity (CD grade III-V)

	Extended resection (n=96)	Major, minor resection (n=507)	*P* value
Liver failure	6 (6.2)	9 (1.8)	0.01[a]
Bile leak	13 (13.5)	17 (3.4)	<0.0001[a]
Bleeding	4 (4.2)	7 (1.4)	0.08[b]
Intra-abdominal abscess	10 (10.4)	21 (4.1)	0.01[a]
Mortality	6 (6.2)	3 (0.6)	0.0008[b]

[a] χ^2 test, [b] Fishers exact test. Data are presented as n(%).

Table 32. Morbidity and mortality after extended resection

8.5 Discussion

This study reports complication and mortality rates of 34.3% and 1.5% respectively. Mortality rates have been shown by several studies to be reduced in the more recent data presentations. Generally mortality rates of less than 5% are accepted but rates have decreased steadily from 4.9% [117], 3.1% [71] and 2.3% [81] when compared to more historical data. The present study represents data from 2006-2012, some of the most recent outcome data and continues this trend of steadily improving mortality rates after liver resection.

Morbidity rates after liver surgery have been reported in several large database studies at between 22 and 45%. [71, 73, 81, 117] A recent meta-analysis of ERAS liver surgery identified overall morbidity rates of between 11% and 46% [172] following resection managed with enhanced recovery principles. Morbidity rates remain high and do not seem to be shown to have improved significantly despite awareness of techniques to reduce post-operative liver failure, [76] intra-operative bleeding [180] and improvements in peri-operative care. [172]

Significant independent predictors identified in this study were increased age, extended hepatic resection, thrombocytopenia, hypoalbuminaemia and hyperbilirubinaemia. Although the literature has identified risk factors following liver resection, as discussed below, the impact of enhanced recovery care on factors determining outcome has not been explored before.

Haematological and biochemical markers of biliary obstruction and advanced liver disease were observed in this study to be predictors of morbidity and major morbidity. These factors are well established [72, 117] and these findings add further evidence supporting the pre-operative relief of biliary obstruction and optimisation of hepatic function prior to liver resection.

However, this study also identified factors associated with morbidity that are less universally acknowledged. Increasing age is associated with poorer long term survival [220] as well as higher post-operative mortality. [220, 221] However, a significant proportion of the literature, in contrast to the current findings, advocates that age is not associated with increased morbidity [71, 117, 220, 222, 223] and so is not a contra-indication to resection. These studies all dichotomised age to “old” versus “young” cohorts and failed to show a significant difference in all levels of morbidity. This methodology is potentially flawed if sample size is not adequate. However further studies assessing morbidity risk per year also did not find age as a linear variable to be an independent predictor of morbidity. [73, 80, 221] One study, Mullen *et al* [72] did, and, with the present study represent the minority view in the literature that with increasing age comes increased overall morbidity after liver resection. However Mullen *et al* reported only major resections and so differs slightly from the current cohort.

When predictors of major complications only were assessed in the present study, age was not an independent predictor. This is again in contrast to the majority of published studies that have reported age to be associated with mortality, or major morbidity. [72, 73, 220, 221] These studies differ slightly from the present study in that Reddy *et al* [221] and Mullen *et al* [72] exclusively looked at major resections and so represent a slightly different population at a higher risk than the more heterogeneous cohort examined in the current study (in terms of extent of resection) and Sulpice *et al* [220] reported higher levels of cirrhosis and primary liver tumours than the current study, therefore again reporting a higher risk group where increased age is reported to be associated with poor outcome.

Therefore the current results are at odds with the general accepted wisdom that morbidity is not influenced by age but mortality is, which suggested that complications in the elderly tend to be severe when they occur.

Traditionally age related morbidity following liver resection is associated with the decreased capacity of the liver to regenerate (and altered hepatic perfusion). [224] Moreover, higher rates of cirrhosis associated with old age can all adversely affect the post-operative course. [220] However with increased accuracy of pre-operative volume assessment, the ability to effectively increase the future liver remnant size with PVE, major liver related complications can be anticipated and minimised even in the most elderly patients. [225]

Due to the presence of reduced cardiorespiratory reserve, decreased baseline mobility and decreased muscle mass, the potential for increased "general" post-operative morbidity is evident. Improvements in perioperative care such as high dependency level care, prophylactic measures against chest and line sepsis and early nutrition can all reduce potentially major cardiorespiratory and infective complications in the most vulnerable patients. This has been shown convincingly in the general ERAS literature [58] as well as, to a lesser extent, the liver ERAS data. [172]

However we found age to be an independent predictor of adverse outcome when looking at all levels of complication severity, i.e. when minor complications were included. This suggests that elderly patients are more likely to develop a complication than young patients, although the consequences are not likely to be severe. A recent review of ERAS protocols in the elderly found evidence of higher morbidity rates and reduced achievement of recovery milestones in elderly patients. [226] An inability to adhere to such protocols is likely to result in a failure to prevent general post-operative morbidity. Therefore when trying to minimise morbidity and formulating ERAS protocols, advanced age must be taken into consideration in order to increase adherence and minimise post-operative complications.

The other factor found to be an independent predictor of all complications as well as, specifically, major complications after liver resection was extended resection, i.e. resection of five or more segments.

The majority of large cohort studies assessing post resectional outcomes have not reported extended hepatic resection to be predictive of all morbidity. [71, 72, 80, 117] These investigators either did not report extended resection separately [117] or reported small percentages of extended resection, [80] thus unlikely to prove independently significant following univariate or indeed multivariate analysis.

However, extended resection, [71] right hepatectomy [221] and number of segments resected [73] have been reported as independently predictive of mortality after resection in concordance with the findings of our study.

Extent of resection has been associated with increased rates of bile leak [81] and liver failure post-operatively. [227] We observed significantly higher rates of liver impairment after extended resection compared to major and minor hepatic resections however the liver failure rate of 6.2% is comparable or lower than other quoted rates when looking at extended resections only - 15% [227] and 13.8%. [228] Despite the use of advanced techniques to prevent liver failure (PVE, neoadjuvant chemotherapy and two stage procedures), and decreased levels of hepatic insufficiency compared with previous studies, this complication remains an on going concern for major resections and continued investigation and implementation of techniques such as ALLPS and PVE is critical to reducing post-operative morbidity after liver resection.

The present study also observed significantly higher rates of bile leak (13.5% v 3.4%) and abscess formation (10.4% v 4.1%) after extended resections compared to non-extended resections. Our overall bile leak rate of 5% compares slightly higher than other published rates - 4.8% [81]; 1% [229], 4.7% [80] and 3.7%. [71] It appears that the majority of these complications occurred following extended hepatic resection.

Complex resections and post-operative morbidity must however be considered in the context of the survival benefit following major resection for, in many cases, colorectal liver metastases. Increasingly favourable long-term outcomes are being achieved following complex, extensive resection for advanced disease, justifying an aggressive surgical approach. [230] The present study suggests that such morbidity will continue to be evident as a result of curative resectional surgery.

Current techniques to reduce post-operative bleeding and bile leak have not routinely been incorporated in ERAS protocols [172] and hepatic specific morbidity has not been affected by ERAS care. [172] CVP minimisation to reduce intra-operative blood loss has been included in only two liver ERAS trials. [88, 122] Therefore further avenues of investigative pursuit to develop methods to reduce such complications after extended resection are mandated.

However, the current study, in contrast to the published literature, also found that extended resection was predictive of developing any type of complication, including minor complications, implying that careful consideration of all aspects of post-operative care is required after extended resection. Not only must key surgical factors be addressed such as prevention of bile leak, bleeding or liver failure, but also appreciation of the susceptibility to more minor complications such as confusion, UTI and wound infection.

This can have implications when considering analgesia, particularly paracetamol that is often contra-indicated following extended liver resection, therefore requiring suitable substitutes, most often opiates or NSAIDS, both associated with post-operative infective complications. These include chest sepsis related to decreased mobilisation secondary to opiate use [45] and increased risk of peptic ulceration and perforation related to NSAIDs. The evidence behind this practice is minimal and an evidence base for optimum multimodal analgesic regimen following major liver resection is lacking. [198]

Nutrition post-operatively is also an important consideration after extended liver resection due to potential nutritional insufficiency related to the increased surgical insult and increased risk of sepsis. [231] Further work is required to investigate the effects of small liver remnant volume on outcome after liver resection and how ERAS protocols need to accommodate this unique aspect of liver surgery that is not translatable from other areas of abdominal surgery.

These results should be taken in context of the limitations of the study. Firstly this was a retrospective study and as a result is susceptible to the various problems associated with this methodology. Specifically for this study the limitations with regard to this aspect were as follows.

The completeness of the patient records introduces reporter bias into the analysis. If complications were not recorded they were not included into the database. We did not have access to the original clinical notes from the time of the admission, but referred to the discharge letter for complications. If the complication was not reported then it was not included and there is a possibility that some complications were missed, most likely minor complications and so the outcomes could be biased towards complications of a higher Clavien Dindo classification. A similar picture is also true for reporting of co-morbidities. As this was a retrospective study, no pre-operative study assessment was made and only the clinic letter was scrutinised for co-morbidities. If no mention of co-morbidities was made then the assumption was made that no significant co-morbidities were present. Therefore, it is possible that some comorbidities were missed from the data collection.

Intra-operative data were not universally available, in particular estimated blood loss. We dealt with this by looking at those patients who had received a blood transfusion, however the findings are likely to be less discriminatory.

In summary, the implications of this study are as follows. The post-operative care of older patients, even without co-morbidities, is critical and any post-operative protocol should accommodate this key difference to ensure compliance and minimise post-operative morbidity. Patients undergoing extended resections are susceptible to increased complication rates of all levels as well as major morbidity and future research should focus on areas that can improve the post-operative outcomes following resection of five or more segments.

8.6 Research Requirements identified

Extended hepatic resection is becoming an increasingly performed operation. The above study has identified its association with overall and severe morbidity. The following two chapters will investigate two key issues impacting on the peri-operative care of patients who have a small liver remnant, namely analgesia and energy requirements.

9 Energy Expenditure After Liver Resection

9.1 Summary

Ensuring adequate post-operative nutrition relies on replacing energy expended. Resting energy expenditure (REE) is the major component of total energy expenditure. REE after liver surgery is not well investigated and measurement, performed by indirect calorimetry (IC), is challenging. A mobile device (SenseWear Armband) (SWA) has been validated when measuring REE in other clinical settings but not liver resection. The aims of this study are to validate SWA versus IC, quantify REE change following liver resection and determine factors associated with REE change. Patients listed for open liver resection prospectively underwent IC and SWA REE measurements pre- and post-operatively. Additionally the SWA was worn continuously post-operatively to record daily REE for the first five post-operative days. To determine acceptability of the SWA, validation analysis was performed. To assess REE change, peak post-operative REE was compared to pre-operative levels. Factors associated with REE change were also analysed. SWA showed satisfactory validity compared with IC when measuring REE although the post-operative 95% levels of agreement (-5.56-3.18 kcal/kg/day) may introduce error. Post-operative REE (median 23.5 (IQR 22.6-25.7) kcal/kg/day) was significantly higher than predicted REE (median 19.7 (IQR 19.1-21.0) kcal/kg/day; $p<0.0001$). Median REE rise was 11% (IQR -1-25%). Factors associated with REE rise of >11% were age ($p=0.017$) and length of operation ($p=0.03$). SWA offers a suitable alternative to IC when measuring post-operative REE however the magnitude of the error (8.74 kcal/kg/day)

could hinder its accuracy. REE quantification after liver resection is important to identify patients who could be prone to energy imbalance and therefore malnutrition.

9.2 Introduction

Adequate nutrition is a vital component of post-operative management following major surgery. Complications of under-nourishment include increased incidence of infection, poor wound healing and reduced mobility. [231] Similarly, over feeding, particularly with parenteral nutrition, can result in increased energy expenditure [232] and even fatty liver induction. [233] Conversely if calorie requirements are met it has been found to reduce mortality in critically ill patients. [234] Therefore an accurate assessment of nutritional requirement is crucial when attempting to optimise patient recovery and minimise morbidity following major abdominal surgery.

Nutritional requirements are calculated by quantifying the total calories used over a specified period. Total energy expenditure is made up of the resting energy expenditure, energy of physical activity and the energy used to digest food. Resting energy expenditure is the major component of total energy expenditure. It can be summarised as the amount of calories used by the body in a 24 hour period of rest and represents the fuel sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs. It accounts for 60-70% of total expenditure. [235]

Resting energy expenditure traditionally is measured by indirect calorimetry. This technique measures the volume of O_2 consumed and CO_2 produced whilst at rest. Indirect calorimetry, despite being acknowledged as a gold standard for measuring resting energy expenditure, is often criticised for being error prone, operator dependent and impractical.

A simpler method of estimation of energy expenditure is the SenseWear Armband device (SWA; Bodymedia, Pittsburgh, PA). The SWA is worn on the upper arm and collects a variety of physiological data through multiple sensors - a three-axis accelerometer, heat flux sensor, skin temperature sensor, near-body ambient temperature sensor, and galvanic skin response sensor. The sensor data is combined with gender, age, height and weight to calculate total and resting energy expenditure. It has been validated against indirect calorimetry for determining resting energy expenditure in various settings including healthy adults, [236] stroke victims [237] and cancer patients. [238] It has not been validated when assessing resting energy expenditure in patients following liver resection or any other type of abdominal surgery.

Liver surgery is often performed on patients following chemotherapy, which is associated with muscle loss [239] making them vulnerable to the effects of inadequate post-operative nutrition. Furthermore, after partial resection of the liver, regeneration occurs – an energy dependent process [240] – potentially adding to the burden of energy requirements.

Outcomes following liver surgery have improved and mortality rates are less than 5% in high volume centres. However, complication rates remain high at up to 45%. [73] Therefore optimisation of post-operative care is vital.

There is no evidence assessing the effects of liver surgery on resting energy expenditure. Hendry *et al* [219] assessed the administration of oral nutritional supplements following liver resection and found no difference in surgical outcomes between those receiving supplements and those receiving standard care. However, if the underlying magnitude of resting energy expenditure change is not known it is impossible to know if calorific targets are being met.

Therefore the aims of this study are to 1) assess the validity of SWA compared to IC, 2) quantify REE after liver resection and 3) determine factors associated with REE change.

9.3 *Methods*

The trial protocol was prospectively published on clinicaltrials.gov (NCT02031094). After gaining approval from the South East Scotland Research Ethics Committee patients undergoing liver resection at the Royal Infirmary of Edinburgh, UK, were approached and given written information regarding the trial after an initial discussion at the pre-admission clinic. Written informed consent was obtained on the day of surgery or sooner if appropriate.

9.3.1 Patients

Patients were not recruited if they were to undergo a laparoscopic procedure, a liver resection combined with a further procedure, had abnormal liver function tests, were below the age of 18 years of age or did not have capacity to provide informed consent to enter the trial. Patients were excluded from the validation analysis if respiratory quotient (RQ) variability exceeded 10% during the IC assessment or if the armband was not worn for at least 95% of the study period.

