AN INVESTIGATION INTO THE ROLE OF EPIDURALS IN PATIENTS UNDERGOING COLORECTAL SURGERY

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Abstract

Background: Thoracic epidural anaesthesia (TEA) is routinely used for the relief of Postoperative pain in patients undergoing major colorectal surgery. TEA is often associated with hypotension, which may be refractory to intravenous fluids, causing concerns over the effect of such hypotension on anastomotic perfusion. Despite the widespread use of TEA in colorectal surgical patients, their effects on intestinal perfusion are not fully understood. Recent anaesthetic advances have provided potential alternatives to TEA for these patients, such as local anaesthetic wound catheters.

Aim: To investigate the effects of epidurals on splanchnic flow and to explore potential alternatives to thoracic epidurals for the management of pain in an enhanced recovery setting.

Methods: One systematic review of the literature, two prospective observational studies and one prospective randomised, controlled clinical trial.

Results: The findings of both the systematic review of the literature and the two prospective observational studies on the effects of TEA on splanchnic blood flow were inconsistent. These studies indicate that epidural mediated hypotension may be accompanied by a reduction in splanchnic blood flow in some patients. This effect was not consistent but when present was not corrected by intravenous fluid therapy but required vasopressor therapy. The randomised controlled trial has demonstrated that wound catheters provide a viable alternative to epidurals within an enhanced recovery program.

Conclusion: A selective approach to the use of TEA in colorectal surgery should be adopted. Their effects on splanchnic flow remain unclear. Local anaesthetic wound catheters are an effective alternative.

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Author's Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Chapter 1 - Introduction

1.1 Colorectal Surgery

Colorectal resections are common. In 2008/09 there were 20,035 completed consultant episodes where the main operation was colorectal resection[1].

Colorectal cancer accounts for many of these resections. It is the 3rd most common malignancy in the UK and is on the increase. In 2002 approximately 30,000 new cases were diagnosed. This has now reached around 40,000 cases per year. The 2014 National Bowel Cancer Audit Progress (NBOCAP) report included 31,723 people diagnosed with colorectal cancer between April 2012 and March 2013[2]. Treatment involves surgical excision of the diseased segment of bowel. Until further significant advances in the treatment of colorectal cancer are made, the numbers of colorectal resections performed will increase in line with the increased incidence of this disease.

1.2 Postoperative Stress Response

Major surgery, such as colorectal surgery, is associated with significant postoperative pain. As well as being unpleasant and causing distress to patients, postoperative pain is associated with a physiological stress response characterised by tachycardia, hypertension, myocardial ischaemia, decrease in alveolar ventilation and poor wound healing. Postoperative pain is largely nociceptive, i.e. as a result of the surgical insult. However, nociceptive pain may be exacerbated, leading to neural sensitisation which may be either peripheral or central[3]. Inadequate postoperative pain control is associated with insomnia and the development of chronic pain[3].

Surgical injury is associated with neuroendocrine and inflammatory response in which catabolically active hormones such as glucagon, cortisol and catecholamines are secreted and cytokines and acute phase proteins are released. This is accompanied by a reduction in the secretion and effects of insulin, an anabolic hormone[4]. As a result, protein catabolism occurs, cardiovascular demands increase and patients may experience both postoperative pain and organ dysfunction. The stress response may be amplified by a number of factors including anxiety, starvation, infection, immobilisation, hypothermia and hypovolaemia. Postoperative pain and stress response may also be associated with paralytic ileus and risk of thromboembolism, all of which contribute to a delay in postoperative recovery[4-6].

1.3 Laparoscopic surgery

The past 20 years have shown significant developments in the field of colorectal surgery. Following the first laparoscopic cholecystectomy performed by Mühe in Germany in 1985[7], interest developed in the application of laparoscopy in colorectal surgery. The first reports of laproscopically assisted colorectal surgery were published in 1991[8]. At first this approach was novel and unproven in terms of safety and efficacy, indeed there were significant initial concerns regarding the incidence of port site metastases[9].

These concerns were investigated by the COST (Clinical Outcomes of Surgical Therapy) trial published in 2004. This was a large multicentre randomised controlled trial to which 872 patients were recruited and 863 were included in the final analysis. Most patients were ASA (American Society of Anaesthesiologists classification system) 1 or 2. This non inferiority study had a median follow up of 4.4 years and found rates of recurrence to be similar in the laparoscopic and open groups. The authors concluded that 'the laparoscopic approach provided an acceptable alternative to open surgery for colon cancer'[10].

The publication of the European COLOR trial followed in 2005. This was a multicentre study of 1248 patients, with 1082 included in the final analysis[11]. In this trial patients with rectal cancer were excluded, as were those with metastatic disease, synchronous tumours and tumours of the splenic or hepatic flexure. This multicentre non inferiority study was designed to assess short term outcomes and disease free survival, but could not rule out a difference in disease free survival at 3 years as the 95% confidence interval exceeded the predefined non-inferiority margin[12]. The authors comment that some patients may have received mechanical bowel preparation depending on the preferences of the institution. This study also excluded patients with a body mass index (BMI) of less than 30.

Also published in 2005 were the short term results of the CLASICC trial. This was a large multicentre trial in which patients with colon and rectal carcinomas were randomised on a 2:1 basis to laparoscopic or open surgery. Initial findings were of similar short term outcomes for laparoscopic and open surgery for colon cancers. However, they found a higher percentage of overall complications in the laparoscopic group for patients with rectal carcinoma 18(14%) in the open group versus 45(18%) in the laparoscopic group. They also found a non significant difference in circumferential resection margin positivity and suggested this may equate to an increased risk of local recurrence. They concluded that their results did not yet justify routine use of a laparoscopic approach for rectal carcinoma[13]. The difference in circumferential margin positivity for rectal carcinoma did not translate into a difference in local recurrence at 3 years. The trial found no significant difference in overall survival between the two groups at 3 years[14] and 10 years[15]. They did however find that conversion to open surgery was associated with a poorer prognosis. Conversion to open was defined as a midline incision larger than required to retrieve the specimen. This finding was attributed to advanced disease. Laparoscopic surgery has been associated with a number of benefits including swifter return of gut function, decreased postoperative pain and reduction in length of

stay[9,16]. A further Cochrane Review published in 2008 found no difference in long term outcomes[17].

At the time of publication of the COST study only a small number of colorectal resections in the UK were performed laparoscopically. Hospital episode statistics for 2005/2006 showed that 5% of colorectal resections were performed laparoscopically[18]. However, as laparoscopic surgery has increased in popularity this figure has steadily risen. The 2014 NBOCAP Annual Progress report found that 61% of elective major resections were attempted or completed laparoscopically, whilst 45% were completed laparoscopically compared to 25% in 2008[2]. In a discussion article published in the Annals of the Royal college of Surgeons Kennedy and King state that laparoscopic resection of colorectal cancer is possible in 85-90% of patients presenting electively[19]. However, as can be seen from the recent NBOCAP statistics, less than 50% of patients undergoing colorectal cancer resections in recent years had their operation completed laparoscopically. There are likely to be a number of reasons for this.

Laparoscopic surgery remains a controversial topic[19,20]. Patients with colorectal cancer may be older with significant comorbidities and may not be suitable for lengthy operations, or they may have advanced disease which may not favour a laparoscopic approach. Not all colorectal surgeons are happy to perform laparoscopic surgery. As laparoscopic surgery is associated with a significant learning curve, surgeons who are more advanced in their careers may have elected not to retrain. Some patients may even request open operations. Simply put, until every patient can successfully undergo laparoscopic surgery, other methods are needed to improve overall postoperative recovery and pain.

Whilst the potential benefits in selected patients are clear, patient selection is important and much of the literature does not compare laparoscopic surgery with open surgery in an enhanced recovery

program[21]. Indeed, one well designed double blind randomised controlled trial conducted by Basse *et al* found no difference in return to function between patients randomised to laparoscopic or open surgery in the context of an enhanced recovery program[22]. This study included patients undergoing right hemicolectomy or sigmoid resections but excluded patients with stomas or anterior resections. Patients, ward staff and research assistants were blinded to whether the patient had undergone laparoscopic or open surgery by the use of an opaque dressing covering the entire abdomen. Pain scores were higher in the laparoscopic patients on day one and were similar thereafter. They concluded that in the absence of full blinding, outcomes of such trials are likely to reflect traditions of care rather than any actual benefit[22].

1.4 ERAS

In recent years several avenues of attack have been used to modulate the surgical stress response with a view to improving postoperative recovery. The term Enhanced Recovery After Surgery is often used to describe a multimodal, evidence based approach to perioperative care designed to improve outcomes and reduce complications and the length of hospital stay. In 1997 Kehlet first described a multimodal approach designed to control postoperative physiology and rehabilitation. This comprised preoperative information and teaching, attenuation of the stress response, pain relief, exercise, enteral nutrition and growth factors in order to reduce morbidity and accelerate convalescence[23]. The term Enhanced Recovery After Surgery (ERAS) was developed by a group of academic surgeons who formed the enhanced recovery after surgery study group in London in 2001[24]. They advocated that ERAS protocols should be evidence based and should evolve through regular audit, quality improvement and collaboration amongst members of a multidisciplinary team[24,25].

Broadly speaking, ERAS protocols involve a number of evidence based interventions which used together confer significant improvements in outcome. Whilst not all protocols are the same, many commonalities exist. Problems commonly faced by patients undergoing major abdominal surgery are pain, poor mobility, impairment of gut function and potential complications. The principles behind ERAS are based on maintaining fluid homeostasis and attenuating the postoperative stress response[24].

A number of interventions have been used to maintain fluid homeostasis. Patients do not receive mechanical bowel preparation and undergo a curtailed preoperative fast. Goal directed fluid therapy is used intraoperatively to avoid fluid overload and vasopressors are used to treat hypotension once a patient is adequately filled. Postoperatively, oral fluids and diet are reintroduced as tolerated and steps, such as the avoidance of nasogastric tubes and drains, are taken to avoid excessive fluid losses. Measures are also taken to minimise postoperative nausea and vomiting. These include multimodal nausea and vomiting prophylaxis, short acting anaesthetic agents and the avoidance of sedation and opioid analgesia[24].

Many components of ERAS protocols are designed to attenuate the postoperative stress response. The release of catabolic hormones in the stress response leads to loss of muscle mass and postoperative insulin resistance, which is associated with postoperative complications[4]. Preoperative carbohydrate loading and the avoidance of fasting have been found to significantly reduce insulin resistance and improve patient comfort[26]. Minimally invasive surgery is advocated as this has been shown to reduce postoperative pain and the postoperative stress response[27]. Transverse laparotomy incisions have also been found to be associated with reduced pain and length of stay[28]. Postoperative pain has been shown to be associated with insulin resistance. Regional anaesthesia in the form of thoracic epidurals helps to prevent insulin

resistance by reducing postoperative pain, blocking the afferent fibres responsible for mediating the stress response[4].

Other components of ERAS such as preoperative counselling, and the early removal of urinary catheters have been shown to be significantly associated with a shorter length of hospital stay[29]. As infection can amplify the surgical stress response, antimicrobial prophylaxis and skin preparation are used. Venous thromboembolism prophylaxis is also routinely given.

Following the development of the ERAS study group in 2001, a number of studies have proven the safety and efficacy of ERAS programs or fast track surgery as they were initially known. A recent rapid evidence synthesis published in the BMJ found consistent evidence that enhanced recovery programs reduced length of stay without increasing readmission rates[30]. In the past decade ERAS has moved from being experimental and is now largely accepted as standard perioperative care for all patients undergoing colorectal surgery. It is the evidence based multimodal approach of ERAS protocols which has been adopted rather than a fixed set of components. For this reason ERAS protocols are continually evolving as new, effective interventions are identified[25].

1.5 Thoracic Epidural Analgesia

Thoracic epidurals may be used as part of ERAS protocols to attenuate the postoperative stress response, facilitate the avoidance of opiates and provide postoperative analgesia.

Epidural analgesia utilises a fine bore epidural catheter, inserted into the lower thoracic epidural space. Local anaesthetic with or without a short acting opiate is then infused. The local anaesthetic solution acts on the spinal nerve roots by stabilising their neuronal membranes and preventing the initiation and transmission of nerve impulses. Smaller, unmyelinated Type C (pain and temperature) fibres are preferentially

affected by the local anaesthetic solution. Consequently a predominantly analgesic effect is produced at and below the level of the block with relative motor sparing.

The technique of epidural analgesia is widely accepted as effective in reducing postoperative pain in patients undergoing major colorectal surgery. In addition, there is evidence that epidurals may also be associated with decreased pulmonary, gastrointestinal and cardiovascular morbidity, attenuation of the postoperative stress response and a possible reduction in morbidity. As a consequence epidural analgesia has been regarded as the gold standard for postoperative pain management following major abdominal surgery. The use of epidural anaesthesia has become standard practice in many colorectal units as well as being adopted as an important part of enhanced recovery plans.

1.6 Benefits of Thoracic Epidural Analgesia

Benefits of thoracic epidural anaesthesia include their attenuation of the postoperative stress response. As previously discussed, the afferent neural sympathetic blockade that they produce reduces the secretion of the catabolically active hormones glucagon, cortisol and catecholamines[4]. However, single dose spinal or epidural anaesthesia has been shown to have only a transient effect on this stress response[31]. For this reason thoracic epidural anaesthesia has been recommended for 24- 48 hours postoperatively. This reduction in stress response is seen with local anaesthetic epidural anaesthesia and not with epidural opioids[32].

The postoperative stress response is clinically relevant in patients with cardiovascular disease. The increased cardiac workload mediated by catecholamines and associated tachycardia result in higher workload with reduced time for coronary artery filling. In the presence of significant coronary artery disease these vessels are unable to

compensate. The stress response may also be associated with a hypercoaguable state and proinflammatory response which may lead to plaque instability. Under such conditions patients are at risk of acute coronary syndrome or myocardial infarction. It would follow that attenuation of the postoperative stress response may have an effect on reducing postoperative cardiovascular complications.

Thoracic epidurals are associated with increased coronary artery blood flow and improvement in myocardial oxygen balance however their benefits in terms of reducing cardiovascular morbidity are unclear and may be dependent on the site of the catheter.

In a meta-analysis of patients receiving epidural anaesthesia during and for 24 hours after surgery versus controls Beattie *et al* found a reduction of postoperative myocardial infarction in the epidural group. They commented that this effect was greater in patients receiving thoracic rather than lumbar epidural anaesthesia with a 40% reduction in postoperative myocardial infarction. The surgical populations assessed were patients undergoing peripheral vascular, aortic and abdominal surgery[33]. A similar effect was also seen by Rodgers *et al* although the authors concluded the finding was of uncertain significance due to broad confidence intervals[34]. Again this meta-analysis included a range of different surgical procedures including General, Obstetrics and Gynaecology, Urology, Orthopaedic and Vascular. The authors found that thoracic but not lumbar epidurals were associated with a reduction in mortality.

There is little evidence that thoracic epidurals reduce postoperative cardiovascular morbidity in a low risk population. The MASTER Anaesthesia Trial of 915 high risk patients undergoing either major open abdominal surgery or oesophagectomy was designed to evaluate the beneficial effects of epidurals in high risk patients[35]. They compared intra and postoperative epidural anaesthesia and general anaesthesia with general anaesthesia and patient or physician controlled opioid analgesia. The study was powered to detect a decrease in mortality and

major postoperative complications from 50% to 40% in the epidural group. The authors found no significant difference in either overall mortality or postoperative complications between the two groups. They found a significant difference in pain scores at rest and on coughing in the morning of the first postoperative day. Thereafter there was no significant difference in pain scores at rest, but the difference in pain scores on coughing remained until day 3. These were likely to be clinically as well as statistically significant as patients with opioids had scores >5 on coughing on day 1 and >4 on coughing on day 2, both classed as moderate pain. The clinical concern as regards the pain on coughing for these patients is respiratory compromise and potential pulmonary complications. This is reflected in the statistically significant difference in the numbers of patients with respiratory failure in this study. However, it should be noted that with the inclusion of upper gastrointestinal surgery in the subject group that this may not be applicable to colorectal surgery[35].

Respiratory problems are common in patients undergoing abdominal surgery. This is due to a number of factors. Patients have a reduction in functional residual capacity due to diaphragmatic dysfunction, reduced chest wall compliance and pain limiting their inspiratory effort[36]. Functional residual capacity has been shown to decrease by 20% following surgery, with maximal effects seen at 24 to 28 hours post operatively and does not return to baseline levels one week postoperatively[36]. Good evidence exists for the protective effects of thoracic epidurals in reducing postoperative pneumonia, although this protective effect appears to be decreasing, presumably as a result of a decreased overall risk of surgery[37]. It may be that benefits are more pronounced in higher risk patient groups. Epidurals have been shown to have a protective effect in obese patients undergoing laparotomy, significantly minimising the reduction in vital capacity in the immediate post operative period and were associated with a quicker return to preoperative spirometric values[38]. With the advent of minimally invasive surgical techniques the risk of pulmonary complications is reduced,

thereby potentially negating the beneficial effects of epidurals. None of the data for such benefits come from patients with laparoscopic surgery.