9.3.2 Peri-operative care

Patients were admitted on the morning of surgery having fasted for six hours and taken clear fluids up to two hours prior to surgery. All patients underwent induction of anaesthesia with propofol, atracurium and fentanyl (1-2 microg/kg). Maintenance of anaesthesia was achieved by desflurane or sevoflurane. At induction patients routinely received a central venous catheter in the right internal jugular vein, radial arterial cannulation and a urethral catheter. Routine monitoring of central venous pressure (CVP), invasive continuous blood pressure and mean arterial pressure, end tidal CO_2, heart rate, oxygen saturations and urine output was performed throughout the operation.

The peritoneal cavity was entered via a right subcostal incision that was extended superiorly in the midline if required. A full laparotomy was performed to ensure no contra-indications to resection were evident. Intra-operative ultrasound was undertaken by the operating surgeon to establish resectability and to formulate a final operative approach. Transection of the liver parenchyma was performed with Cavitron Ultrasonic Aspirator (CUSA, ValleyLab, Boulder, Colorado, USA) and monopolar diathermy. Transection was performed in accordance with the patient's pathological, oncological and physiological requirements to ensure optimum short and long term outcome.

Routine thromboprophylaxis and peri-operative antibiotics were administered immediately prior to incision. Intra-operative warming was routinely performed. Intra-peritoneal drains and NG tubes were not routinely administered and intra-operative fluid management was restricted to 80-100 mls/hour.

Patients were transferred from theatre to the recovery ward where they were extubated and monitored until observations and pain scores were satisfactory according to the unit protocol. They were subsequently transferred to the high dependency ward where they remained until they achieved discharge criteria and could be transferred to the general ward.

9.3.3 SWA Validation

The first aim of the study was to assess the validity of the SWA when measuring REE. Prior to resection patients underwent a pre-operative measurement of their resting energy expenditure. This was performed by both methods simultaneously: SWA and IC. In order to achieve optimum conditions patients underwent IC between 0800hrs and 1000hrs prior to eating breakfast so they had fasted for approximately 12 hours.

Patients underwent 30 minutes of indirect calorimtery (GEMnutrition, Cheshire, UK) under standardised conditions. This technique measures the volume of O_2 consumed and the volume of CO_2 produced whilst at rest. This is achieved by comparing the concentrations of O_2 and CO_2 in the air inspired by the participant with the concentrations in the air expired. The Weir equation [241] is used to convert the volume of O_2 consumed and the volume of CO_2 produced per minute into a value for resting energy expenditure expressed in calories.

The Weir Equation:
Energy expenditure (kcal) = [(VO₂ L/min) (3.941) + (VCO₂ L/min)(1.11)] x 1.44

The tests were performed in the same room maintained at 24 degrees centigrade. Patients were advised to lie semi-reclined on a bed and to achieve a relaxed state without sleeping. No physical exercise was permitted on the morning of the test. The IC was performed for 30 minutes after the first 10 minutes were discounted until a steady state had been achieved. RQ variation of more than 10 per cent was an indication to exclude the result.

During this period patients wore the SWA simultaneously and therefore under identical conditions. This resulted in a REE quantity for 30 minutes. This result was then multiplied up to give a kcal/day reading similar to the IC. To eliminate the influence of fat free mass REE was presented as kcal/kg/day. The same protocol was repeated post-operatively between POD3-5.

9.3.4 REE Change After Liver Resection

The second aim of the study was to evaluate the effect of liver resection on REE. This was performed in two parts. The first part assessed the effect of liver resection itself on REE change. Secondly, factors associated with increased REE rise were investigated.

Patients underwent a pre-operative measurement of REE with the SWA, either in combination with IC or in isolation. Prior to assessment, all participants had measurement of anthropometric and body fat percentage measurements to determine overall body composition. In addition, REE prediction by the Harris Benedict equation was calculated. Patients subsequently underwent liver resection according to their oncological requirements. Post-operatively the SWA was placed on the patient's arm at the mid-humerus level. This remained in situ until POD 5.

REE was downloaded on a daily basis. REE was obtained by recording a period of time where no active energy expenditure was evident and the value multiplied to achieve a daily REE of kcal/day. To eliminate the influence of fat free mass REE was presented as kcal/kg/day. To determine patients' maximum metabolic state the peak REE observed was recorded and referred to as peak REE. Changes in REE from baseline were reported as either percentage rise or absolute values.

9.3.5 Data Collected

Demographic patient data were collected including age, sex, ASA, weight, height and BMI. Pre-operatively anthropometric data were collected. Mid upper arm circumference (MUAC) and waist circumference were obtained with a tape measure. Skin fold thickness (SFT) of the biceps, triceps and subscapular region were obtained with skin fold callipers (Harpenden Calliper, West Sussex, UK). SFT measurement was performed according to a standardised protocol by a single investigator (MH) as described by Rona *et al*. [242] Body fat percentage (BF%) and fat mass (FM) were obtained by using bio-impedance analysis (Omron Healthcare, Milton Keynes, UK). Fat free mass (FFM) was subsequently obtained from these data.

Intra-operative data were collected. Operation performed, length of operation and estimated blood loss (EBL) were prospectively recorded. Extent of resection was assessed in two ways. The first was to report the number of segments resected, and secondly estimated residual liver volume (RLV) was obtained by estimating the liver volume based on a formula from Chouker *et al* [243] and subtracting the percentage of liver resected according to pre-determined values as described by Schindl *et al*. [244]

The pathology of the resected specimen was also obtained and details of background liver parenchyma, size and pathology of tumour were obtained directly from the original pathology report.

Post-operatively clinical data were collected. Length of stay, i.e. length of time spent in hospital and morbidity rate was recorded. Patients were observed for complications on a twice daily basis by the researcher. Complications were classified according to pre-determined definitions, [202] diagnosed and managed by the clinical team and morbidity rates reported accordingly. Routine post-operative blood tests were recorded daily from POD 1-4.

Resting energy expenditure (REE) was calculated by the two methods as described above. REE was reported as kcal/kg/day. The effect of resection extent, and therefore regeneration, was investigated. Patients were initially divided according to extent of resection: either resections of more than three segments or less than or equal to three segments. After that patients were divided according to RLV with the median RLV forming the cut off point between groups. Furthermore the percentage rise in REE from baseline was used to split the cohort between the median percentage rise in REE to determine factors associated with REE rise.

9.3.6 Statistical Analysis

All statistical analysis was performed using SPSS version 19.0 (IBM, Armonk, New York, USA). A p value of <0.05 was adjudged to represent statistical significance.

9.3.6.1 Validation

The validation of the SWA compared to IC was performed via linear regression analysis to determine relationship of the REE measurement between the two techniques. Bland Altman charts were plotted to further investigate the validity and agreement of the SWA compared with IC. [245] Pre- and post-operative REE was compared between modalities with Wilcoxon signed-rank test for comparison of different measuring techniques on the same patients.

9.3.6.2 Assessment Of Effect Of Resection On REE

Pre- and post-operative REE was compared with Wilcoxon signed-rank test for comparison of REE on the same patients. When assessing for factors associated with a rise in REE, univariate analysis was performed to assess any differences in baseline characteristic between the two groups. For dichotomous data Chi square or Fishers exact tests were performed. Continuous independent data were compared with Mann Whitney *U* test.

9.4 Results

The trial was conducted between February and August 2014 at the Royal Infirmary of Edinburgh, UK. 28 patients undergoing open liver resection were recruited into the trial.

9.4.1 Patients

The consort diagram is shown in Figure 20. Seven patients pre-operatively did not undergo IC as they were unable to attend for the assessment prior to their operation due to logistical difficulties. Of the 21 patients who underwent pre-operative IC, post-operatively one patient died on the third post-operative day, one refused post-operative IC and one patient was contra-indicated to IC due to infection control restrictions.

Therefore for the validation analysis, 21 patients underwent a pre-operative assessment with IC. Of these 21 patients, 18 underwent post-operative IC. Four patents had two recordings and three patients were excluded due to high RQ variability leading to unreliable IC recordings. Therefore a total of 21 pre-operative and 19 post-operative recordings of IC and SWA were made on which the validation analysis was performed.

For the REE SWA assessment all 28 patients commenced the study. Five patients were excluded. One patient died on POD 3 and four patients did not wear the SWA for over 95% of the time and so were excluded from the analysis. 23 patients were therefore included for this analysis. Table 33 shows the baseline characteristics of the patients included in the pre-operative and post-operative validation analysis and the SWA REE assessment. Table 34 reports the post-operative course of the included patients.

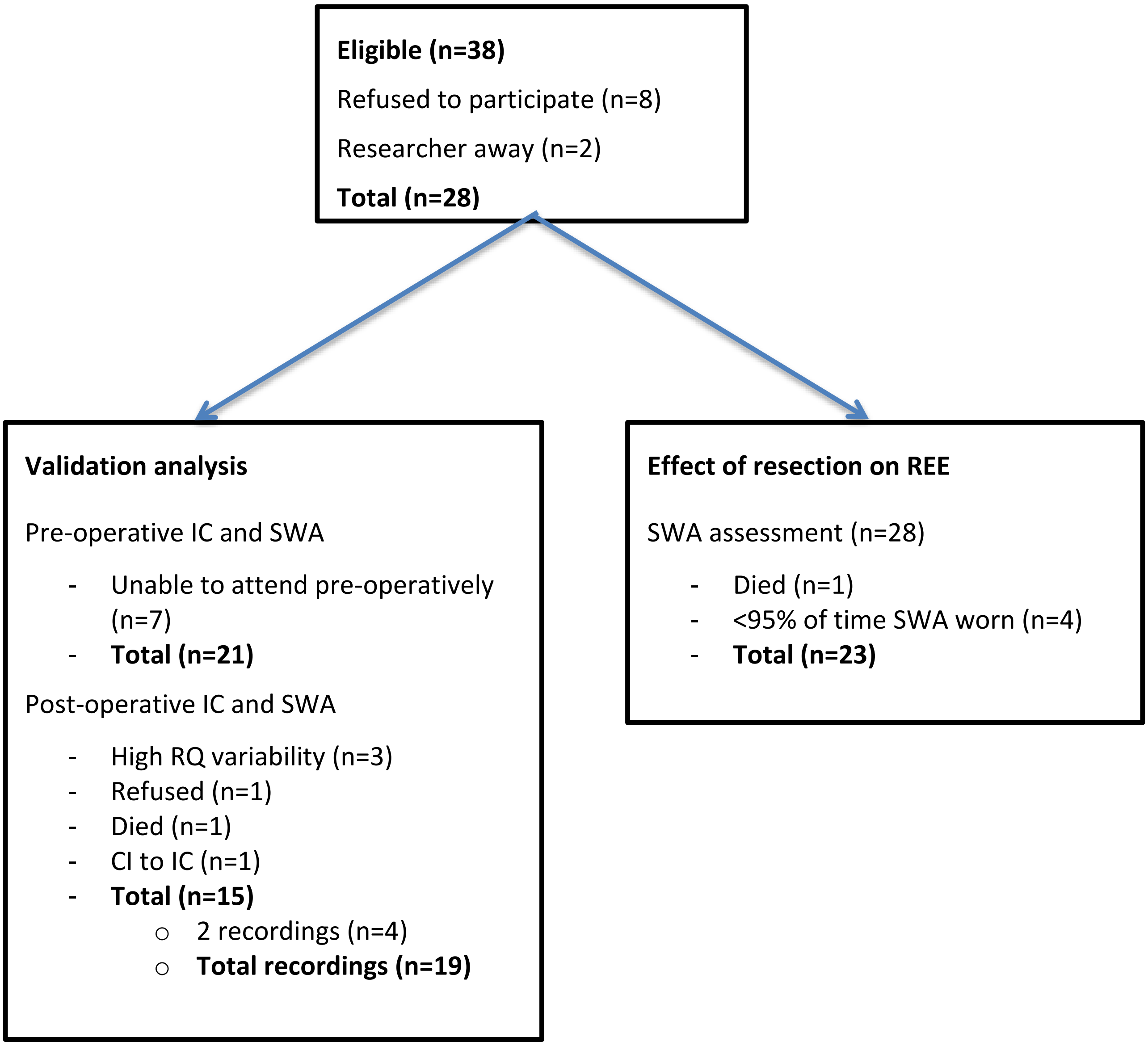


Figure 20. CONSORT diagram.

Patient Variable	IC/SWA validation (n=21)	SWA REE analysis (n=23)
Age (years)	64 (55-71.5)	64 (53-70)
Male	17 (81.0)	17 (73.9)
Weight (kg)	84 (70-94.4)	84 (70-96)
BMI (kg/m^2)	28 (25.4-31.6)	27.4 (25.0-30.9)
EBL(ml)	750 (350-1100)	750 (300-1500)
Length of operation (mins)	216 (178-255)	225 (160-285)
Pringle time (mins)	19 (0-29)	10 (0-28)
Biceps SFT (mm)	10.2 (7-12.6)	11 (7.4-12.2)
Triceps SFT (mm)	15.4 (8.5-21.0)	15.5 (9.0-19.0)
Subscapular SFT (mm)	17.5 (15-23.5)	17 (15.0-24.0)
MUAC (cm)	29 (27-30.2)	29.0 (27.0-30.0)
Waist circumference (cm)	98 (93-102.5)	97 (93.0-102.0)
FM (kg)	24.9 (20.1-35.0)	24.4 (18.8-30.7)
BF%	29.6 (25.2-34.9)	28.9 (25.2-33.9)
Pathology		
CLM	16 (76.2)	16 (69.6)
HCC	3 (14.3)	3 (13.0)
Cholangiocarcinoma	0 (0)	1 (4.3)
Other malignant tumour	2 (9.5)	3 (13.0)
ASA		
I	1 (4.7)	2 (8.7)
II	17 (81.0)	20 (87.0)
III	3 (14.3)	1 (4.3)

CLM – Colorectal liver metastasis, HCC – Hepatocellular Carcinoma, EBL – Estimated Blood Loss, SFT –Skin fold thickness, MUAC – Mid upper arm circumference, FM – Fat mass, BF – Body fat. Data are presented as median (IQR) or n (%)

Table 33. Baseline characteristics

Post-operative Factor	IC/SWA validation (n=21)	SWA REE analysis (n=23)
LOS (days)	6 (5-10)	7 (5-10)
Complications	8 (38.1)	9 (39.1)
Segments resected	3 (2-5)	4 (2-4)
Peak ALT (U/L)	258 (109-484)	258 (162-534)
Peak bilirubin (µmol/L)	24 (16-56)	28 (23-38)
Peak WCC ($x10^9$/L)	12.8 (11.5-15.6)	12.8 (11.4-15.4)
Peak temp (degrees C)	38.0 (37.8-38.4)	38.0 (37.8-38.4)
Peak PT (secs)	17 (14-20)	18 (15-19)

LOS – Length of stay, ALT – Alanine Transaminase, WCC – White cell count, PT – Prothrombin Time. Data are presented as median (IQR).