Postoperative ileus is a common complication of colorectal surgery. Thoracic epidural administration of local anaesthetic has been associated with a swifter return of gut function[39]. The effects on postoperative stay have been variable. Liu *et al* found that use of epidural bupivacaine with or without the addition of epidural morphine was associated with a swifter return of gut function and shorter time to fulfilment of discharge criteria[39]. They did not find this effect with epidural morphine alone, although a retrospective study of patients undergoing ileal pouch – anal canal anastomosis found epidural fentanyl to be associated with a swifter return of gut function compared with controls receiving systemic opioids[40]. Bradshaw *et al* also found a swifter return of gut function as defined by time to first flatus and bowel movement with epidural which was associated with a statistically significant decrease in length of stay. This was, however, a case control study and a mixture of epidural local anaesthetic, epidural local anaesthetic and narcotic and epidural narcotic were used, making it difficult to apply their findings[41]. In a prospective randomised controlled study of 42 patients undergoing elective colorectal surgery Carli *et al* found a statistically significant difference in gut function in favour of epidural anaesthesia as compared with PCA. However, this did not translate to a decrease in the length of postoperative stay[42]. It should be noted that these studies have defined return of gut function as time to passage of first motion or flatus, which does not necessarily fully correlate with gut function[43]. An alternate measure of gut function is time to tolerance of 80% of oral intake, which is a marker of the organs ability to function rather than its output[44]. It is also notable that the control group for these studies were patients receiving patient controlled parenteral opioids. However, in several recent studies comparing standard care and epidural anaesthesia with multimodal optimisation and epidural anaesthesia found a swifter return in gut

function in the multimodal optimisation groups[45-47]. This suggests that epidurals may not necessarily preserve gut function when used in isolation. This effect has also been seen in patients undergoing laparoscopic colorectal surgery, however this was in the context of 'traditional care' and not an enhanced recovery program[48].

It is unknown whether or not thoracic epidurals affect the rate of anastomotic leakage. A Meta analysis by Holte and Kehlet found no difference in the incidence of anastomotic leak between patients with and without epidurals[49]. They did conclude that there was insufficient power in the data analysed and calculated that over 1000 patents would be needed in each group to detect an increase in leak rate from 3.4% to 6% with a power of 80%. It has been postulated that forceful contractions resulting from unopposed parasympathetic stimulation may place patients at increased risk but no evidence of this effect has been found. The effects of thoracic epidurals on splanchnic flow and anastomotic perfusion are unknown.

1.7 Risks of Thoracic Epidurals

Thoracic epidural analgesia is not without risk. Complications of the technique include epidural abscess, epidural haematoma and potential neurological damage. In a Swedish retrospective study of 450,000 epidural and 1,26000 spinal blockades, 127 patients suffered a severe neurological complication, with 85 of these patients experiencing permanent neurological damage[50]. While such complications are rare they are clearly significant for those individuals affected.

Thoracic epidurals can be time consuming to place and have a significant failure rate. In a study of 2140 surgical patients failure rates of 32% for thoracic epidurals and 27 % for lumbar epidurals were described[51]. Reasons for failure included permanent dislodgement, catheters which were clearly not positioned in the epidural space on testing with local a bolus of anaesthetic, a unilateral block or leak. A

specific cause for the failure was not identified in more than half of cases[51]. Other common adverse effects include pruritis, urinary retention and arterial hypotension[52].

1.8 Thoracic Epidurals and Hypotension

The association of thoracic epidural analgesia with arterial hypotension is well documented. In addition to blocking type C pain and temperature fibres, thoracic epidural anaesthesia can also block sympathetic nerve fibres, resulting in peripheral and splanchnic vasodilatation, functional hypovolaemia and hypotension. Hypotension is associated with the spread of local anaesthetic block[53] and low postoperative pain scores[54]. Rates of hypotension in the literature are variable, ranging from 2.2%[55] to 56%[54]. The variability in the incidence of hypotension largely relates to differences in the criteria used to define hypotension. In a retrospective case note review Godden *et al* compared rectus sheath catheters with thoracic epidurals[56]. Their chosen endpoint was the incidence of hypotension, selected due to concerns over hypoperfusion. Whilst the authors reported a significantly higher incidence of hypotension on postoperative day 1, this was defined as a systolic pressure of less than 130mmHg (milimeters of mercury). Other measures of hypotension define this as a systolic pressure of less than 100 or 90mmHg, although hypotension may be calculated as a percentage of the patient's normal blood pressure. This latter definition may offer greater clinical significance[56].

There is evidence that such hypotension is better treated with vasopressors, as plasma expanders have been found to significantly reduce haemoglobin concentration[57]. Depending on the way in which this hypotension is managed colorectal patients with thoracic epidurals may be placed at risk of fluid overload if receiving multiple fluid challenges.

1.9 Thoracic Epidurals and Splanchnic Flow

Epidural mediated hypotension in colorectal patients is an area of growing concern, not least because of the potential consequences in terms of the effect on splanchnic flow and anastomotic perfusion.

The splanchnic blood supply is provided by coeliac and mesenteric arteries which anastomose extensively to provide a vast collateral supply to the fore, mid and hindgut. Splanchnic blood flow is determined by many intrinsic and extrinsic mechanisms including cardiac function, the autonomic nervous system and neuroendocrine mediators. The effect of thoracic epidural anaesthesia (TEA) on intestinal perfusion is not fully understood. In animal models TEA has been shown to increase gut mucosal perfusion[58, 59]. However, epidural anaesthesia with bupivacaine has been shown to cause a significant decrease in the oxygen-perfusion state of colorectal anastomosis in humans, although this was not associated with anastomotic or other complications[60]. Most studies into the effect of TEA on splanchnic blood flow in patients have utilised indirect measurements such as tonometry. Gould *et al* performed an intraoperative study of 15 patients in which they directly measured inferior mesenteric artery flow and colonic serosal red cell flux. They found that the measured reduction in colonic blood flow caused by epidural block did not respond to an increase in cardiac output with fluid resuscitation, but required the use of a vasopressor to restore blood flow[61].

Gould *et al*'s findings raise significant concerns about current practice. The trend towards goal directed fluid therapy using oesophageal Doppler measurements of cardiac output in colorectal patients is called into question in light of this new evidence that cardiac output may not correspond to colonic blood flow in the presence of TEA. This is a particular area of concern in colorectal patients with an anastomosis. Recent literature suggests that restrictive fluid regimes may reduce morbidity after colorectal resection[62]. Fluid challenges in patients with

TEA induced hypotension may not only be ineffective in restoring gut blood flow but may also place them at risk of potential fluid overload with its associated morbidity.

Epidurals may potentially hinder postoperative mobilisation due to a combination of altered sensation and the cumbersome equipment that they entail. In 2 recent retrospective studies epidural anaesthesia was deemed to have affected postoperative mobilisation in 11 %[63] and 21.6%[64] of patients. Early mobilisation is an important aspect of postoperative recovery and has been shown to reduce the risk of venous thromboembolism and pulmonary complications[65]. Conversely bed rest and immobility has been shown to reduce VO2 Max, this is the maximal rate of oxygen consumption as measured by incremental exercise and is a measure of cardiovascular fitness[66, 67]. This reduction has been seen in healthy volunteers after just 20 days of bed rest and was unaffected by supine exercises. The authors of this study attributed the effects to a reduction in stroke volume[67].

Much of the evidence for epidurals is from patients undergoing open colorectal or abdominal surgery. Marret *et al* cautioned against transferring this to laparoscopic surgery[52]. It should be noted that for patients undergoing open surgery within an enhanced recovery program incision size is minimised and transverse incisions are used where possible. Consequently, the potential benefits in these patients of thoracic epidural analgesia may also be less significant than for patients with large xyphisternum to pubis incisions. In a systematic review of 12 randomised controlled trials of postoperative pain management in laparoscopic colorectal surgery, Joshi *et al* found a variety of techniques to be effective in reducing postoperative pain. Due to the heterogeneity of studies involved a meta-analysis was not possible. They found pain relief to be superior in patients receiving epidurals. Using a L'Abbe plot the authors demonstrated that analgesia was superior in the epidural group but concluded that as the pain scores were largely <4 that this was acceptable[68]. A VAS of 4 is classed as moderate pain whereas a

score of <4 is classed as mild[69]. Joshi et al did not recommend epidurals for laparoscopic colorectal patients due to the risk benefit ratio but instead recommended non-steroidal anti-inflammatory drug, paracetamol and rescue opiates[68].

Such findings indicate the need for further study into alternate forms of analgesia following colorectal resection. Simple non-opioid analgesia such as NSAIDs (non steroidal anti-inflammatory drugs) and paracetamol are already advocated by ERAS protocols[70] and are routinely used. These provide good baseline analgesia but are likely to be insufficient for adequate pain control in the initial postoperative period.

1.10 PCA

Several randomised controlled trials have compared the use of epidurals with patient controlled parenteral opiates. Senagore *et al* conducted a randomised controlled trial in 47 patients undergoing laparoscopic colorectal surgery in the context of a fast track program[71]. Types of surgical procedure were right hemicolectomy or sigmoid colectomy and patients who were converted to open were excluded from the final analysis. This was a small study, with only 38 patients included in the final analysis and was powered to detect a decrease of length of stay of 1 day. Patients were not fully managed in accordance with accepted enhanced recovery protocols in that they received only a clear liquid diet for 24 hours prior to surgery. The epidural and PCA were removed on the first postoperative day and the urinary catheter was removed the morning following surgery. Pain scores 'during ambulation' were significantly higher at 6 and 18 hours post op in PCA group with mean pain scores of 6.6 and 4.0 at 6 and 18 hours respectively. Thereafter they were less than 4.There was also a trend towards improved pain at 24 hours although this was not statistically significant. The authors concluded that TEA was still of benefit in laparoscopic surgery. However no significant difference was found in mean LOS which was 2.4 days in the epidural group and 2.3 days in the PCA group[71].

In 2007 Taqi *et al* reported their findings from their randomised controlled trial of 50 patients comparing thoracic epidurals with PCA[72]. This was not in the context of multimodal optimisation but in the setting of traditional care. Patients received bowel prep and were restricted to clear fluids for 24 hours pre operatively. Their primary outcome was return of bowel function as defined by passage of stool or flatus. Urinary catheters were removed on day 2 for patients with PCA and were removed once the epidural infusion was discontinued for the epidural group. The epidurals were continued for a mean of 2.8 days. It is notable that many patients in the study by Senagore *et al* had been discharged by this time point[71]. Taqi et al reported a swifter return to gut function in the epidural group as defined by time to flatus, stool, tolerance of liquid and solid diet, all of which was statistically significant. Pain scores were significantly lower at rest, on coughing and whilst walking on days 1 and 2. Median pain scores on coughing were 7 and 6 in the PCA group and 3 and 3 in the epidural group on postoperative days 1 and 2 respectively. Pain scores of 7/10 are usually classed as severe. This is likely to be clinically significant although transient and is not mentioned in the systematic review by Joshi et al [68]. There was no significant difference in length of stay between the groups.

A further study which compared patient controlled opiate analgesia with epidural was published by Neudecker et al in1999[73]. Patients undergoing laparoscopic colorectal resection were randomised to either PCA alone or PCA with epidural analgesia. Once again, this was not within the setting of an enhanced recovery program as patients were not allowed to consume a normal diet until the 3rd postoperative day. As expected, less the opiate consumption was significantly reduced whilst the epidural in situ. Rather than report the quantity of opiates consumed per postoperative day the authors have reported the total opiate consumption over 4 days. There was a trend towards a reduction in opiate requirements in the epidural group but this was not statistically significant. This study has a significant limitation in that it is

extremely small (n=20 patients) and no power calculation was presented in the literature. The epidurals were removed on postoperative day 2. The authors present their cumulative pain scores from surgery until day 2 but have not supplied data pertaining to each postoperative day. This may be significant as in other studies the greatest difference in pain scores between epidurals and PCA is seen on first post operative day.

1.11 Spinal Analgesia

This potential protective effect of epidurals on postoperative pain over the first 12 hours has led to an interest in spinal analgesia. Wongyinsinn *et al* conducted a prospective randomised controlled trial comparing spinal anaesthesia with PCA in patients undergoing laparoscopic colorectal resection[74]. Their primary outcome measure was postoperative opiate consumption in first 3 post op days, although their power calculation was based on a 50% decrease in opioid consumption in first 24 hours. They reported a significant reduction in pain at rest in the spinal analgesia group at 24 hours, although such a reduction was not seen on walking or coughing. No significant difference was found in terms of gut function, defined as time to first flatus and tolerance of diet, or LOS[74].

In their systematic review of postoperative analgesia in laparoscopic colorectal surgery, Levy et al concluded that there was a paucity of data[75]. They later conducted a randomised controlled trial comparing epidural analgesia, spinal analgesia and PCA in laparoscopic colorectal surgical patients. They found poorer outcomes in terms of LOS and gut function in the epidural group as compared with both the PCA and spinal group, with spinal analgesia providing the shortest LOS[76]. They did however conclude that other analgesic modalities should also be assessed.

1.12 TAP block

In recent years other modalities of postoperative pain relief for patients undergoing abdominal procedures have been explored. One such technique is the transversus abdominis plane or TAP block, first reported by Rafi in 2001[77]. The anterior branches of 7 spinal nerves, which innervate dermatomes T10 to L1, pass through plane between the internal oblique and transversus abdominis muscles. This is known as the TAP plane. Blockade of these nerves can be produced by infiltration of local anaesthesia into this potential space. Differing approaches have been used for TAP block. The traditional landmark based 'double pop' technique which is administered in the triangle of petit. Whist this has been shown to be effective, concerns exist regarding inadvertent peritoneal puncture and potential for visceral injury. A study by McDermott et al published in 2012 evaluated this blind placement post procedure with ultrasound. The study was terminated early after recruiting 36 patients due to an unacceptably high rate of peritoneal catheter placement[78]. Ultrasound guided TAP blockade may be posterior or subcostal. Subcostal TAP has been shown to provide superior pain relief for upper abdominal procedures such as laparoscopic cholecystectomy[79], whilst posterior TAP is used for lower abdominal procedures[80]. Posterior TAP block is also known as quadratus lumborum block. A case report documenting the use of QL block for provision of analgesia following laparotomy described the technique as effective for 15 hours in conjunction with PCA, providing a blockade of dermatomes T8 to L1[81].

A Cochrane Systematic review published in 2010 found TAP blocks to be safe, with a decrease in pain scores. Although the authors commented that it was unclear whether this reduction had clinical significance as there were no data regarding a reduction in opiate side effects or increased patient satisfaction[82]. Another recently published study by Park et al in laparoscopic colorectal surgical patients found that TAP blocks reduce cumulative morphine requirements at 24 and 48 hours

post operatively when compared with a single dose of local anaesthetic wound infiltration[83].

However, whilst TAP blocks have been shown to reduce pain and analgesic requirements in the immediate postoperative period their effects are finite. Their reported duration is 6-8 hours although this can be prolonged with the use of additional analgesia[80]. Further studies have examined the effects of continuous TAP blockade. Niraj *et al* conducted a non inferiority study of 70 patients undergoing laparoscopic colorectal surgery. Patients were randomised to 4 quadrant TAP block and continuous posterior TAP analgesia or epidural. Their primary endpoint was VAS (visual analogue scale for pain) on coughing at 24hrs post operatively. Patients whose operations were converted to open procedures were included if the upper limit of their incision was at or below T10 dermatome. Endpoints were similar between the two groups, although urinary catheters were removed earlier in the TAP group. The authors noted that TAP analgesia did not cover visceral pain and reported two notable treatment failures in patients with inflammatory bowel disease[84].

1.13 Continuous Local Anaesthetic Wound Infiltration

Continuous infusion of local anaesthesia may also be given either into the surgical wound or the muscles surrounding it in the form of rectus sheath catheters. Continuous wound infiltration has been shown to be safe and effective in providing postoperative pain relief in a variety of surgical procedures. Schell *et al* conducted a double blind randomised controlled trial of local anaesthetic wound infiltration in 27 patients undergoing axillary lymph node dissection. They demonstrated significantly improved pain relief in their intervention group compared with the placebo and control groups[85]. A retrospective review of 49 consecutive mastectomies found that the use of local anaesthetic wound infiltration was associated with a higher frequency of patients not requiring any opioid analgesia after postoperative day 1. They also

demonstrated lower opioid consumption in the local anaesthetic wound infiltration group on postoperative days 1 and 2[86]. The effectiveness of this technique has also been shown in inguinal hernia repair. LeBlanc *et al* conducted a double blind randomised controlled trial comparing wound infiltration with 0.5% bupivacaine and saline in patients undergoing inguinal hernia repair. Wound infiltration was found to be associated with significantly lower pain scores and lower analgesic requirements, and the authors noted no increase in rates of wound infection[87]. Lau *et al* also used subfascial infusion of 0.5% bupivacaine for inguinal hernia repair and found this to be associated with a significant decrease in postoperative pain scores on the day of surgery and first postoperative day[88].A similar study conducted by Sanchez *et al* using, 0.25% bupivacaine, found that this significantly decreased pain scores on postoperative days 2 , 3 , 4 and 5. The authors noted that this reduction in pain scores persisted after wound catheter removal[89].

Local anaesthetic wound infiltration may also be used to provide postoperative analgesia in abdominal procedures. Liu *et al* conducted a systematic review and meta-analysis of 44 randomised controlled trials of local anaesthetic wound infiltration involving a total of 2141 patients[90]. Of these 11 trials were grouped as general surgery. The most commonly used local anaesthetics were bupivacaine or ropivicaine and infusion was commonly continued for 2 days. The authors reported a significant reduction in pain scores at rest for all groups, a reduction in opiate rescue medication administered during the infusion period and an associated reduction in post operative nausea and vomiting scores. Few of the trials included under general surgery included length of stay. Two colorectal studies were included in this analysis[91,92] and one study assessed patient controlled wound infiltration following laparotomy[93].

A further systematic review and meta-analysis of continuous wound infusions of local anaesthetic following colorectal surgery was published in 2008[94]. This review identified 5 randomised controlled trials involving a total of 542 laparotomy incisions. Three of these trails had be included

by the previous meta-analysis by Liu et al[90]. The outcome measures analysed included VAS for pain at rest and on coughing or movement, opioid consumption, time to return of bowel function and length of postoperative stay. This meta-analysis found a significant reduction in VAS pain scores on postoperative days 1,2 and 3. This was associated with a significant decrease in total opioid consumption. A statistically significant decrease in VAS at rest was seen on the third postoperative day, but not on the first or second. No significant difference was seen in terms of time to return of bowel function or length of postoperative stay[94].