Table 34. Post-operative data

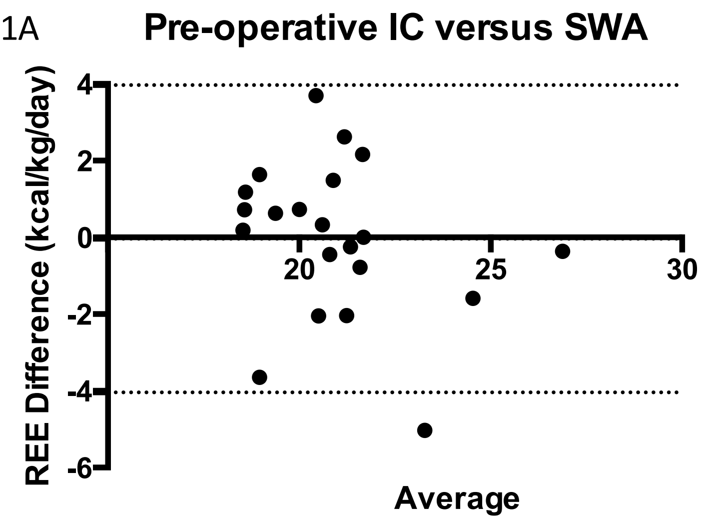
9.4.2 Validation

A validation analysis was performed of SWA compared to IC. Both instruments were used to measure REE simultaneously pre- and post-operatively (Figures 21 and 22). The pre-operative analysis is shown in Figure 21A and 21B (n=21). The Bland-Altman analysis is shown below (Figure 21A) and shows a 95% limits of agreement of -4.042-3.968 kcal/kg/day. Significant linear regression analysis was observed (p=0.003) between the two measuring techniques (Figure 21B).

The same comparison between IC and SWA was made post-operatively (n=19). The IC measurement was performed between POD 3 and 5 depending on the clinical condition of the patient. A similar significant linear regression analysis was observed (Figure 22B) as were the 95% limits of agreement (-5.56-3.18 kcal/kg/day) after the Bland Altman analysis (Figure 22A).

No significant differences were seen (after assessment with Wilcoxon-ranked sum test) between the median values of REE measured by IC and SWA on the same patients both pre-operatively (IC 20.6 kcal/kg/day IQR 18.8 – 21.8; SWA 20.8 kcal/kg/day IQR 19.6-22.0) (Figure 23A) and post-operatively (IC median 22.2 kcal/kg/day IQR 21.2-24.5; SWA median 21.3 kcal/kg/day IQR 20.6-22.8) (Figure 23B).

Figure 21A



95% limits of agreements -4.042-3.968

Figure 21B

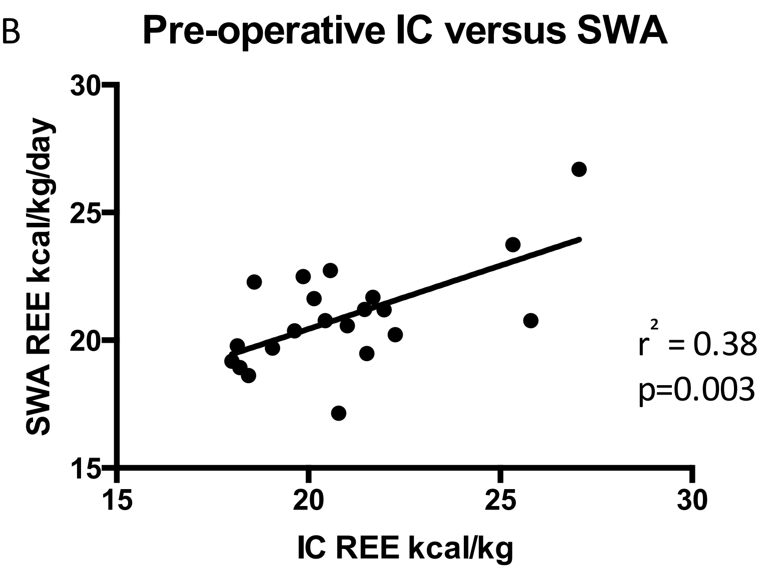
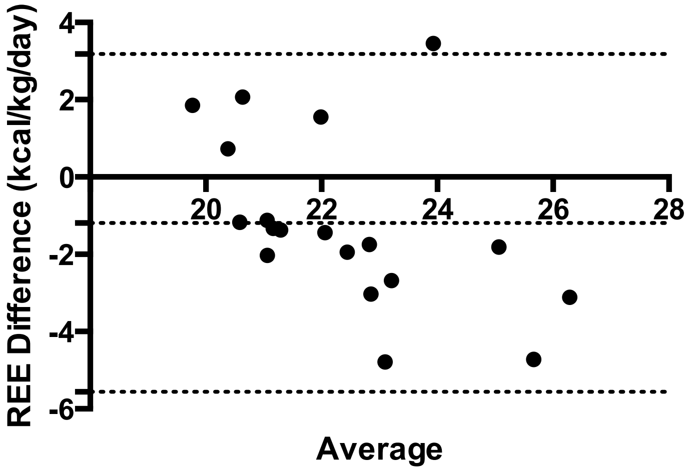


Figure 21A. Bland Altman comparing IC to SWA pre-operatively when measuring REE.

Figure 21B. Linear regression analysis of pre-operative IC versus SWA REE measurement.

Figure 21. Pre-operative IC versus SWA

Figure 22A **Post-operative IC versus SWA**



95% limits of agreement -5.56-3.18

Figure 22 B **Post-operative IC versus SWA**

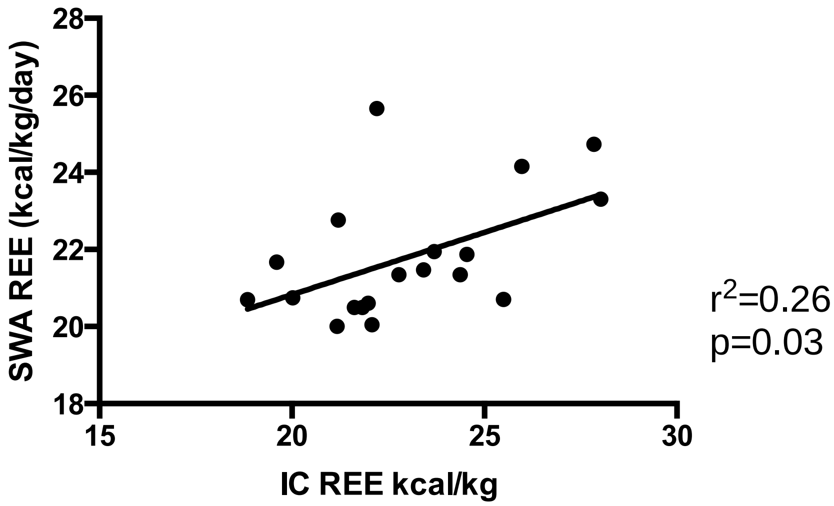


Figure 22A. Bland Altman plot comparing IC to SWA post-operatively when measuring REE.

Figure 22B. Linear regression analysis of post-operative IC versus SWA REE measurement.

Figure 22. Post-operative IC versus SWA

Figure 23A **Pre-operative REE measurement**

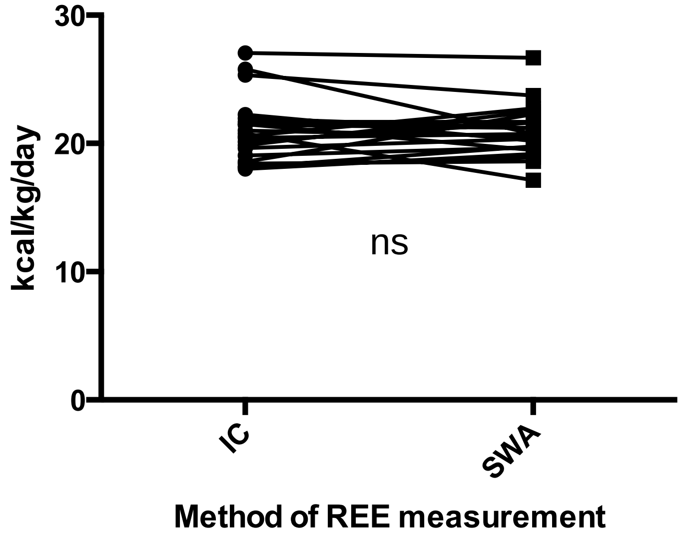
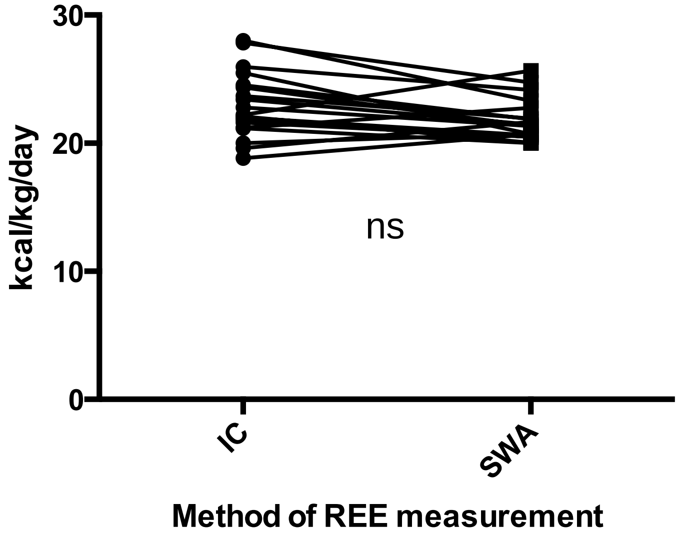


Figure 23 B **Post-operative REE measurement**



Figures 23A and 23B. Comparison of REE measurements obtained by IC and SWA pre- (n=21) and post-operatively (n=19). No significant difference was observed between the two methodologies. Both REE measuring techniques were performed simultaneously under standardised conditions.

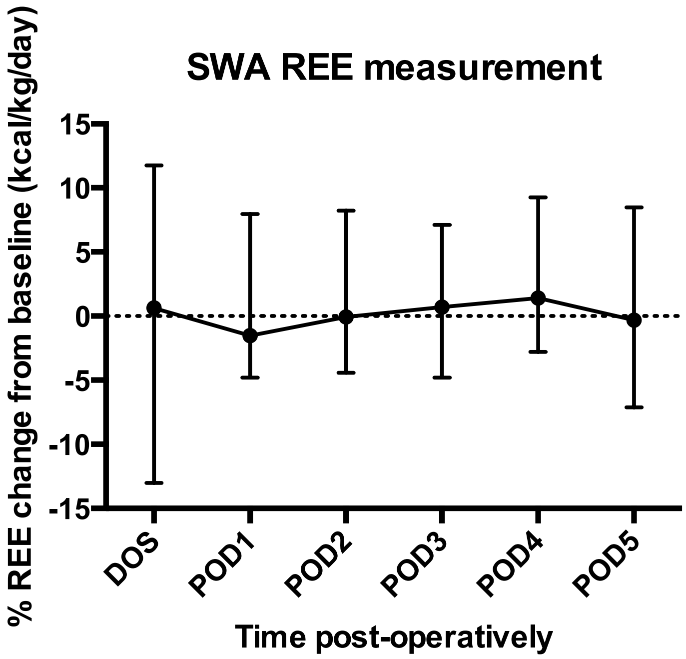
Figure 23. Pre- and post-operative REE measurement

9.4.3 The Effect Of Liver Resection On REE

In order to assess the effect of liver resection over the whole post-operative period the SWA was placed on the patient's arm and worn continuously for the first five days after surgery (n=23) to assess REE change. Daily REE was calculated and the percentage change from the pre-operative baseline was recorded below. Minimal median change was observed, however the magnitude of the inter-individual variance was high (Figure 24).

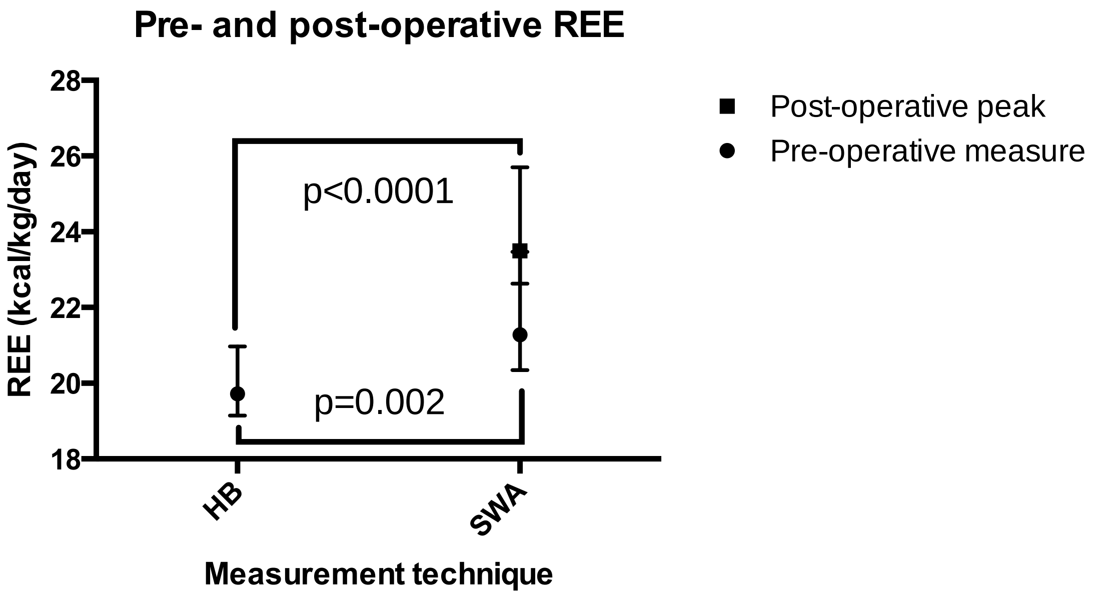
Therefore, to determine if liver resection had an effect on REE beyond predictable levels, an analysis was performed comparing the Harris Benedict (HB) equation to the REE recorded by the SWA pre-operatively and the post-operative peak REE. When compared to the predictive Harris Benedict formula, SWA recorded hypermetabolic states in both the post-operative patients and pre-operative recordings (Figure 25, n=23). SWA pre-operative (median 21.3 (IQR 20.3-23.5) kcal/kg/day) and post-operative (median 23.5 (IQR 22.6-25.7) kcal/kg/day) measurements were significantly higher than the predicted HB REE (median 19.7 (IQR 19.1-21.0) kcal/kg/day). Post-operative peak REE was also significantly higher than the pre-operative SWA REE measurement (p=0.01).

The peak post-operative REE recorded for each patient over the five post-operative days was calculated. The percentage peak rise in REE over the 5 post-operative days from pre-operative baseline was then calculated. The median rise from baseline observed in the peak REE was 11 per cent (IQR -1-25 per cent) (Figure 26).