The safety of local anaesthetic wound infiltration is well documented, however, results in terms of efficacy for abdominal surgery have been mixed. Polglase *et al* conducted a well designed fully blinded randomised placebo controlled trial of continuous wound infiltration with 1% Ropivicaine[95]. They hypothesised that wound infiltration would provide a safe and effective adjunct to best practice and based their power calculation on detecting a 20% decrease in both VAS and total morphine requirements. This was a large study of 326 patients with 138 Ropivicaine and 160 placebo patients included in the final analysis. Although not specifically stated in their paper it would appear that midline incisions were used. Contrary to other published studies the effects were minimal. The authors reported a small statistically significant decrease in postoperative pain on movement on the first postoperative day. Thereafter they found trends towards a decrease in pain scores but this did not reach statistical significance. The wound infiltration technique selected for this study bears further scrutiny. The authors state that a dual catheter technique was used, however these catheters were placed on one side of the wound above the fascia, away from the side of the stoma. The authors noted a significant amount of wound leakage, to be expected as this was a subcutaneous infusion. This one sided technique would not have infiltrated the muscle or peritoneum and may not have been as effective in blocking the sensory innervations of the abdominal wall[95]. A similar technique was reported

in patient controlled wound infiltration, where catheters were also placed above the fascia[93]. In this study patient controlled wound infiltration without background local anaesthetic infusion was not found to be effective in reducing pain from laparotomy incision when compared with placebo. The selected endpoint in this study was a 5mg reduction in 'rescue morphine'[93].

The findings of a prospective randomised controlled trial by Baig *et al* were published in 2006[91]. Seventy patients undergoing elective open intestinal surgery through a midline laparotomy were randomised to receive wound infiltration with bupivacaine 0.5% or saline. The catheters were tunnelled and placed into midline wound above the mass closure of abdominal wall but below the skin. The authors found no significant difference in pain scores apart from on the afternoon of the second postoperative day. It is unclear from the data presented whether these pain scores were obtained at rest or on coughing. The authors did report a significant reduction in opioid consumption in the intervention group and that fewer attempts at PCA were made in the intervention group on postoperative days 1, 2 and overall. The clinical relevance of this reduction in opioid consumption did not equate to a decreased length of stay. However, this study was not conducted in the setting of an enhanced recovery program[91].

These findings are in contrast to those of Beaussier *et al* who conducted a randomised controlled trial of continuous preperitoneal infusion of 0.2% ropivicaine and saline after colorectal surgery[96]. Patients underwent elective open cancer resections through midline incisions. The catheters were tunnelled and inserted after closure of the peritoneum but prior to closure of the fascia, so as to facilitate infiltration of the peritoneum. This technique would also have provided a degree of infiltration of the rectus abdominis below the arctuate line. The authors reported a statistically significantly decrease in pain at rest for 12 hrs and pain on coughing for 2 days following surgery. The total morphine consumption was also found to be significantly lower in the

intervention group. This was accompanied by a significant decrease in time to first faeces and length of postoperative stay, suggesting that this decrease in opioid consumption was clinically relevant[96].

Local anaesthetic wound infiltration has also been shown to reduce morphine requirements in transverse laparotomy incisions. Cheong and colleagues conducted a prospective randomised controlled trial of 70 patients undergoing laparotomy for major colorectal surgery using a left iliac fossa skin crease incision[92]. This study compared continuous infusion with 0.5% bupivacaine with morphine PCA. The wound catheters placed subcutaneously after mass closure of abdominal wall. Pain scores were comparable apart from pain at rest on day 1 post op which was significantly less in the bupivacaine group. However, the median total morphine requirement was 0 in the continuous wound infiltration group and 38mg in the PCA group. Whilst the authors did not detect a reduction in length of stay they concluded that the technique was safe[92].

Local anaesthetic wound infiltration has been shown to decrease length of stay. Forastiere and co-workers conducted a placebo controlled double blind randomised controlled trial of 168 pts undergoing open nephrectomy[97]. Patients were randomised to receive 0.5% ropivacaine or saline via wound catheters placed into muscle layer and subcutaneously. They found a statistically significant decrease in pain at rest and on coughing in the intervention group. This was associated with a statistically significant decrease in morphine requirements. This finding was felt to be of clinical significance as it was associated with significantly faster return of gut function and decreased length of postoperative stay. The authors calculated cost savings of 273 Euros in the continuous wound infiltration group[97].

At the time of study design randomised controlled trials comparing local anaesthetic wound infiltration with thoracic epidurals for colorectal

surgery had not been published. Retrospective case controlled studies had suggested that local anaesthetic wound infiltration might be of benefit in the place of thoracic epidurals for patients undergoing abdominal surgery. Parsons *et al* reported their 12 month experience of using rectus sheath catheters for patients undergoing radical cystectomy[98]. Ten patients received ultrasound guided rectus sheath catheters prior to abdominal incision. Their outcomes were then compared to those of the preceding 10 patients who had been managed with thoracic epidurals. The authors reported that the rectus sheath catheters were safe and effective and that patients receiving these had similar postoperative pain scores and analgesic requirements as patients managed with epidurals. The authors noted a non significant reduction in LOS. Despite not being a randomised controlled trial this study was of interest as most of the existing data for wound infiltration was in comparison with morphine PCA. The authors commented on potential advantages of rectus sheath catheters including earlier mobilisation and reduced burden on nursing and medical staff[98].

Although thoracic epidurals have long been seen as the gold standard mode of analgesia for colorectal resections, recent evidence has raised doubts about certain issues surrounding their use. This has been accompanied by innovations within the field of colorectal surgery towards minimally invasive surgical techniques and multimodal optimisation. Local anaesthetic wound catheters have been shown to decrease opiate requirements[90,94] and there is some evidence to suggest that this may translate to swifter return to gut function and a reduction in length of stay[96, 97]. Local anaesthetic wound infiltration may offer an alternative approach to providing adequate analgesia without some of the disadvantages associated with epidurals, such as poor mobility, hypotension and potential for fluid overload or anastomotic hypoperfusion. Further research is necessary to compare the safety and efficacy of epidurals and wound catheters in conjunction with an enhanced recovery program. The development of a novel device for the continuous administration of local anaesthetic via a wound catheter may

offer a viable alternative to epidurals. Various studies have shown this to be a safe and effective method of pain relief[85-89].

1.14 Hypothesis

Whilst there is a substantial evidence base for the use for thoracic epidurals to provide postoperative pain control they are not without risk. The growing trend towards minimally invasive surgery has brought about a reduction in postoperative pain, ileus, stress response and length of postoperative stay. This has altered the balance between risk and benefits of the use of thoracic epidurals.

Concurrently, there has been advancement in anaesthetic techniques for managing postoperative pain. Much of the evidence supporting thoracic epidurals is from studies comparing thoracic epidural analgesia with parenteral opioids, however, there have since been advances in anaesthetic technique which may render these studies outdated. The advent of local anaesthetic wound catheters and transversus abdominis plane (TAP) blocks offers potential alternatives, providing non-opiate analgesia without the systemic effects of thoracic epidurals. In light of this changing situation a re-evaluation of the role of thoracic epidurals in colorectal surgery is called for.

The central hypothesis of this thesis is that thoracic epidurals are no longer routinely required as part of enhanced recovery protocols in colorectal patients. They may pose significant risks in terms of their effect on splanchnic flow if not managed appropriately and may unnecessarily complicate the postoperative management of colorectal patients in return for minimal clinical benefit.

In order to determine whether the benefits of thoracic epidurals outweigh the risks, greater understanding of the risks is clearly

required. The effects of epidural mediated hypotension on splanchnic blood flow are unclear. Concern exists that this may cause a reduction in blood flow which does not resolve with restoration of cardiac output. However, other studies have shown conflicting results. This necessitates a systematic review of the literature on the effects of thoracic epidurals on splanchnic flow. Further prospective studies on the effects of thoracic epidurals on splanchnic flow are also required.

If concerns regarding splanchnic flow are well founded then the postoperative management of colorectal patients with thoracic epidurals requires careful assessment. It is unclear to what extent thoracic epidurals are still favoured amongst colorectal surgeons. Despite the longstanding use of thoracic epidurals for management of postoperative pain in colorectal patients, potential effects on splanchnic flow have not been widely publicised in the literature.

To complete such a re-evaluation of the role of thoracic epidurals in colorectal surgery there is a need for prospective randomised controlled studies comparing them with novel anaesthetic techniques such as local anaesthetic wound catheters in the context of an enhanced recovery program. This thesis aims to explore these areas in more detail.

Chapter 2 - Aims and Sequence of Studies

2.1 Aims

Despite their widespread use in the management of postoperative pain there are many unknowns surrounding the beneficial and adverse effects of thoracic epidurals. In order to re-evaluate their role in patients undergoing colorectal surgery these risks and benefits must be assessed and comparison must be made with current, non opioid methods of postoperative pain control. The main aims of this thesis will therefore be as follows:

1. Investigate the effects of epidurals on splanchnic flow
2. Explore alternatives to epidurals

2.2 Sequence of Studies

All studies were performed at Scarborough General Hospital with the exception of the randomised controlled trial comparing thoracic epidurals with local anaesthetic wound catheters which was conducted in Scarborough Hospital and Castle Hill Hospital in Hull. Work towards the completion of these studies including protocol design, submission for ethical and research and development approval, informed consent, recruitment, data collection, statistical analysis and write up was performed by the author except where specifically stated in the relevant sections. Due recognition has been given to the work of others where appropriate. One systematic review of the literature, three clinical studies two audits and one survey will be described.