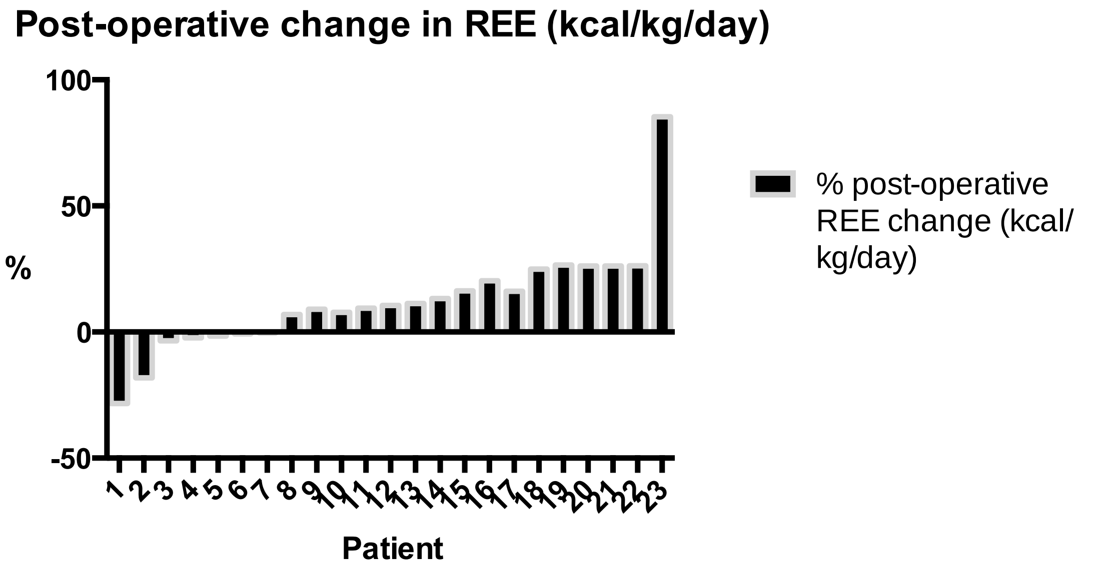
Serial REE measurement with SWA (n=23). Daily post-operative REE was compared with pre-operative REE and the difference recorded from DOS to POD5. Error bars indicate median (IQR).

Figure 24. REE change after liver resection



Comparison of pre and post-operative REE measurement (median and IQR) by SWA (n=23). SWA REE measurements were significantly higher pre- and post-operatively than the HB REE estimation.

Figure 25. Post-operative REE compared to predicted values



Post-operative change in REE.

Figure 26. Individual post-operative REE change

9.4.4 Factors Associated With REE Rise

A further aim of the study was to assess if the extent of resection had an effect on post-operative REE. The cohort was divided into those patients who had resections of greater than three segments and those who had three or fewer segments resected.

When REE was compared for the first five post-operative days REE was significantly greater in the group who underwent resection of > 3 segments when assessing kcal/day directly. However when REE was compared per kg of mass, this effect was negated and no difference was seen between the two groups (Figures 27A and 27B). A similar picture was observed when RLV was calculated. The median RLV was 1164g and the two groups above and below this median were compared for repeated measures of REE. Again, this did not show a significant difference (Figure 28).

The cohort was subsequently divided to compare those whose REE increased to a greater extent to those whose REE rose less or decreased post-operatively. The group that had a median rise of over 11% compared to baseline REE had significantly greater age and length of operation after univariate analysis (Table 35). No differences were observed in the post-operative outcomes of the two groups (Table 36).

Figure 27A **REE (kcal/day) - Effect of resection extent**

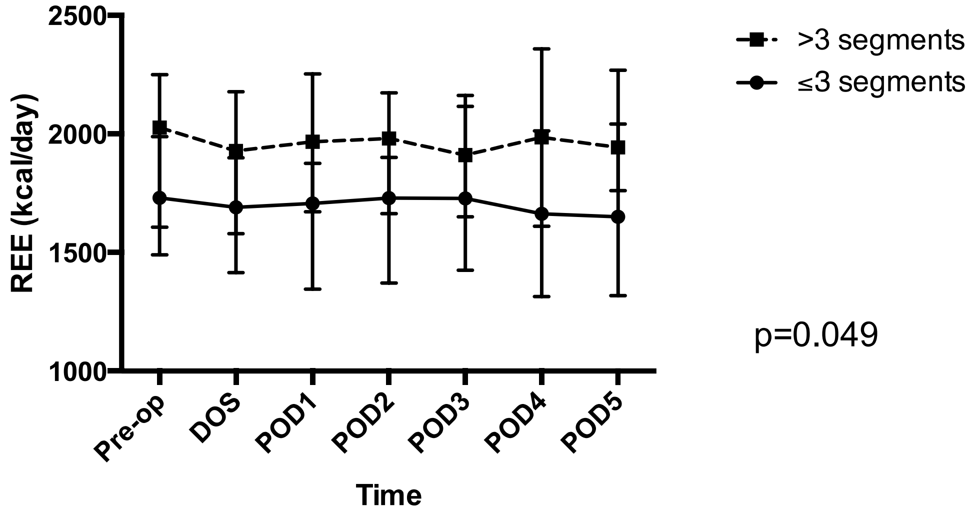
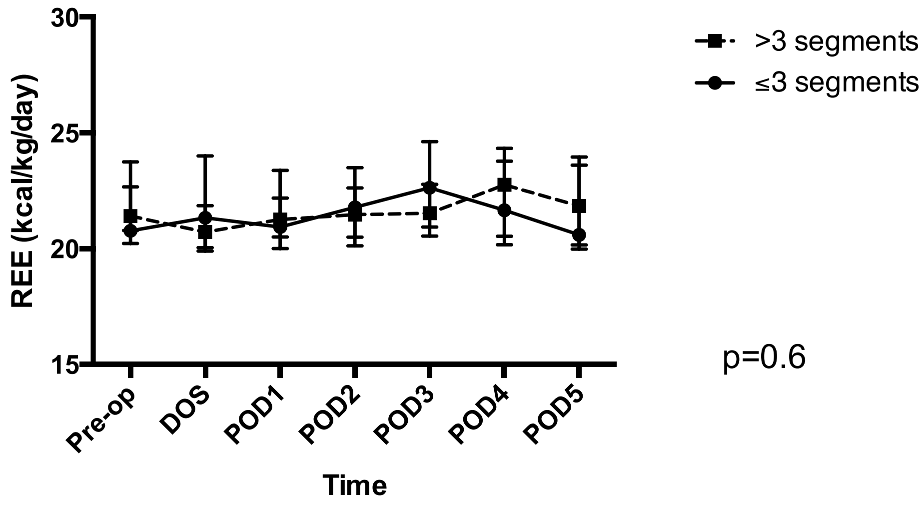
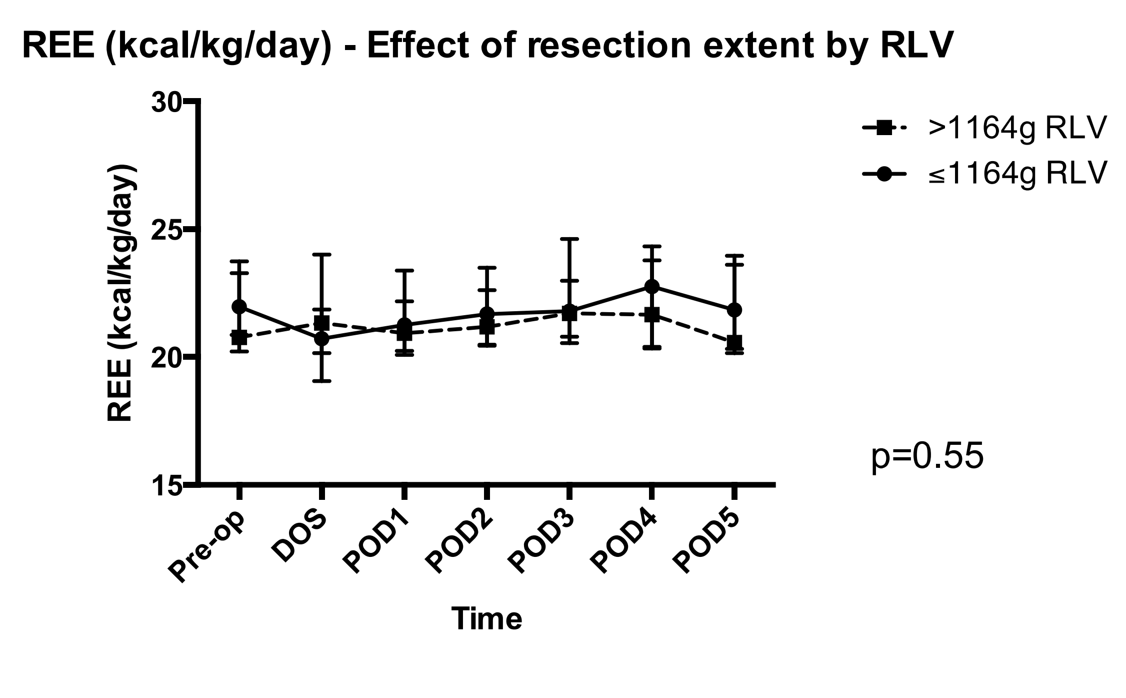


Figure 27B **REE (kcal/kg/day) - Effect of resection extent**



Figures 27A-B. The effect of the extent of resection on REE. Figure 27A compares daily REE (median, IQR) between patients as measured by kcal/day. Figure 27B compares the same factor but assessed kcal/kg/day.

Figure 27. Effect of resection extent on REE



Data presented as median (IQR)

Figure 28. Effect of resection extent on REE by RLV

Patient Variable	≤11% REE rise (n=12)	>11% REE rise (n=11)	P value
Age (years)	56.5 (53.0-64.8)	70 (56.0-74.0)	0.017[a]
Male	9 (75)	8 (72.7)	1.0[b]
Weight (kg)	78 (67.2-91.2)	89 (77.4-101.0)	0.17[a]
BMI (kg/m²)	25.4 (22.6-29.35)	28 (25.9-34.3)	0.08[a]
EBL (ml)	675 (325-975)	1500 (250-2000)	0.2[a]
Length of operation (mins)	207 (141-229)	255 (210-388)	0.03[a]
Pringle (mins)	0 (0-25)	27 (0-60)	0.13[a]
RLV (g)	1059 (859-1739)	1590 (951-2018)	0.25[a]
Neoadjuvant Chemotherapy	9 (75)	5 (45)	0.2[b]
Biceps (mm)	8.8 (7-12.8)	11.2 (10-14.1)	0.17[a]
Triceps (mm)	17.6 (10.0-19.0)	15 (8.0-17.0)	0.28[a]
Subscapular (mm)	16 (14.2-18.9)	18.0 (16.0-25.8)	0.14[a]
MUAC (cm)	27.5 (24.8-29.8)	29 (27.0-30.5)	0.4[a]
Waist (cm)	96 (92.2-101.8)	98.0 (94.0-114.0)	0.35[a]
FFM (kg)	58.0 (44.6-65.3)	63.4 (51.0-69.1)	0.44[a]
BF%	26.2 (22.8-32.1)	29.6 (28.4-35.3)	0.2[a]
Pathology			
CLM	9 (75)	7 (63.6)	0.67[b]
HCC	1 (8.3)	2 (18.2)	0.59[b]
Cholangiocarcinoma	1 (8.3)	0 (0)	1.0[b]
Other metastasis	1 (8.3)	2 (18.2)	0.59[b]
ASA			
I	2 (16.7)	0 (0)	0.48[b]
II	10 (83.3)	10 (90.9)	1.0[b]
III	0 (0)	1 (9.1)	0.48[b]

CLM – Colorectal liver metastasis, HCC – Hepatocellular carcinoma. EBL – Estimated Blood Loss, SFT –Skin fold thickness, MUAC – Mid upper arm circumference, FM – Fat mass, BF – Body fat. [a] Mann Whitney *U* test, [b]Fishers exact test. Data are presented as median (IQR) or n (%).

Table 35. Baseline characteristics of two groups divided according to REE rise

Post-operative Factor	≤11% REE rise (n=12)	>11% REE rise (n=11)	P value
LOS (days)	7 (5-10)	7 (5-10)	0.87[a]
Complications	5 (41.7)	4 (36.4)	0.8[b]
Segments resected	4 (1-5)	3 (2-4)	0.45[b]
Peak ALT (U/L)	286 (169-504.5)	258 (82-534)	1.0[a]
Peak Bilirubin (μmol/L)	28 (23.2-46.2)	26 (16-38)	0.51[a]
Peak WCC (x10^9/L)	13.65 (11.6-17.7)	12.5 (9.5-14.1)	0.24[a]
Peak temp (degrees C)	37.9 (37.8-38.3)	38.2 (37.5-38.4)	0.92[a]
Peak PT (seconds)	17 (14-21.5)	18 (16-19)	0.75[a]

LOS – Length of stay, ALT – Alanine Transaminase, WCC – White cell count, PT – Prothrombin Time. [a] Mann Whitney *U* test, [b]Fisher's exact test. Data are presented as median (IQR) or n(%)

Table 36. Post-operative data of two groups divided according to REE rise

9.5 Discussion

This study attempted to validate the measurement of REE with a mobile device after liver resection. We were able to show validation and agreement of the two methods although the 95% limits of agreement were wide.

No significant difference was observed between the pre and post-operative REE recorded by the two methods. Pre- and post-operatively the IC and SWA showed significant regression coefficients, providing evidence that the two methods of measuring REE are in agreement with each other. However it is crucial when validating a measuring device to establish the accuracy with which it is measuring the intended outcome and to what degree the two devices are reaching the same measurement. For this reason the Bland Altman plots were performed.

In this study pre-operative REE measurement between IC and SWA showed 95% limits of agreement of 8.01 kcal/kg/day. Post-operatively, similar significant correlation coefficients were seen, and the 95% limits of agreement were 8.74 kcal/kg/day. This means that any measurement of REE by SWA could be erroneous by as much as 8.74 kcal/kg/day. And so, for a 70kg man this would equate to a potential error of up to 611 kcal/day when compared to indirect calorimetry, the gold standard REE measuring device. The acceptability of this is challenging to determine definitively and it is the clinical relevance of the potential error that is important to consider.

The SenseWear Armband has been validated in healthy adults. [236] It has also been validated in patients with underlying disease including malignancy [238] and chronic respiratory disease. [246] Magnitudes of between 444kcal/day and 572kcal/day were seen in these studies when assessing the limits of agreement. In our study the post-operative limits of agreement are comparable to these findings. This difference is unlikely to represent a significant clinical compromise but this is important to consider when measurements are performed.

The SWA has never been validated with IC in patients who have recently undergone abdominal surgery. The SWA detects movement, temperature change and heat flux to estimate the REE based on proprietary logarithms. The influence of the host post-operative response to trauma on resting energy expenditure is unpredictable. Crisafulli *et al* [246] found the SWA to underestimate REE in patients with chronic respiratory failure when compared to the IC measurement. Factors such as post-operative infection and respiratory dysfunction may affect REE and not be detected by the SWA. In this study, an overall under-estimation of REE by the SWA is suggested and is therefore a potential disadvantage of the SWA in this set of circumstances.

The second focus of the study was to establish the effects of liver resection on REE. Initially an assessment was made with pre- and peak post-operative REE measurements with SWA and these were compared with the Harris Benedict equation.

SWA pre- and post-operative REE measurements were significantly higher than REE predicted by the HB formula. This suggests that pre-operative patients with liver tumours are actually hypermetabolic. Okamoto *et al* [247] found patients with oesophageal carcinoma to have higher measured REE when compared to healthy controls. Conversely, in patients undergoing Whipples procedure, Sasaki *et al* [248] and Vaismon *et al* [249] found that measured REE by IC was no different to REE predicted by the Harris Benedict equation, suggesting that these patients, with mainly cholangiocarcinomas and pancreatic tumours, were not in a hypermetabolic state. The potential explanation for high pre-operative metabolic rate in the current study is the presence of advanced malignancy, and subsequently, cachexia that is not necessarily a contra-indication to surgery, therefore allowing inclusion into the study. This is unlike other malignancies, where patients with advanced disease, associated with hypermetabolic states, are often deemed irresectable and therefore not put forward for surgery or included in similar studies. [249]

Post-operatively, there were significantly higher REE recordings for the SWA REE groups when compared to HB prediction of REE and when compared to pre-operative levels as measured by SWA. This suggests that post-operatively, patients become even more hypermetabolic, as a result of the surgery, in a manner that is not predicted by formulaic equations.