The systematic review of the literature on the effects of thoracic epidurals on splanchnic flow (Chapter 3) has been designed to attempt to clarify what effect thoracic epidurals have on the splanchnic blood flow and subsequent anastomotic perfusion. However, it is anticipated

that this review will be hampered by insufficient evidence or conflicting evidence precluding the drawing of firm conclusions.

The requirement of further studies investigating the effects of thoracic epidurals on splanchnic flow will be addressed in two prospective observational studies (Chapter 4). These studies will aim to investigate the effects of thoracic epidurals on superior and inferior mesenteric artery flow respectively, whilst also investigating the effects of intravenous fluids and vasopressors in correcting any changes in blood flow.

Much of the data demonstrating the benefits of thoracic epidurals has involved their comparison with parenteral opioids. The advent of alternative non opioid methods of pain control such as local anaesthetic wound catheters has provided a viable alternative. Whilst there are good data supporting their safety and efficacy, there have been no prospective randomised studies comparing them with thoracic epidurals in the context of an enhanced recovery program. The final study in this thesis is a prospective, randomised, controlled trial comparing thoracic epidurals with local anaesthetic wound catheters for colorectal patients in an enhanced recovery program. The aim of this study will be to determine whether the use of local anaesthetic wound catheters will reduce the length of postoperative stay.

Chapter 3 - The Effect of Thoracic Epidural Anaesthesia on Splanchnic Flow – A Systematic Review of the Literature

In order to better understand the effects of thoracic epidurals on splanchnic flow (Aim 1) a systematic review of the literature was performed. This has been published in the British Journal of Surgery[99] Richards E.R. et al. (2013). "Effect of thoracic epidural anaesthesia on splanchnic blood flow." British Journal of Surgery **100**(3): 316-321.

3.1 Introduction

It is now generally accepted that epidural blockade is effective in reducing postoperative pain in patients undergoing major abdominal surgery. In addition, epidurals may be associated with improved postoperative respiratory function and attenuation of the neuroendocrine stress response to surgery. Not surprisingly therefore the use of epidural anaesthesia has become standard practice in many colorectal units as well as being adopted as an important part of enhanced recovery plans.

However, there is increasing concern that the use of epidural anaesthesia is associated with postoperative hypotension and a reduction in splanchnic blood flow. This, it has been suggested, might impact on anastomotic perfusion, although any effects on subsequent anastomotic leakage remain unproven[49]. Indeed, one animal study demonstrated an increase in anastomotic bursting pressures with epidural analgesia[100].

The splanchnic blood supply is provided by celiac and mesenteric arteries which anastomosis extensively to provide a vast collateral supply to the fore, mid and hindgut. Splanchnic blood flow is determined by many intrinsic and extrinsic mechanisms including

cardiac function, the autonomic nervous system and neuroendocrine mediators. In experimental studies epidural blockade of the sympathetic outflow from segments T1-L1 results in splanchnic and peripheral vasodilatation and functional hypovolaemia. It is unclear however what the situation is in patients undergoing abdominal surgery. The aim of this systematic review was an attempt to resolve this question.

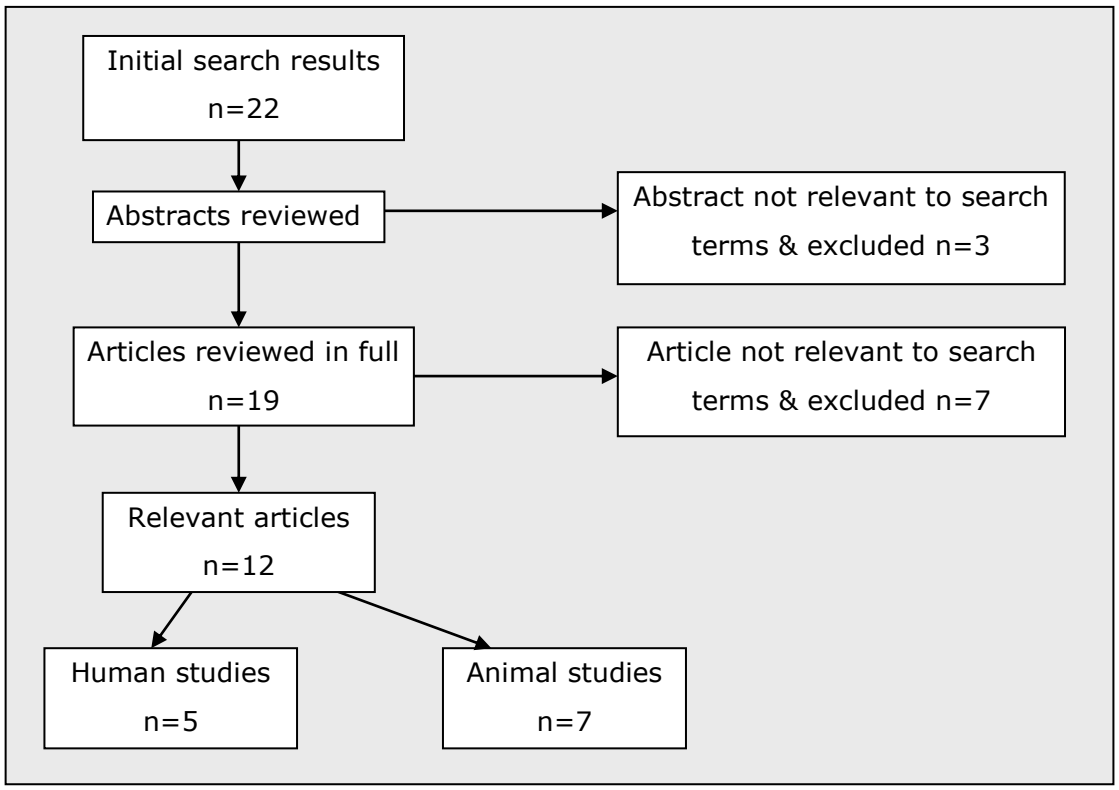
3.2 Methods

PubMed and Cochrane databases were searched using the following search terms: English language, 'thoracic epidural splanchnic flow', 'thoracic epidural gut blood flow' thoracic epidural intestinal blood flow' and 'thoracic epidural colonic blood flow'. The abstracts were reviewed by two independent researchers and those not relevant to the search were excluded. The full text of the remaining articles was obtained and reviewed. JADAD scores[101] were then performed by each of the independent researchers for each relevant article.

3.3 Results

The above search produced 22 articles. Following review of the abstracts three articles were excluded as they were found not to be relevant to the search terms. The full text of the remaining 19 articles was then reviewed. The systematic review found a total of 7 animal and 5 human studies which investigated the effects of thoracic epidurals on splanchnic flow. The remaining 7 articles reviewed did not investigate the effects of epidurals on splanchnic flow and were excluded. The results are shown in the tables 1 and 2. Due to the wide variety of measures of splanchnic flow and differing methodologies used, a meta-analysis was not feasible.

Figure 1 - Flow chart of search results



3.4 Human Studies

There were 5 human studies identified.

Two studies directly measured splanchnic arterial blood flow. Lundberg and colleagues measured superior mesenteric artery (SMA) flow in 9 patients having aortic surgery using a cuffed electromagnetic flow probe. In addition, they took blood samples from the radial artery, superior mesenteric vein and pulmonary artery and calculated the systemic and mesenteric arteriovenous oxygen differences and lactate levels. They found that a thoracic epidural reduced the SMA flow by 23%, with a decrease in systemic and mesenteric vascular resistance, but no change in cardiac output. This was associated with an increased mesenteric arteriovenous oxygen difference, suggesting reduced intestinal perfusion. These changes were partially corrected by the use of dopamine[102]. A more recent study by Gould *et al* measured inferior mesenteric artery (IMA) flow using a cuffed Doppler in 15 patients

undergoing anterior resection for rectal malignancy. They correlated this with measurements of colonic serosal red cell flux (presumed to equate to colonic mucosal red cell flux). They demonstrated that thoracic epidural was associated with a reduction in mean arterial pressure (MAP), reduced IMA flow and reduced colonic serosal red cell flux. There was a strong association between MAP, IMA flow and colonic red cell flux. Changes in cardiac output were poorly associated with IMA flow. Interestingly, the splanchnic flow was not corrected by oesophageal Doppler guided bolus intravenous fluid administration, but only by the use of vasopressors[61].