Several studies have assessed REE after abdominal surgery. As mentioned above Okomato *et al* [247] and Sasaki *et al* [248] looked at oesophagectomies and Whipples procedure respectively and both reported a significant post-operative REE rise (as measured by IC and compared to HB and pre-operative values). Fredrix *et al* [235] also reported a 10% rise in REE following major gastrointestinal surgery.

The current study is in agreement with these findings with a median rise of 11% being reported in patients after liver resection. One investigator [250] found patients who had undergone liver resection had significantly higher REE post-operatively compared to those who had undergone gastrointestinal surgery. This may indeed be the case, however the crucial factor when determining the effect of a procedure on REE is the change in REE above pre-operative baseline rather than an isolated measurement.

The likely reason for the post-operative rise in REE is related to the inflammatory response to the trauma of surgery. [250] The resultant increase in muscle catabolism, gluconeogenesis and lipolysis as a result of endocrine, immune and sympathetic response to tissue injury, requires calories as part of the energy dependent processes. The current study, in agreement with previous work suggests this is, on average about 11 per cent rise from baseline after liver resection.

However the range of change of REE from baseline was wide, with some patients actually dropping REE post-operatively and others increasing much beyond eleven per cent. Previous investigators have addressed post-operative REE rise by adding a stress factor to the Harris Benedict equation to account for the post-operative rise. [248] However the ability to measure REE on a real time basis and tailor nutritional input according to REE is preferable and is associated with improved mortality rates in critically ill patients. [234] Optimisation of nutritional status in the critically ill or post-operative patient is increasingly viewed as a key care component. [251] This is a therapeutic area where the SWA could provide benefit. In light of the practical difficulties associated with IC measurement, notably the fact that it can only be used for short periods and is not particularly comfortable for patients, SWA use post-operatively can provide individualised REE updates to guide nutritional input, based on the validated findings of this study.

The final focus of the study was to determine if any factors were associated with a greater rise in REE. After we had divided the cohort into two groups based on their rise in REE from baseline, factors associated with the rise were sought. Surprisingly the group with a higher rise in REE were significantly older. This is surprising because REE decreases with age. [252, 253] However the effects of age on REE post-operatively are not well investigated with no previous study assessing age and REE after liver surgery.

Ishikawa *et al* [250] found hypermetabolic changes in elderly patients undergoing gastrointestinal surgery compared to younger patients. Older patients have been shown to have an exaggerated post-operative inflammatory response [254] and this is likely to contribute to REE increase. Aging is however associated with a decreased sympathetically mediated component of REE [255] and so other factors are likely to contribute to the rise beyond merely age. The length of operation was also significantly longer in patients experiencing a greater REE rise. Blood loss was also higher in this group, but this was not statistically significant. A combination of these factors is likely to result in an increased surgical insult and corresponding inflammatory surge, which could all manifest in an increased post-operative REE rise.

Body composition is another important variant when predicting REE. In this study the BMI was higher in the group with an increased rise (although not significantly so), yet the FFM was not significantly different. Lean body tissue is known to consume a greater proportion of oxygen than adipose tissue [256] and is a predictor of REE. However the effect of body composition on REE change after surgery is not well known and our study suggests that patients with a high BMI, may have a greater magnitude of REE rise compared to their baseline REE, and could represent those at greatest risk of post-operative malnutrition secondary to inadequate replacement of calories expended.

The volume of liver resected was not associated with a significant rise in REE. This had previously been speculated due to the effect of liver regeneration on metabolic rate. This did not affect REE rise, indeed the residual liver volume was lower in the group with a smaller rise in REE. Therefore other factors should be considered following liver resection when determining nutritional requirements, namely, length of procedure itself.

The small number of participants in the study prevented meaningful multivariate analysis to be performed thus preventing independent predictors of REE rise to be fully identified.

The findings of this prospective observational study suggest that the effects of liver resection on post-operative REE are variable and not necessarily predictable. Current literature has a large evidence base on REE and particularly, predictors of baseline

REE. However the effects of surgery on REE are less well investigated. No previous study has investigated the effects of liver surgery on REE change or factors associated with REE rise.

The implications of these findings are that certain patients are likely to have unpredictable nutritional requirements. Measurement of REE pre- and post-operatively could be a useful adjunct to dietician care in order to screen for those who might benefit from additional nutritional support as a result of an increased REE rise. The use of SWA to assist with this would allow an acceptable, lightweight monitoring device to provide updated REE measurement.

The results of this study should be interpreted in light of the following limitations. First of all it is a small sample size. This therefore potentially allows type two error to be introduced to the analysis. Moreover, the small cohort reduces the potential power of the validation of the two methods of REE measurement and prevented meaningful multivariate analysis.

Secondly the IC assessment was only able to be performed once the patients were able to be mobilised to the clinical research facility where the IC was housed. This meant that they were free of oxygen requirements and well enough to be off the general ward for one hour. This meant that the first two post-operative days were not assessed. However the primary purpose of the IC was to validate the SWA that was worn continuously to review POD 1 and 2 REE.

In conclusion, the SWA provides a validated alternative to IC in measuring REE after liver resection. REE increases after liver resection and certain factors, namely age, and operative time are associated with an increased rise in REE. The use of SWA to determine REE after liver resection could guide post-operative nutritional input.

9.6 Chapter Publication

Energy Expenditure After Liver Resection: Validation of a mobile device for estimating resting energy expenditure and an investigation of energy expenditure change after liver resection. Hughes MJ, Harrison EM, Wigmore SJ. Accepted for publication by Journal of Parenteral and Enteral Nutrition July 2015.

10 Acetaminophen Metabolism After Liver Resection: A Prospective Case Control Study

10.1 Summary

Acetaminophen has an important role as part of a multimodal analgesic regimen following major surgery. Little is known about acetaminophen metabolism after liver resection, in particular if it is affected by residual liver volume (RLV). This study aims to investigate the effects of major liver resection on acetaminophen metabolism. Patients undergoing liver resection were administered post-operative oral acetaminophen at a therapeutic dose. Urinary acetaminophen metabolites were prospectively measured by High Pressure Liquid Chromatography (HPLC) over the first three post-operative days following liver resection. Whole blood glutathione was also measured pre-operatively and the first and third post-operative days. A subgroup analysis was performed to assess the effect of therapeutic acetaminophen on patients with low RLV. Two way repeated measures ANOVA was used to compare metabolite levels between groups over three days. 41 patients completed the study. For the whole cohort, the glutathione dependent metabolites (cysteine and mercapturate) increased over the study period. Glutathione significantly reduced by POD3. Group A (n=11) had a median RLV of 876g (IQR 708-892) and was compared with a matched control group B (n=11) with median RLV of 2434g (IQR 2305-2493). Group A had significantly higher levels of cysteine (p=0.048) and sulphate (p=0.047). No difference was observed in glutathione or 5-oxoproline levels over three post-operative days between the groups suggesting replete glutathione levels despite low RLV. In conclusion**,** low RLV results in altered acetaminophen metabolism, however,

in this study, no evidence of glutathione deficiency was evident, suggesting that therapeutic acetaminophen is safe when RLV is low, providing the liver is functioning adequately.

10.2 Introduction

Liver resection is now an established surgical treatment for both primary and secondary liver tumours. The most common indication in the UK is for colorectal liver metastases, and it can offer long term survival for these patients of up to 60% over five years. [257] Although contemporary approaches aim to minimise the resection volume, extended resections remain necessary, depending on the bulk and distribution of the disease. The limits of resectability centre on the future liver remnant (FLR), and in patients with normal liver parenchyma, up to 75% of the liver can be removed. [258]

Liver resection is a major procedure with mortality rates of up to five per cent and morbidity rates of up to 45 per cent. [73] Common complications include biliary leaks, liver remnant failure and infective complications including intra-abdominal abscess and respiratory infections. [81]

Following liver resection enhanced recovery care protocols have contributed to improving post-operative recoveries by reducing overall morbidity rate and lengths of hospital stay. [172] Optimum pain control is an essential component of the enhanced recovery post-operative care pathway. Multimodal analgesia is used involving a combination of simple analgesia and regional techniques in an attempt to minimise opiate consumption. High opiate use is associated with reduced mobility, respiratory infections, post-operative nausea, vomiting and prolonged hospital stay. [45] The combination of analgesic techniques allows a reduction in the use of opiate analgesia.

Therefore a good basis of simple analgesia at the appropriate dose is required when attempting to control post-operative pain with more advanced techniques, enhance recovery and reduce complications. [259]

Acetaminophen is the mainstay of simple analgesia and is given routinely to patients following liver resection in doses of up to four grammes per 24 hours. Dosing guides have been established based on use of the drug in healthy individuals. Acetaminophen taken in excess can lead to hepatotoxicity. This has been observed in healthy individuals at doses of less than twice the recommended limit. [260] The appropriate dose to use following liver resection is unclear. Hepatotoxicity in patients following liver resection results in the increased risk of liver remnant failure, which is a major cause (18%) of post-operative mortality following liver resection. [261]

Acetaminophen is metabolised by the liver (Figure 29). Glucuronidation and sulphation produces non-toxic end products. In normal individuals, approximately five per cent of acetaminophen is metabolised via the cytochrome P450 pathway producing the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). If NAPQI is not metabolised by glutathione to cysteine or mercapturate it binds to hepatocytes and leads to cell death. [262] In acetaminophen overdose, the cytochrome P450 pathway is overwhelmed and glutathione rapidly depleted, resulting in a toxic accumulation of NAPQI. Clinically this may manifest with fulminant hepatic failure, multi-organ failure and death.

5-oxoproline is produced as a result of disordered glutathione metabolism or glutathione deficiency. Glutathione is produced by the gamma-glutamyl cycle. In this cycle, formation of glutathione leads to a negative feedback inhibition of G-glutamylcysteine synthase therefore stopping further production of glutathione. When glutathione is deficient, g-glutacysteine synthase is not inhibited by g-glutacysteine. High levels of g-glutamylcysteine leads to formation of 5-oxoproline. [263]

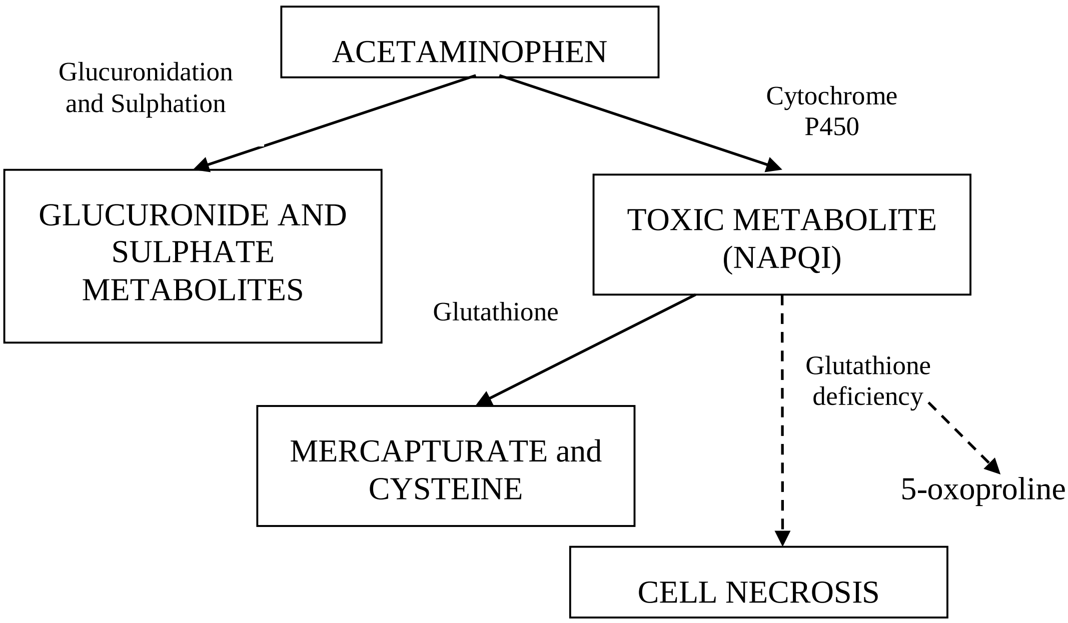


Figure 29. Acetaminophen metabolism

Liver resection results in a predictable reduction in liver remnant volume. [244] The clinical concern is that following a significant reduction in liver volume inadvertent acetaminophen overdose could occur following therapeutic dosage. To use acetaminophen safely in these patients it is imperative to know if therapeutic doses are potentially hepatotoxic following liver resection.

Currently, due to a lack of evidence, acetaminophen is either administered in a reduced dose or avoided entirely in patients following extended liver resection, particularly in patients of low body weight. This is empirical and dose reduction or avoidance is instituted at the discretion of the operating surgeon. Whilst this concern is often expressed in patients who have had an extended resection (70-75% of liver excised), those patients undergoing a hemihepatectomy (40 or 60% of liver excised) are usually administered full dose acetaminophen. It is not known if this may contribute to the postoperative liver impairment that can be seen in these patients.

Therefore this study prospectively analysed the acetaminophen metabolism of patients undergoing liver resection, and related this to liver remnant volume. Acetaminophen levels and the markers of hepatotoxic risk, mercapturate and cysteine, were quantified in all patients. Metabolites of patients who had small RLV were compared to patients undergoing minimal liver resection to provide comparison levels.

10.3 Methods

The trial protocol was prospectively published on clinicaltrials.gov (NCT01770041). After gaining approval from the South East Scotland Research Ethics Committee patients undergoing liver resection at the Royal Infirmary of Edinburgh, UK, were approached and given written information regarding the trial after an initial discussion at the pre-admission clinic. Written informed consent was obtained on the day of surgery or sooner if appropriate.

10.3.1 Patients

Patients undergoing liver resection were approached to enter the study. The exclusion criteria were: contra-indication to acetaminophen administration, inability to give written, informed consent, jaundice (Bilirubin > 100 μmol/L), liver resection combined with secondary surgical procedure, age < 18 years and pregnancy.

10.3.2 Perioperative Care

Patients were admitted on the morning of surgery having fasted for six hours and taken clear fluids up to two hours prior to surgery. Patients underwent induction of anaesthesia with propofol, atracurium and fentanyl (1-2 microg/kg). Maintenance of anaesthesia was achieved by desflurane or sevoflurane. At induction patients routinely received a central venous catheter in the right internal jugular vein, radial arterial cannulation and a urethral catheter. Routine monitoring of CVP, invasive continuous blood pressure and mean arterial pressure, end tidal CO_2, heart rate, oxygen saturations and urine output were performed throughout the operation.

The peritoneal cavity was entered via a right subcostal incision that was extended if required superiorly in the midline. A full laparotomy was performed to ensure no contra-indications to resection were evident. Intra-operative ultrasound was performed by the operating surgeon to establish resectability and to formulate a final operative approach. Transection of the liver parenchyma was performed with Cavitron Ultrasonic Aspirator (CUSA, ValleyLab, Boulder, Colorado, USA) and monopolar diathermy. Transection was performed in accordance with the patient's pathological, oncological and physiological requirements to ensure optimum short and long term outcome.

Routine thromboprophylaxis and peri-operative antibiotics were administered immediately prior to incision. Intra-operative warming was routinely performed. Intra-peritoneal drains and NG tubes were not routinely administered and intra-operative fluid management was restricted to 80-100mls/hour.

10.3.3 Acetaminophen Administration

Patients were administered 1g of acetaminophen every six hours with a maximum of four grammes per 24 hours. The first dose was administered intravenously at the end of the operation prior to extubation. Subsequent doses were administered orally. Acetaminophen administration continued to at least the fourth post-operative day as per unit protocol. Patients were excluded from analysis if they did not receive complete administration of acetaminophen from day of surgery to the end of post-operative day three.

10.3.4 Sample Collection

24 hour urine collections were performed daily until the morning of the fourth post-operative day. From this, 20ml aliquots of urine were taken on each post-operative day and stored at -20 degrees centigrade for subsequent analysis of acetaminophen metabolites.

Blood tests were obtained by venepuncture pre-operatively and on the morning of post-operative days one and three. Collection of 10mls of whole blood was obtained in one heparinised tube and one EDTA tube. Whole blood aliquots were obtained from the EDTA tube and transferred to 1.5ml polypropylene Eppendorf tubes and stored at -80 degrees centigrade until batch analysis was performed.

10.3.5 Data Collection

Demographic patient data were collected including age, sex, ASA and weight. Intra-operative data were collected. Operation performed, length of operation and estimated blood loss (EBL) were prospectively recorded. Extent of resection was assessed in two ways. The first was to report the number of segments resected, and secondly we calculated the residual liver volume (RLV) by calculating the liver volume based on

Chouker *et al* [243] and subtracting the percentage of liver resected according to pre-determined values. [244]

The pathology of the resected specimen was also obtained and details of background liver parenchyma and pathology of tumour were obtained directly from the original pathology report.

Post-operatively clinical data were collected. Length of stay, i.e. length of time spent in hospital, and morbidity rate were recorded. Patients were observed for complications on a twice daily basis by the researcher. Complications were diagnosed and managed by the clinical team and morbidity rates reported accordingly. Routine post-operative blood tests were taken daily from POD 1-4.

10.3.6 Primary Outcome

The primary outcome assessed was the urinary metabolite levels of the glutathione dependent mercapturate and cysteine.

10.3.7 Secondary Outcomes

Further metabolites were assessed: 5-oxoproline, glucuronamide and sulphate. Glutathione and plasma acetaminophen levels were obtained pre-operatively and on POD 1 and POD 3.

10.3.8 Groups

A comparison of metabolite levels was made between groups of differing residual liver volume. Predicted RLV of <35.5% was determined to be a volume at risk of therapeutic acetaminophen overdose. [244] This was combined with a weight based estimation of liver volume [243] and a group was populated with the patients with estimated RLV of <1000g and estimated remaining volume of <35.5% (group A). A matched comparison group of patients who had undergone minimal or no liver resection was also created to provide a control group. Patients with a resection volume of <10% and with the largest estimated RLV were observed to act as a control group (group B) in which normal acetaminophen metabolism, after liver resection, would be expected.

10.3.9 Hypothesis

It was hypothesised that the glutathione dependent metabolites (cysteine and mercapturate) would be greater in Group A when compared to the control group B when measured repeatedly over three post-operative days following liver resection.

10.3.10 Analysis

Plasma acetaminophen levels were analysed in the biochemistry laboratory of the Royal Infirmary of Edinburgh. Levels of urinary mercapturate, cysteine, 5-oxoproline, sulphate and glucuronamide were quantified by High Pressure Liquid Chromatography (HPLC). This is a well-validated technique and has been used to establish urinary acetaminophen metabolite levels in other clinical settings including major surgery [264] and acute liver failure. [265] Glutathione levels were obtained from samples of whole blood via enzymatic recycling method as described by Rahman *et al*. [266]

10.3.11 Statistical Analysis

All statistical analysis was performed using SPSS version 19.0 (IBM, Armonk, New York, USA). A p value of <0.05 was adjudged to represent statistical significance. Assessment of the entire cohort was performed initially and then the patients were divided into two groups depending on residual liver volume (RLV). T-test or Mann-Whitney *U* test was used to assess differences between independent continuous data. Linear regression analysis was performed to assess the relationship between RLV and logged concentration of the urinary metabolite levels. Paired t-test or Wilcoxon signed-rank analysis was performed to assess differences between dependent continuous data. Chi square analysis was performed to compare dichotomous data. Two way repeated measures ANOVA test was performed to compare differences between metabolite levels between groups over the first three post-operative days.

10.4 Results

The trial was conducted between March 2013 and March 2014. 79 patients were recruited initially. Of these, 37 were subsequently excluded because they did not compete the full course of acetaminophen. Of these, 17 patients had a reduced dose of acetaminophen due to concern over liver function and so were excluded from the analysis. A further 20 patients were excluded because they did not complete the acetaminophen administration over the first three post-operative days because of either refusing acetaminophen or missing a dose therefore not receiving the standard full administration. 42 patients completed the acetaminophen administration. One patient did not comply with urine collection and so was unable to be included. 41 patients were included in the final analysis.

10.4.1 Demographic Characteristics

The baseline data of the whole patient cohort are shown in Table 37. The patients received resection for colorectal liver metastases (CLM) in the majority of cases. 19 (46.3%) patients underwent a major resection (more than or equal to three segments resected) with the remainder undergoing minor resection. The majority of patients had evidence of chemotherapy related liver injury with 15 (36.6%) patients having normal background liver parenchyma after pathological examination. Post-operative morbidity is reported in Table 38.

Variable	Total cohort (n=41)
Female	17 (41)
Age	62 (53-72)
ASA	
I	4 (9.8)
II	28 (68.3)
III	9 (22.0)
Weight (kg)	78.0 (72.4-86.5)
Operation length (mins)	180 (135-250)
EBL (mls)	600 (378-1124)
Pringle time (mins)	0 (0-21)
Segments resected	
5	3 (7.3)
4	11 (26.8)
3	5 (12.2)
2	1 (2.4)
1	12 (29.3)
<1	9 (22.0)
Pathology of tumour	
CLM	29 (70.7)
HCC	5 (12.2)
Cholangiocarcinoma	1 (2.4)
Benign	6 (14.6)
Background liver	
Steatosis	22 (53.7)
Steatohepatitis	7 (17.1)
Sinusoidal dilatation	9 (22.0)
Fibrosis	9 (22.0)
Cirrhosis	4 (9.8)
Normal liver	15 (36.6)

CLM – Colorectal liver metastasis, HCC – Hepatocellular Carcinoma. Data are presented as n(%) or median (IQR).

Table 37. Patient characteristics

Morbidity	**n(%)**
Intra-abdominal abscess	3 (7.3)
Pneumothorax	1 (1.7)
Bile leak	1 (1.7)
Confusion	1 (1.7)
Lower respiratory tract infection	2 (4.9)
Cardiac	1 (1.7)
Wound infection	2 (4.9)
Ileus	1 (1.7)
Acute urinary retention	1 (1.7)
Nausea and vomiting	2 (4.9)
Acute kidney injury	4 (9.8)
Sepsis	1 (1.7)
Hypotension	1 (1.7)
Total	**21 (51.2)**

Data are presented as n (%).

Table 38. Complications after liver resection

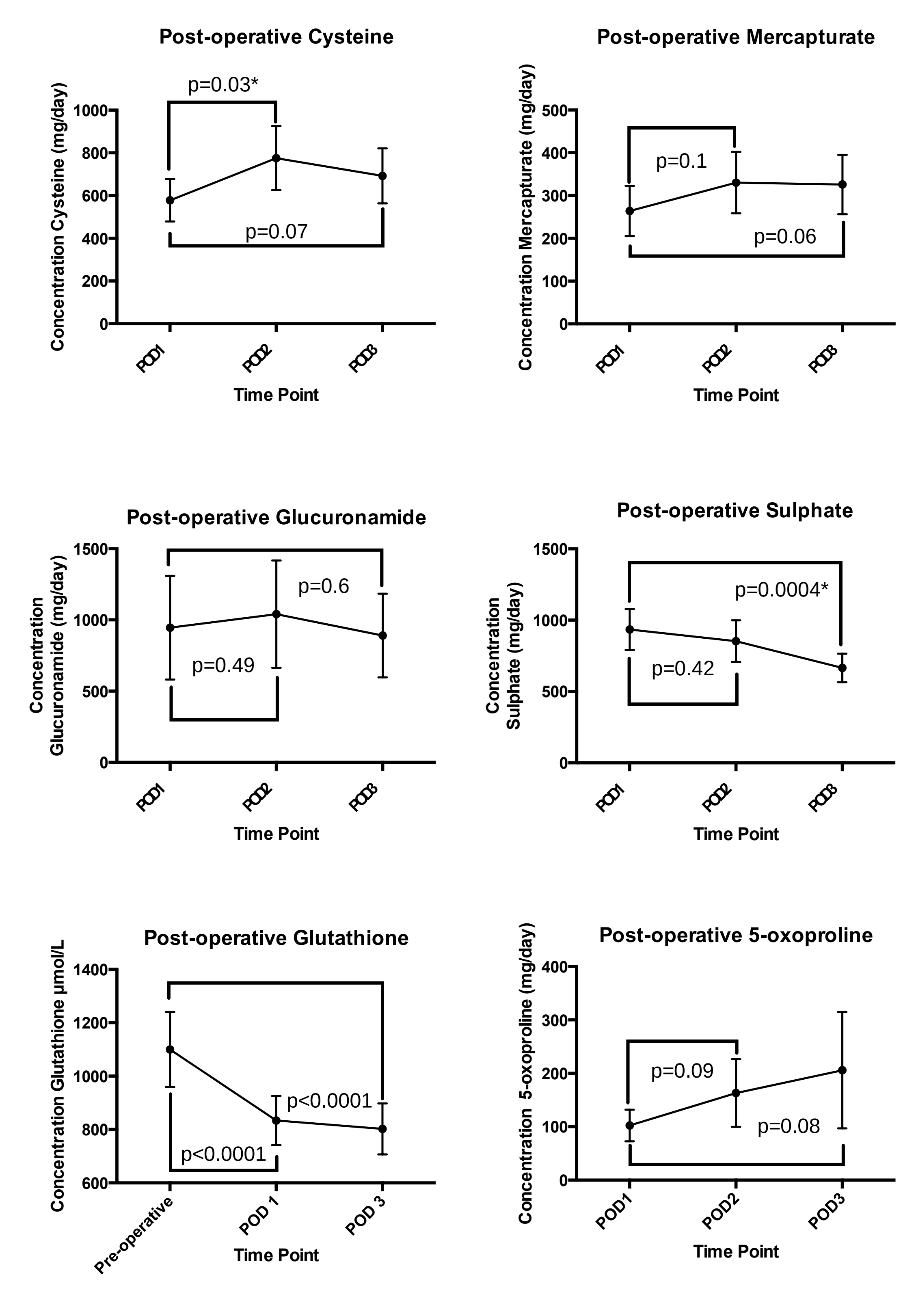
10.4.2 Urinary Metabolites After All Liver Resections

Figure 30 shows the urinary metabolites quantified over the first three post-operative days after liver resection. Urine collection was performed from the morning of POD1 to the morning of POD 4.

The glutathione dependent pathway metabolites were quantified. Cysteine was significantly raised on POD 2 compared to POD 1 however a drop from POD 2 to POD 3 was observed. The other glutathione dependent metabolite, mercapturate, increased over the measuring period although statistical significance was not reached ($p=0.06$) (Figure 30).

The normal metabolic pathway results in glucuronidation and sulphation of acetaminophen to produce the end products of glucuronamide and sulphate. Glucuronamide levels did not change over the three post-operative days with no significant difference observed between POD1 and POD3. In contrast sulphate levels were seen to decrease over the three post-operative days with significantly lower levels observed on POD3 when compared to POD1 (Figure 30).

Gluthathione levels dropped significantly post-operatively when compared to pre-operative levels. 5-oxoproline levels, a marker of glutathione deficiency, rose post-operatively but a statistically significant rise was not observed (Figure 30).



Data are presented as mean (95%CI)

Figure 30. Acetaminophen metabolite levels after liver resection

10.4.3 Residual Liver Volume And Acetaminophen Metabolites

The glutathione dependent metabolites are shown in Figures 31A-F. The relationship between volume and the glutathione dependent metabolites – cysteine (Figures 31A-C) and mercapturate (Figures 31D-F) – changed over the study period. On POD 2 a significant linear regression analysis between each of these metabolites and RLV was observed suggesting increased metabolite levels in lower volume livers. This was not evident on the other post-operative days.

When the non-glutathione metabolite levels were assessed, the same pattern of relationship between RLV and urinary levels of glucuronamide from days 1-3 was not observed (Figures 32A-C). Conversely, sulphate levels were seen to be significantly related to RLV on POD 2 representing higher urinary levels of sulphate in the patients with a smaller volume of remaining liver (Figures 32 D-F). This pattern, however, was not observed with 5-oxoproline (Figures 33A-C).