A total of three studies assessed splanchnic flow by indirect methods. Michelet *et al* measured gastric mucosal blood flow on the presumption that a thoracic epidural would increase the gastric tube microcirculation through enhanced splanchnic perfusion. In a prospective, non randomised, controlled study of 27 human subjects who had undergone oesphagectomy, they measured gastric mucosal blood flow by placing an endoscopic laser Doppler probe 5cm beyond the oesphago-gastric anastomosis. They found that thoracic epidurals increased gastric mucosal blood flow by over 30% as compared to the control group and suggested this was related to splanchnic vasodilatation[103]. These patients were kept haemodynamically stable on an intensive care unit throughout the duration of the study. As a consequence the results are not comparable to the preceding two studies where epidural mediated hypotension was observed prior to treatment with vasoconstrictors or inotropes.

Kortgen and colleagues used indocyanine green to measure the effects of thoracic (T5/6 – T9/10) and lumbar (L1/2- L4/5) epidurals on splanchnic perfusion. This technique estimates hepatosplenic blood flow according to the Fick principle. The study was conducted under general anaesthesia on the intensive care unit (ICU) in the postoperative setting. Thirty four patients were recruited of which 17 had thoracic and 17 had lumbar epidurals. The study was not randomised as the site of

catheter insertion was determined by the type of surgery. Patients were kept haemodynamically stable with some requiring the use of inotropes throughout the study. PDR_{ICG} (Plasma disappearance rate of indocyanine green) was measured noninvasively and taken to be a marker of splanchnic perfusion and hepatic blood flow. The authors demonstrated a significant increase in PDR_{ICG} in the thoracic but not lumbar epidural group suggesting that thoracic epidurals increased hepatic perfusion after major abdominal surgery[104].

Väïsänen and peers conducted a prospective randomised controlled study of patients undergoing aortic reconstruction surgery. They measured the effects of thoracic epidurals (T12-L1) on gastric and sigmoid tonometry (measures of mucosal pH and pCO_2) and splanchnic flow as measured by indocyanine green. They found no change in pH, pCO_2 or splanchnic flow between the epidural and control groups[105].

3.5 Animal Studies

Seven animal studies were identified. A wide variety of study designs, animal models and surrogate measures of splanchnic flow were used.

Intravital microscopy was employed in four studies. This technique employs a high powered video-microscope to image a section of in-vivo rat ileum. After the animal is anaesthetised a segment of ileum is exteriorised with its blood supply intact, is incised along its antimesenteric border and placed on a specially constructed microscope stage. High powered video microscopy is then performed and images recoded for subsequent analysis. Perfusion is determined by the passage of erythrocytes through vessels and flow is estimated using erythrocyte velocity and vessel diameter, whilst perfusion is equated to capillary recruitment[58,106]. In a randomised controlled study of 19 rats, Sielenkämper *et al* (2000) found that despite a fall in mean arterial pressure (MAP), thoracic epidural anaesthesia (TEA) was associated with a transition from partial to continuous perfusion in rat ileum as well

as increased erythrocyte velocity with no associated change in vessel diameter[58]. The authors have interpreted this as an increase in ileal mucosal blood flow in view of the greater capillary recruitment and increased erythrocyte velocity. They postulated that this might be due to inter/intra-organ redistribution of blood flow.

Two studies in rats have investigated the role of TEA in animal models of endotoxic shock. Schäper *et al* (2010) used fluorescent microspheres in a rat model of normotensive endotoxaemia. They found that despite an initially decreased MAP, TEA prevented the decrease in intestinal perfusion following the administration of e-coli LPS, which they attributed to the attenuation of endotoxin induced vasoconstriction[107]. Adolphs *et al* (2004) conducted a randomised controlled study of 32 rats in which intravital microscopy was used to measure ileal blood flow. Eight animals were randomised to a no epidural group and given e-coli lipopolysaccaride (LPS) or saline, whilst the remaining animals were randomised to a further four groups and given an epidural with either saline or lidocaine with microscopy of ileal mucosa or muscularis. These animals were observed at baseline, after epidural or sham epidural and after LPS. The authors concluded that TEA seemed to impede the normal redistribution of blood flow towards the mucosa seen in endotoxaemia, resulting in improved muscularis and worsened mucosal microvascular perfusion[106].

In a randomised controlled animal study of the effects of TEA on a rat model of acute pancreatitis Freise *et al* (2006) used intravital microscopy to assess ileal blood flow. They concluded that TEA attenuated the systemic response to pancreatitis and improved survival. Their results showed a 66% decrease in mortality and that ileal blood flow, which decreased by 50% in untreated pancreatitis, was preserved by TEA[108]. This effect is representative of the prevention by TEA of the vasoconstriction associated with inflammation, rather than an actual increase in blood flow.

Meissner *et al* studied the effects of a limited upper thoracic epidural block (LUTEB) of T1-T5 (sparing splanchnic sympathetic fibres) on splanchnic flow in awake and anaesthetized dogs using coloured microsphere to assess perfusion. They found a decreased MAP in the anaesthetized but not the awake group and concluded that whilst propofol increased liver blood flow LUTEB had no effect on splanchnic flow[109]. The authors of this study had hypothesised that LUTEB would decrease splanchnic perfusion because of reflex sympathetic activity in the spared sympathetic fibres, causing vasoconstriction and ischaemia. This study is therefore not comparable to other studies investigating the effects of a traditional thoracic epidural on splanchnic flow. It is however interesting as it is the only study in the search which specifically questions the role of the sympathetics in gut blood flow.

In a randomised controlled animal study of 19 pigs Vagts *et al* (2003) found decreased MAP but no associated change in SMA flow, jejunal pH or mucosal pO_2 with TEA. They also noted no benefit from volume loading despite significant hypotension[110]. In contrast to these findings Schwarte *et al* (2004) measured gastric mucosal oxygenation in normovolaemic and circulatory compromised dogs with TEA and found a decrease in gastric mucosal oxygenation in the circulatory compromised group which was corrected with fluid resuscitation[111].

Table 1 - Human studies

Author	Date	Title	Type of study	Subjects	Surrogate measure of splanchnic flow	Findings	JADAD score
Gould et al	2002	Effect of thoracic epidural anaesthesia on colonic blood flow	Observational study	Humans n=15	Inferior Mesenteric Artery (IMA) flow Colonic serosal red call flux	Reduction in flow not corrected with intravenous (IV) fluids, required vasoconstrictors	1
Väïsänen et al	1998	Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery	Prospective randomised controlled study in patients undergoing elective abdominal aortic surgery	Humans n=20	Gastric and sigmoid mucosal pCO_2 & pH Indocyanine green	Blood Pressure (BP) maintained. No improvement in perfusion with TEA	4
Lundberg et al	1990	Intestinal haemodynamics during laparotomy: effect of thoracic epidural anaesthesia and dopamine in humans	Prospective observational study (Not RCT) in patients undergoing elective aorto-bifemoral reconstruction surgery ASA 2-3	Humans n=9	Superior Mesenteric Artery (SMA) flow (electromagnetic flow probe)	TEA reduced SMA blood flow, effects corrected by dopamine	0

Author	Date	Title	Type of study	Subjects	Surrogate measure of splanchnic flow	Findings	JADAD score
Kortgen et al	2009	Thoracic but not lumbar epidural anaesthesia increases liver blood flow after major abdominal surgery	Prospective study (Not RCT) ASA 2-3	Humans n=34	Plasma disappearance rate of indocyanine green (PDR_{ICG} marker of hepatic perfusion / hepatocellular function) Blood lactate	All patients in Intensive care unit (ITU) setting, some given intotropes, Mean arterial pressure (MAP) maintained Significant increase in liver blood flow with thoracic but not lumbar epidural	0
Michelet et al	2007	Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy	Prospective (non randomised) controlled study (18 TEA, 9 no TEA)	Humans n=27	Gastric mucosal blood flow using laser Doppler flowometer at 1hr & 18hrs (placed nasogastrically)	All patients kept haemodynamically stable TEA increased gastric mucosal blood flow	0

Table 2 - Animal studies

Author	Date	Title	Type of study	Subjects	Surrogate measure of splanchnic flow	Findings	JADAD score
Meissner et al	1999	Limited upper thoracic epidural block (LUTEB) and splanchnic perfusion in dogs	Prospective observational animal study 7- Awake 6- General Anaesthetic (GA)	Dogs n=13	Regional blood flow determined by coloured microspheres. Processed and measured in end organs post mortem	Decreased MAP in GA not awake group propofol increased liver blood flow LUTEB (T1-T5 therefore sparing splanchnic sympathetic fibres) has no effect on splanchnic flow	0
Schäper et al	2010	Thoracic epidural anaesthesia attenuates endotoxin-induced impairment of gastrointestinal organ perfusion	Randomised controlled animal study TEA (local anaesthetic (LA)) vs TEA(saline) in a model of normotensive endotoxaemia	Rats n=18	Fluorescent microspheres. Processed & harvested post mortem	Initially decreased MAP TEA prevents the decrease in intestinal perfusion following the administration of e-coli Lipopolysaccharide (LPS) – likely by attenuating endotoxin mediated vasoconstriction	2