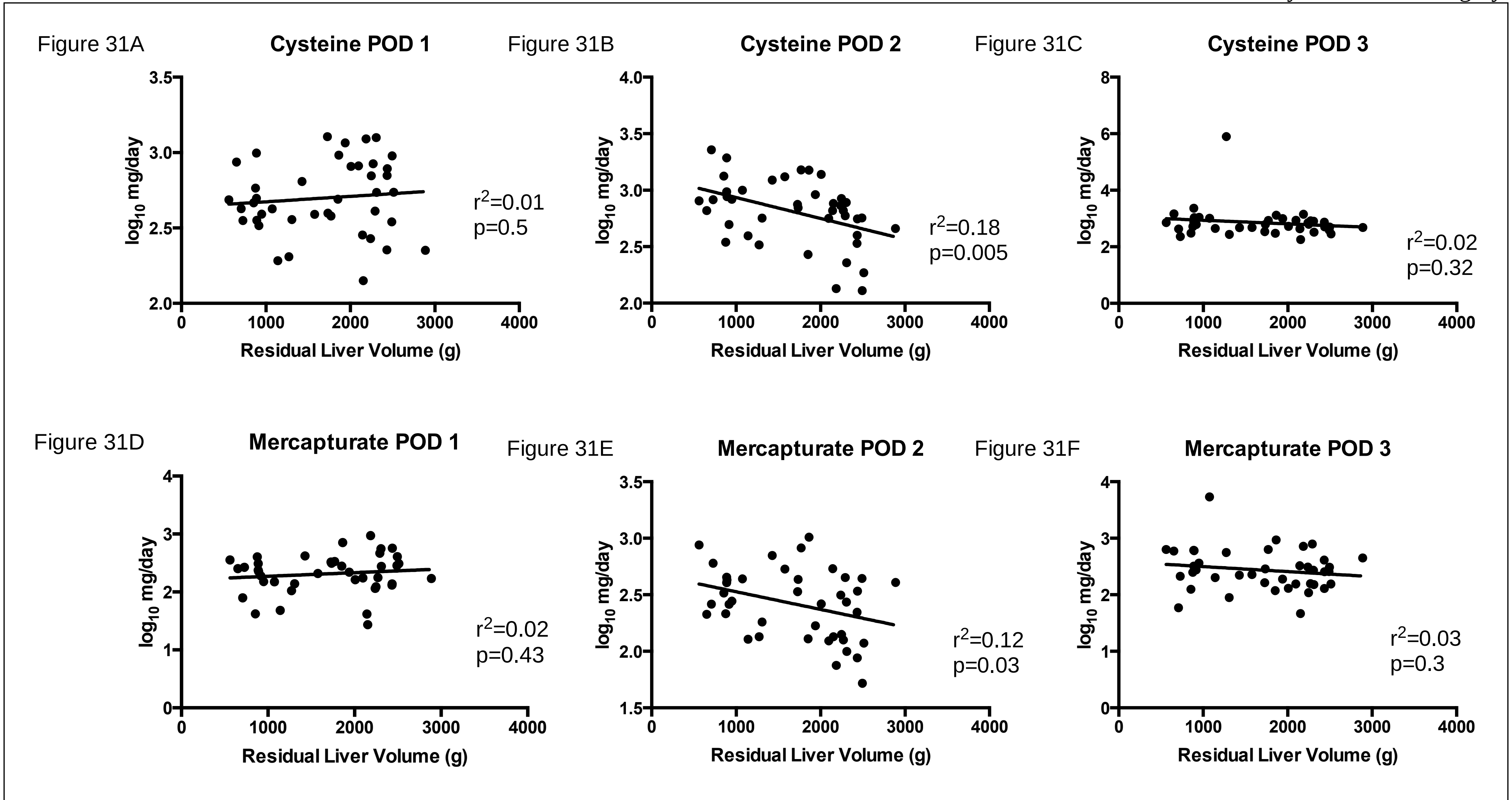


Figure 31. Glutathione dependent metabolites and RLV

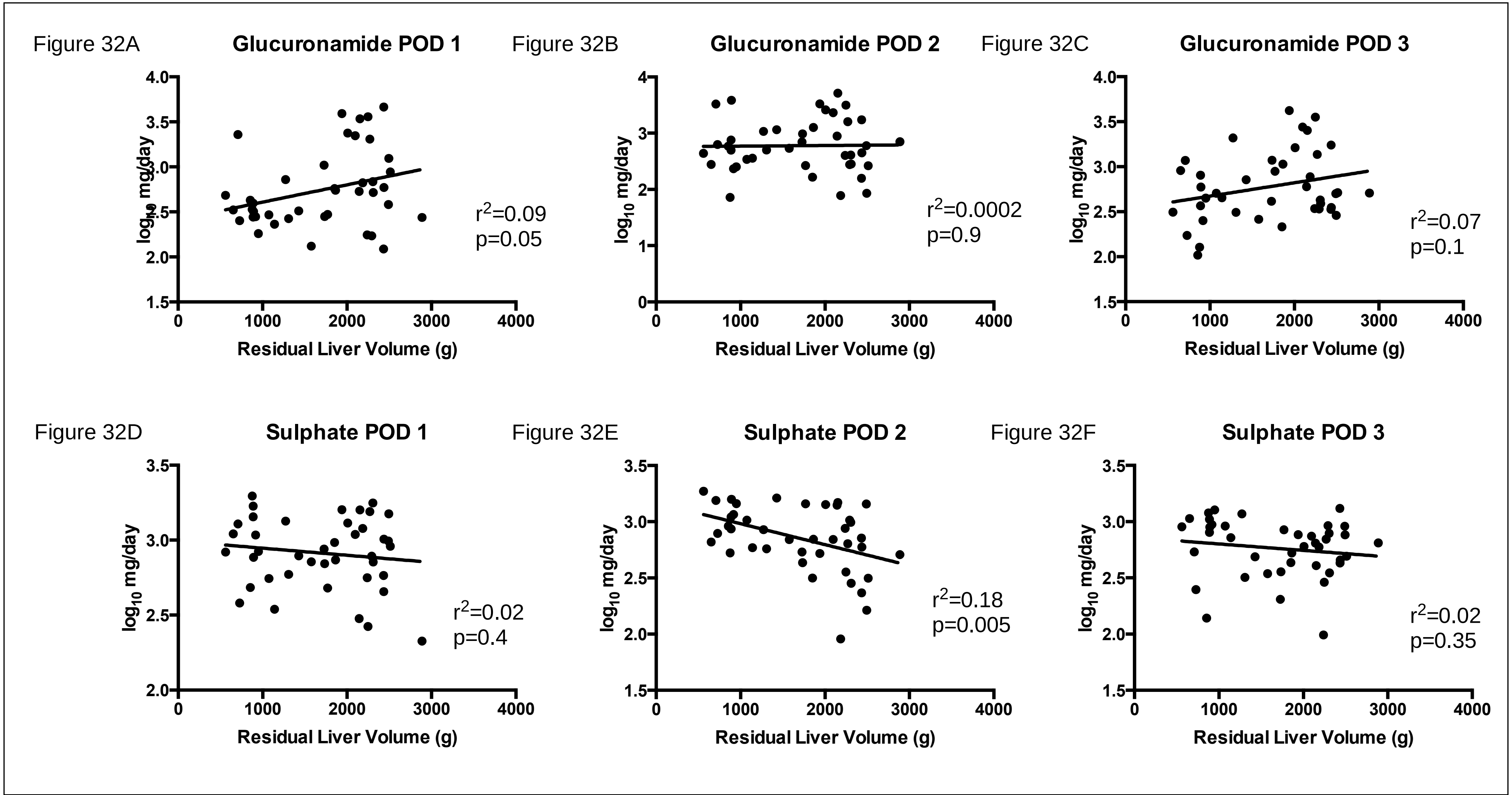


Figure 32. Non glutathione dependent metabolites and RLV

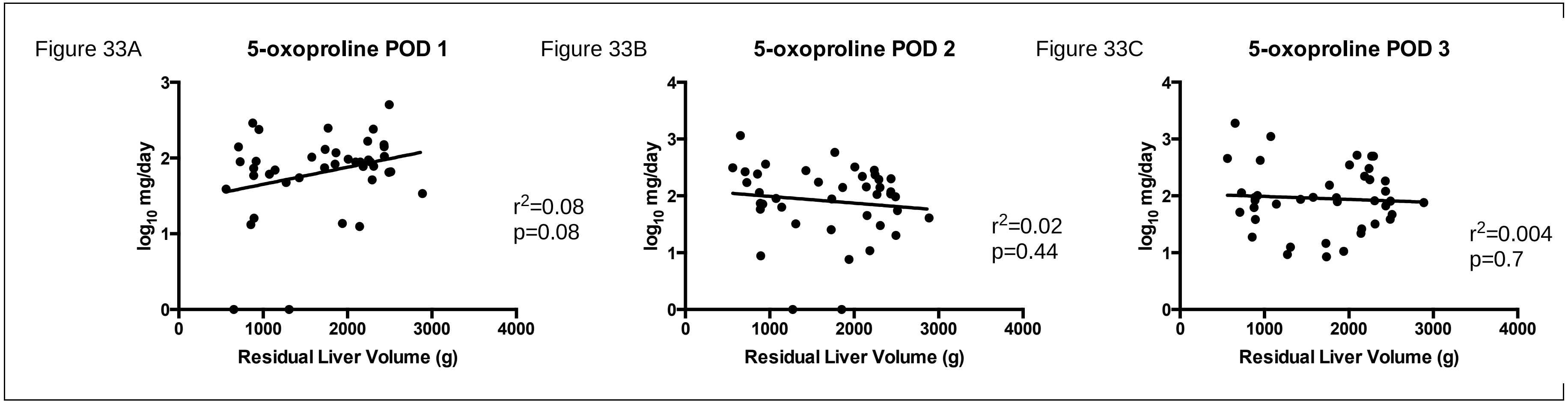


Figure 33. 5-oxoproline and RLV

10.4.4 Extent Of Liver Resection And Urinary Acetaminophen Metabolites

For the final stage of the analysis the cohort was split into two groups. The case group was comprised of patients who had low RLV, as defined as having less than or equal to 35.5% of their pre-operative volume and less than 1000g of residual liver remaining (group A; n=11). This group was matched with those with the highest RLV and less than 10% of liver resected (group B; n=11).

The demographic, operative and pathological characteristics of the two groups are reported in Table 39. As might be expected, median weight was higher in group B due to liver volume estimation being weight based. Group A had a greater number of segments resected and the greater length of operation observed reflecting the greater complexity of surgery in this group.

Plasma acetaminophen levels were significantly higher in group A over the study period and rose significantly from baseline in both groups (Figure 34). No difference was observed in post-operative ALT (Figure 34). Post-operatively group A were reported to have significantly higher levels of bilirubin over the three post-operative days (Figure 34).

Urinary acetaminophen metabolites were compared between groups. The glutathione dependent metabolites are reported in Figure 35. In group A, both cysteine and mercapturate levels rose significantly after POD 1 whereas the same metabolites in group B did not. Moreover group A cysteine levels were significantly higher over all three post-operative days after two way RM ANOVA analysis.

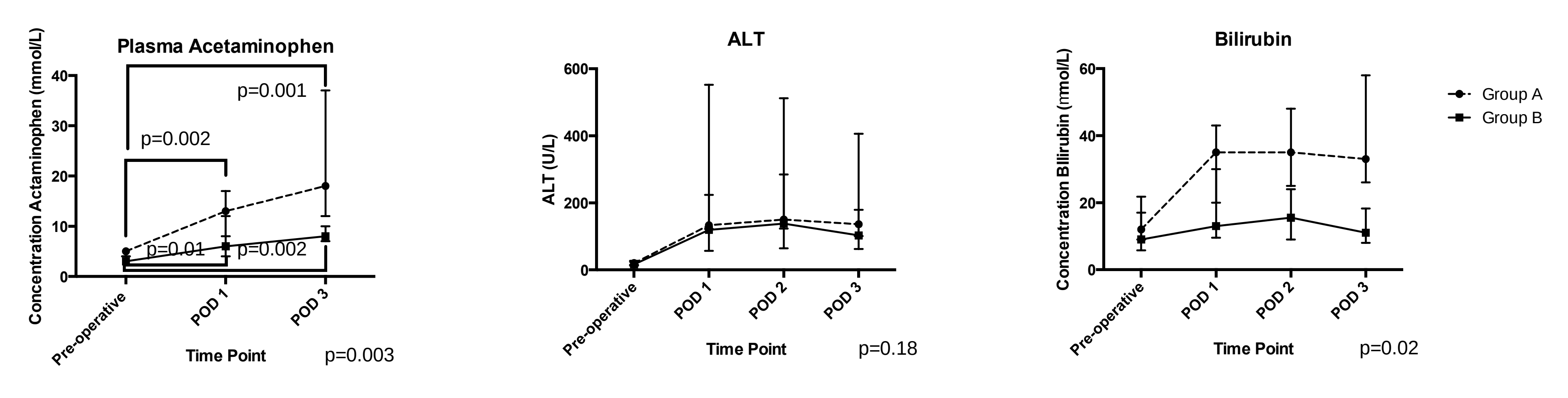
Metabolites produced as a result of the “normal” acetaminophen breakdown pathway, glucuronamide and sulphate, were also assessed. No difference was observed in glucuronamide between the groups over the three days (Figure 35), but sulphate levels were significantly higher in group A compared to group B although no rise from POD 1 was observed in either group (Figure 35).

Glutathione levels however, dropped significantly from pre-operative levels but were not altered between the two groups (Figure 35) and no difference in post-operative 5-oxoproline levels was observed (Figure 35).

Variable	Group A (n=11)	Group B (n=11)	*P* value
Female	4 (36.4)	0 (0)	0.09[a]
Age (years)	67 (56-77)	62 (57-70)	0.66[b]
ASA			
I	1(9.1)	0(0)	1.0[a]
II	7(63.6)	6(54.5)	1.0[a]
III	3(27.3)	5(45.5)	0.66[a]
Weight (kg)	75.0 (63.6-79.1)	87 (79.0-94.0)	0.002[b]
Operation length (mins)	250 (180-330)	135 (116-150)	0.0015[b]
Pringle (mins)	0(0-23)	0(0-22)	0.8[b]
Segments resected			
5	2(18.2)	-	
4	9(81.8)	-	
1	-	5(45.5)	
<1	-	6(54.5)	
RLV (g)	876 (708-892)	2434 (2305-2493)	<0.0001[b]
RLV (%)	35.5 (35.5-35.5)	90.3 (90.3-90.3)	<0.0001[b]
Pathology of tumour			
CLM	9 (81.8)	9 (81.8)	1.0[a]
HCC	0 (0)	1 (9.1)	1.0[a]
Cholangiocarcinoma	1 (9.1)	0 (0)	1.0[a]
Benign	1 (9.1)	1 (9.1)	1.0[a]
Background liver			
Steatosis	4 (36.4)	7 (63.6)	0.39[a]
Sinusoidal dilatation	5 (45.5)	0 (0)	0.04[a]
Steatohepatitis	1 (9.1)	2 (18.2)	1.0[a]
Fibrosis	3 (27.3)	2 (18.2)	1.0[a]
Cirrhosis	0 (0)	1 (9.1)	1.0[a]
Normal liver	5 (45.5)	4 (36.4)	1.0[a]

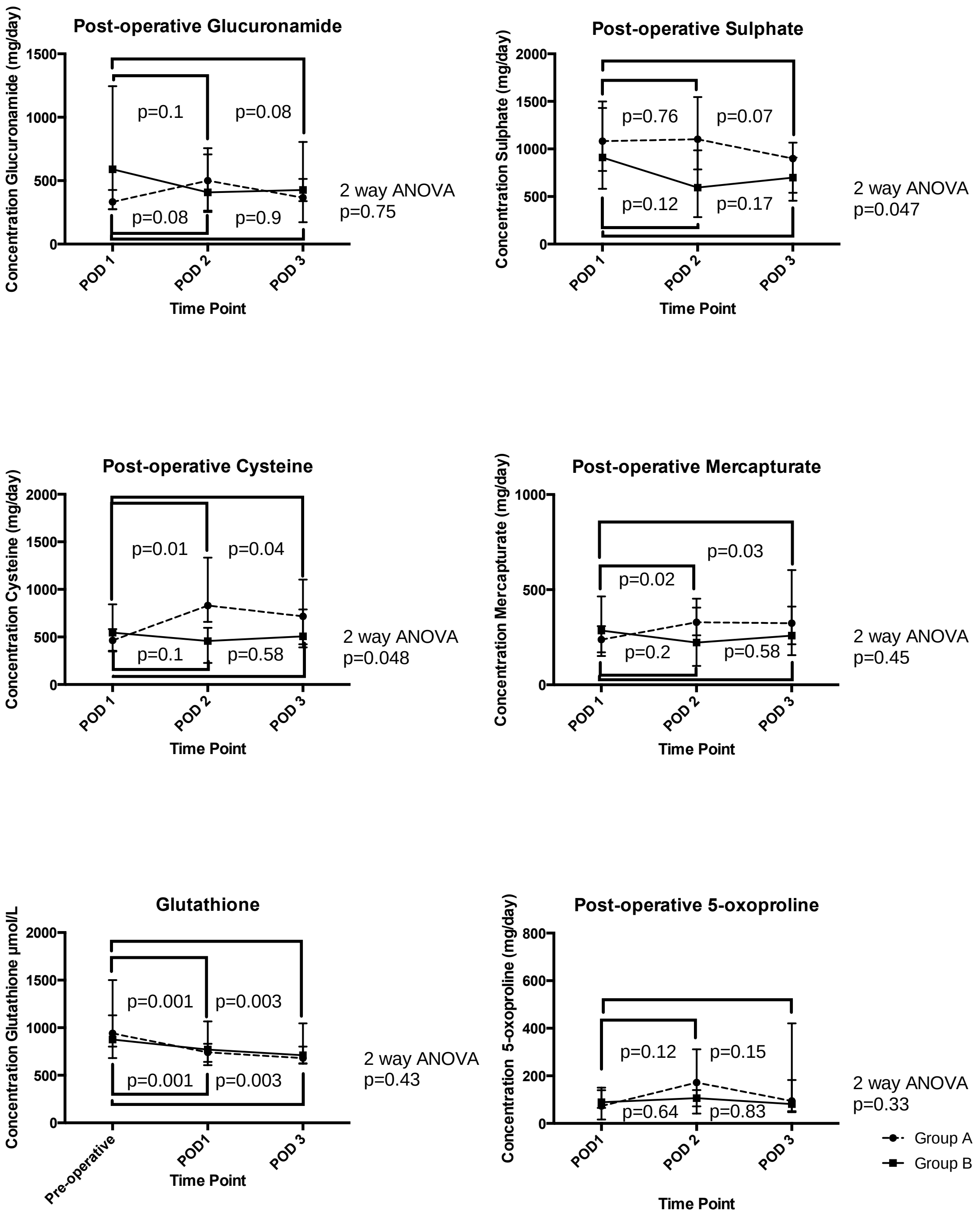
CLM – Colorectal liver metastasis, HCC – Hepatocellular Carcinoma. [a] Fishers exact test, [b] Mann Whitney *U* test. Data are presented as n(%) or median (IQR).

Table 39. Patient characteristics



Data are presented as median (IQR)

Figure 34. Post-operative plasma acetaminophen and liver function tests between groups.



Data are presented as median (IQR)

Figure 35. Comparison of metabolite levels between groups.

10.5 Discussion

This trial has shown that glutathione dependent metabolites are raised to a greater extent in patients with smaller volumes of remaining liver after liver resection however, no evidence of glutathione deficiency was observed in this group when compared to those with minimal volumes of liver resected.

Acetaminophen metabolism is a concern following liver resection however no previous evidence exists to guide clinicians when attempting to implement a multimodal analgesic regimen. Galinski *et al* [136] showed increased levels of plasma acetaminophen being evident after liver resection compared with non-liver resections. In our study acetaminophen levels rose significantly above baseline, and were significantly higher in the patients who had undergone the greatest volume of resection, thus corroborating Galinski’s findings and also suggesting a volume related component to acetaminophen metabolism.

However the clinical significance of a raised plasma acetaminophen level is not immediately clear as it is the depletion of glutathione that precipitates the accumulation of hepatotoxic end-products. Therefore assessment of the urinary acetaminophen metabolites has gained increased importance when determining the effect of acetaminophen on liver function.

When the whole cohort was assessed the “normal” metabolic pathway metabolite glucuronamide remained static over the post-operative period, but sulphate levels were seen to decrease significantly from the high early post-operative levels. The glutathione dependent metabolites, namely cysteine and mercapturate, increased over the study period. Glutathione was also seen to decrease significantly. This suggests involvement of the cytochrome P450 pathway after therapeutic acetaminophen administration and utilisation of glutathione stores.

However, again, the significance of liver resection specifically on these results is not certain. These findings are similar to those of Pickering *et al* [264] who quantified the levels of urinary metabolites after major abdominal (aortic) surgery. In this study, as in ours, a rise in the glutathione dependent metabolites cysteine and mercapturate was observed when compared to early post-operative levels. They also observed a reduction in glucuronamide and sulphate. This finding may therefore reflect normal post-operative therapeutic acetaminophen administration that is unaltered by liver resection. Furthermore the clinical significance of this finding is not immediately obvious as liver damage occurs after depletion of glutathione with a rise in glutathione dependent metabolites not necessarily corresponding to subsequent liver damage.

Until now, very little evidence is available looking at the effect of liver resection on acetaminophen metabolism. Galinski *et al* [267] looked at five patients who underwent liver resection and did not identify an increase in the levels of a NAPQI related metabolite, indicative of NAPQI accumulation, however the small sample size may have contributed to the negative finding. Acetaminophen administration after liver transplant was investigated by Park *et al*. [268] They too measured NAPQI accumulation but reported a rise in NAPQI of up to 10 per cent in the early post-operative period as well as a decrease in glucuronamide and sulphate, which recovered over follow up.

Our study differed to these in that we assessed the change in glutathione dependent metabolites and evidence of glutathione deficiency - the precursor to liver damage as NAPQI accumulation is an end stage process and unlikely to occur unless acetaminophen is administered to a failing resected liver. Furthermore our study continued observation of acetaminophen administration and metabolism until the morning of the fourth post-operative day allowing for full assessment of any liver damage.

In the current study we observed 5-oxoproline levels, as a marker of glutathione deficiency, which is likely to be evident prior to the hepatotoxic NAPQI. Clinically 5-oxoproline is evident when glutathione is deficient and is used selectively in acetaminophen overdose, is indicative of high anion gap metabolic acidosis as well as a marker of glutathione metabolic dysfunction in children. [263] When looking at the whole cohort of liver resections 5-oxoproline was observed to increase, although not significantly, over the study period, indicative of potential glutathione deficiency in some patients. This has not been assessed before.

The aim of the current study was to assess the effect that the extent of resection had on acetaminophen metabolism and to see if those patients with the least volume of liver remaining showed evidence of altered acetaminophen metabolism. Low residual liver volumes are associated with increased morbidity after liver resection and are vulnerable to liver failure due to inadequate liver remnant. [244] This study compared the patients with the smallest estimated residual liver volume with a control group that was populated with patients with low volume resections (mainly less than one segment) and high estimated pre-operative liver volumes. This represented a convenient control group with functioning livers, with the advantage of having had otherwise identical procedures.

In the literature assessing liver failure and transplantation after acetaminophen overdose, risk factors for poor outcome after overdose have been investigated. Although controversy remains, several factors are suggested as being associated with increased rates of liver failure, transplant or death, including increased age, tobacco smoking, alcohol use, being in a fasted state [269] or elderly. [270]

The effect on liver volume has not been investigated before. Reduced acetaminophen administration in patients under 50kg is advised to prevent unintentional therapeutic overdose. Patients with low body mass have been reported as suffering fatal hepatotoxicity after receiving therapeutic acetaminophen doses. [271] Liver volume is predictable when considering age, weight and sex [243] and low liver volume is suspected as a risk factor for acetaminophen related liver injury after overdose. Although this is key for post-operative care of the patient undergoing liver resection, this has not been formally assessed before.

We observed significant differences in the glutathione dependent metabolites between those who had higher and lower RLVs. This seemed to peak during the collection over the second post-operative day. Furthermore we showed a change in the relationship between the glutathione dependent metabolites and RLV on post-operative day two with an inverse relationship being observed between RLV and cysteine and mercapturate that was not evident before or after this time point. Bilirubin was also significantly higher in patients with lower RLVs in the post-operative study period.

Davern *et al* [265] assessed acetaminophen metabolites in patients with acute liver failure following supra-therapeutic acetaminophen ingestion and observed high initial cysteine levels and then a fall in cysteine levels with a fall in ALT levels. This however was not the case for our patients where the ALT peaked early and decreased on a daily basis, in contrast to the metabolite levels that peaked at POD 2 or continued to rise until POD 3. A potential explanation for the higher levels of glutathione dependent metabolites on POD 2 and 3 is the lag time between high ALT and deranged acetaminophen metabolism that likely corrects itself as liver function normalises post-operatively.

No difference was observed in glutathione or 5-oxoproline when considering volume of remaining liver. This has not been assessed before and suggests that extensive liver resectional surgery is associated with a shift in the metabolism of acetaminophen, but not to the extent that a corresponding depletion of glutathione occurs at this level of administration. 5-oxoproline levels were seen to rise after all liver resections compared to baseline suggesting some patients exhibited glutathione depletion. However, residual liver volume *per se* did not seem to be associated with this finding. Potentially, other risk factors are responsible for this rise and this should be considered in all patients undergoing liver resection.

A possible conclusion from this study is that in view of the rise in the glutathione dependent metabolites after major resection, acetaminophen metabolism is altered with a greater proportion of metabolism being performed via the cytochrome P450 mediated pathway. However, in a healthy liver remnant that is functioning adequately, therapeutic acetaminophen does not deplete the glutathione levels to a degree to precipitate hepatotoxicity, regardless of the size of the remaining liver assessed in this cohort. However, in view of the increased rise observed in glutathione dependent metabolites, these patients are potentially at risk of liver damage and consideration of other risk factors should be made, for example underlying liver disease, intra-operative liver ischaemia, age and nutritional status when prescribing acetaminophen and adjustment made accordingly if such factors are evident.

A potential limitation of this study is that we, for ethical reasons, excluded patients whose liver function deteriorated over their post-operative course as they had their acetaminophen treatment withheld due to concern for their liver function. This means that the patients included in this study all had good or improving liver function and so adequate glutathione stores would perhaps be expected, so evidence of glutathione depletion and subsequent hepatotoxicity were de-selected from this population. Furthermore, the majority of patients in group A had 35.5% of their liver remaining which corresponds to a right hepatectomy. [244] Therefore these results are not directly translatable to those who have had extended right hepatectomies, as only two patients in group A had such resections.

Further limitations to this study are as follows. The relationship between acetaminophen ingestion and 5-oxoproline is not well established. It is not specific to acetaminophen toxicity and its clinical usage is not routine and evidence supporting its use is limited. [263] However when attempting to assess for evidence of glutathione deficiency and alteration of the metabolic pathway, its inclusion offers a degree of completeness to the analysis.

Due to the exclusion of several patients who underwent extended resection due to lack of acetaminophen administration, only 11 patients were included in the comparative analysis. Therefore this may have been too small a sample to effectively show a difference between the two groups.

Radiological assessment of future liver volume was not performed and predictive formulae were used to estimate the remaining liver volume. Although this method has been shown to be accurate, it remains an estimation based on population studies and not an assessment of the individual patient and potential errors may have been introduced.

The results of this trial therefore mandate that acetaminophen administration in patients after liver resection is carefully considered. There does appear to be a shift in the metabolic pathway after liver resection and potential evidence of glutathione depletion. There were also significantly higher levels of glutathione dependent metabolites in the major resection group however no evidence of glutathione deficiency was observed after extended liver resections. Therefore, we advocate acetaminophen administration in patients who have undergone a major resection so long as the underlying liver function and risk factor profile is satisfactory.

11 Discussion

This thesis has identified several key areas when considering recovery after liver resection. Evidence assessing post-operative ERAS care protocols after liver resection is limited and there is often considerable influence from the colorectal ERAS literature. The current thesis has identified areas unique to hepatic resection that can be incorporated into ERAS protocols in an attempt to improve outcomes after liver resectional surgery.

The idea that extensive liver resection is not only associated with major morbidity but also increased minor complications highlights the need for a multi-disciplinary approach to post-operative care. In order to achieve the optimum post-operative outcome, all aspects of care need to be scrutinised.

When considering post-operative analgesia, opiate minimisation is often possible with the implementation of a multimodal analgesic regimen. The avoidance of acetaminophen in patients with major resections can result in increased opiate consumption. The findings of this thesis suggest that acetaminophen administration at therapeutic doses is safe after major resection if the liver is functioning satisfactorily and as such can play an important role in post-operative analgesia following live resection.

Post-operative analgesia advice from the colorectal literature advocates post-operative epidural. However the generalisability of this evidence to liver surgery is debatable. Aspects unique to liver surgery demand consideration of individualised peri-operative care. No significant advantage was seen when using epidural analgesia after liver resection when compared to CWI. The main delays to recovery for the TEA group were the increased requirement for HDU care, increased vasopressor requirement and poor pain control once epidural had been removed. The high hypotension rate is symptomatic of the requirement for mid thoracic epidural due to adequate coverage of the dermatomes affected by the subcostal incision, not always encountered in other fields of abdominal surgery. The comparable pain scores, not seen before in similar studies, suggests a CWI protocol capable of providing adequate analgesia without these disadvantages of TEA and rather than epidurals being considered routine, as is often advocated, the current study suggests an alternative, CWI, is suitable as a first line analgesic.

Nutritional requirements after liver resection are not well investigated. Extent of resection and subsequently liver regeneration was hypothesised as being integral to nutritional requirements after major liver resection. This hypothesis was not supported by the study findings. However the requirements for nutrition were seen to be wholly unpredictable with significant variation between subjects. The validation of a mobile device to monitor energy expenditure and therefore nutritional requirements by this thesis will potentially provide increased insight into this aspect of care.

Conversely, there are universal areas that apply to all aspects of peri-operative care. Adherence to ERAS protocols is also important as is determining streamlined implementation policy. The current investigation has shown universal support for ERAS care components but challenges with daily implementation of ERAS care observed, in common with other ERAS trials, highlighted the inherent difficulties in ensuring ERAS protocols reach the bedside and patients benefit from evidence based care.

The future research that will be of benefit should aim to continue the scrutiny of individual peri-operative care components and ascertain their interaction on liver surgery. The employment of wound infiltration devices is not limited to open surgery and assessment of their application to laparoscopic liver surgery is an area of potential development and investigation. A major advantage of CWI is its low nursing requirements and simplistic design. It is conceivable that they could be utilised in an ambulatory setting and could potentially facilitate 24 hour stay laparoscopic liver resection. No previous trial has examined CWI in laparoscopic liver resection or determined if an advantage exists to conventional analgesia however this is an area to investigate in the future.

The results of the two exploratory observational studies could be exploited to provide safety data on which to base randomised trials. The trial assessing acetaminophen metabolism suggested small remnant volume was not associated with glutathione deficiency or liver damage and this knowledge could be utilised to compare formally low and normal doses of acetaminophen following extended resection. Such data were not available prior to this investigation and so exploratory investigation was mandated. Similarly the trial assessing energy expenditure after liver resection provided results that could conceivably link into a comparison of nutrition guided by energy expenditure as measured by SWA compared with standard nutritional care. SWA was not validated prior to this investigation and so any such trial would have relied on IC, which is not practical for daily, real time assessment of energy expenditure in the clinical setting.

In summary, the current thesis identified areas of peri-operative care that were lacking in sufficient evidence to guide practice. As a result of the described studies, several areas of care, namely analgesia and nutrition, have been clarified and provide a basis on which to establish future practice and investigation.

12 Bibliography

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