Author	Date	Title	Type of study	Subjects	Surrogate measure of splanchnic flow	Findings	JADAD score
Freise et al	2006	Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in acute severe pancreatitis in rats	Blinded randomised controlled animal study 4 groups 1) Sham saline TEA 2) Acute Pancreatitis (AP) & saline TEA 3) AP TEA 4) AP delayed TEA + 30 rats assigned to outcome protocol 15 Acute Pancreatitis / 15 TEA	Rats n=28 + n=30	Intravital videomicroscopy	TEA attenuates systemic response to pancreatitis & improved survival. (66% decrease in mortality). Blood flow decreased by 50% in untreated pancreatitis but preserved by TEA	1
Adolphs et al	2004	Effect of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia	Randomised controlled animal study No TEA (5 e-coli),(3 saline) TEA – 4 groups n=6 per group, lidocaine or saline via TEA & allocated to muscularis or mucosa Observed at baseline, following TEA or sham, and following LPS infusion	Rats n=32	Intravital microscopy with fluorescein	LPS alone – no change in BP epidural – lower map Improved muscularis and worsened mucosal perfusion in presence of LPS	2

Author	Date	Title	Type of study	Subjects	Surrogate measure of splanchnic flow	Findings	JADAD score
Vagts et al	2003	Effects of epidural anaesthesia on intestinal oxygenation in pigs	Randomised controlled animal study Control, epidural or epidural + volume loading (3 controls, 8 TEA, 8 TEA + volume loading)	Pigs n=19	Catheterised cranial mesenteric vein Blood gas catheter in jejunum Electrodes to measure tissue surface pO_2 on jejunal mucosa and serosa Ultrasound (USS) flow probe around SMA	Decreased MAP No change in SMA flow, pH, mucosal pO_2 No benefit from volume loading	2
Sielenkämper et al	2000	Thoracic epidural anaesthesia increases mucosal perfusion in ileum of rats	Non blinded Randomised controlled animal study	Rats n=19	Intravital videomicroscopy of ileal mucosa	MAP decreased Transition from partial to continuous perfusion Increased velocity with no change in diameter (extrapolated as increased flow)	3

3.6 Discussion

The influence of thoracic epidurals on splanchnic flow remains unclear. However, the two human studies, in which direct measurements of mesenteric blood flow were recorded, both suggest that epidurals reduce intestinal perfusion, which is not corrected with the restoration of cardiac output through the administration of intravenous fluid alone but required inotropes or vasoconstrictors. If confirmed these results have important implications to the use of epidural anaesthesia.

The author recognises the inconsistency of results obtained between some of these studies. In studies where surrogate markers of intestinal perfusion were used there was evidence to suggest an increase in splanchnic flow. The discrepancy in these results may be a reflection of methodology employed or reflect differences in the physiological status of the patient or animal under investigation. For example, in animal models of shock and sepsis, epidurals appear to have a protective role in preventing splanchnic vasoconstriction. The effects of thoracic epidurals on splanchnic flow may differ depending on haemodynamic status.

In normal physiological circumstances thoraco-lumbar sympathetic outflow mediates vasoconstriction which may be initiated by a variety of factors, including sepsis and stress states such as acute pancreatitis. Such vasoconstriction may impair splanchnic flow as blood is diverted away from the gut to more vital organs. In addition to blocking type C pain and temperature fibres, thoracic epidural anaesthesia can also block sympathetic nerve fibres, resulting in peripheral and splanchnic vasodilatation, functional hypovolaemia and hypotension. The subsequent effect on gut blood flow remains uncertain. Doppler studies by Johansson *et al* suggest that this vasodilatation improves mucosal perfusion[112]. The study by Gould, however, suggests that the splanchnic vasodilatation is offset by the loss of sympathetic tone, the reduced MAP and the more pronounced vasodilatation in the peripheral vascular beds. Recent research has also focused on the potentially protective

role of thoracic epidurals on gut blood flow in the presence of sepsis or shock. Such a role may be attributable to the blockade of sympathetic outflow in these patients in order to maintain baseline perfusion rather than increase flow.

Human studies relating to splanchnic perfusion are scarce due to the methodological difficulties in measuring this quantitatively. There are only two human studies in which splanchnic flow was measured directly. This must reflect the logistical and ethical constraints involved in conducting this type of study. Surrogate markers of splanchnic flow, such as indocyanine green (ICG) have the disadvantage that they can be affected by alteration in liver function and by uptake in extra hepatic tissue, although this is thought to be negligible. The use of contrast enhanced near infrared spectroscopy in conjunction with ICG has been shown to yield quantitative measures of blood flow to a variety of organs including the liver, skeletal, cardiac muscle and the brain. As IGC is cleared from the systemic circulation by the liver a bolus of ICG must be given each time flow is measured and as this takes approximately 10-20 minutes, measurements may only be taken infrequently so as to avoid erroneous results[105]. Whilst gastric tonometry represents a simple and relatively non-invasive technique for measuring mucosal perfusion, it is by no means a direct measure of splanchnic flow. In a previous study by Larson *et al* gastric $pC0_2$ did not start to change until SMA flow decreased to 50% of baseline as measured by Doppler flowometer[113]. Extrapolation of mucosal pH is based on a number of assumptions and is subject to errors of both methodology and interpretation[114, 115].

Whilst the author supports the use of vasopressors in hypotensive euvolamic patients who have received goal directed fluid therapy to ensure adequate restoration of cardiac output, care should be taken with vasopressors in hypovolaemia. In a retrospective study of 223 patients, Zakrison *et al* found Perioperative vasopressors to be associated with a threefold risk of anastomotic leakage. In their

discussion they commented that the reasons for commencing vasopressors were unclear and that these patients may have been hypovolaemic. They emphasise the importance of goal directed fluid therapy to ensure normovolamia prior to commencing vasopressors[116].

Blood flow and oxygen delivery to the healing anastomosis have long been recognised as key factors in anastomotic healing. Levy *et al* found that a reduction in indexed oxygen delivery ($D0_2I$) was associated with an increased risk of anastomotic leakage. However, they found no significant difference in $D0_2I$ between patients with epidural, spinal and patient controlled opiate analgesia[117].

The relationship between any potential reduction in anastomotic perfusion and anastomotic leakage remains unproven. In a study of 14 rabbits randomised to epidural or control, epidural analgesia for 6 hours postoperatively produced significantly higher anastomotic bursting pressures on day 4. This study, although small, suggested a protective effect of epidurals against anastomotic leakage[100]. A review by Holte and Kehlet of 12 randomised, controlled trials found no evidence to indicate that epidural analgesia with local anaesthetic was associated with an increased risk of anastomotic breakdown after colorectal surgery. However, the risk of type II error was 67%, and they calculated that a total of more than 1,037 patients would be needed in each group to provide 80% power. As this review comprised a total of 562 patients, their findings lacked sufficient power to be conclusive[49].

Epidural mediated hypotension is seen on a daily basis in our hospitals. In the first instance this is usually managed by administering bolus aliquots of fluid. The evidence from the human studies which have directly measured splanchnic flow would suggest that in the setting of a postoperative patient who has been adequately filled, that administration of additional intravenous fluid may not only fail to correct this potential reduction in splanchnic flow and subsequent anastomotic perfusion, but also place the patient at risk of fluid overload and its attendant morbidity. Clearly this requires further investigation.

Thoracic epidurals have been shown to attenuate the neuroendocrine stress response[118], provide excellent postoperative analgesia, and are thought to reduce postoperative complications. They are widely used for colorectal patients as part of an enhanced recovery programme. A systematic review of all randomised trials in the last 30 years demonstrated a clinically and statistically significant reduction in morbidity and mortality after surgery with the use of regional anaesthesia[119]. However, this review included trials which compared epidurals with regional anaesthesia, and covered a range of surgical procedures. The authors have commented that for those studies comparing GA and regional anaesthesia with GA alone a similar reduction in postoperative complications was seen, but confidence intervals were wide. The MASTER Anaesthesia Trial of 915 high risk patients undergoing major abdominal surgery did not find a significant difference in mortality or major morbidity between those patients receiving thoracic epidurals as compared to controls[35]. They did however find a significantly lower frequency of respiratory failure. The MASTER trial did have a number of limitations, the epidural and control groups were not homogenous, patients in the control group had more risk factors ($p=0.04$), and the authors have commented that their study may have lacked sufficient power to prove the benefits of thoracic epidurals[35]. Despite the controversy surrounding their results the consensus remains that the benefits of epidural anaesthesia have not been conclusively proven and that further large prospective randomised controlled trials are required.

3.7 Conclusion

The widespread adoption of minimal access and laparoscopic surgery together with other improvements in anaesthetic technique has resulted in a definite shift away from the routine use of thoracic epidurals in colorectal patients. Transversus Abdominis Plane (TAP) blocks and local anaesthetic wound catheters now offer viable alternatives for postoperative pain control, ensuring the avoidance of opiates without

the complications and limitations of thoracic epidurals. Current advances in the fields of colorectal surgery and anaesthesia coupled with the absence of concrete evidence to support the use of thoracic epidurals have led to a more selective approach to their use. The routine use of epidurals in laparoscopic colorectal resection is no longer deemed necessary. The authors would suggest that the routine use of epidurals in patients undergoing minimal invasive open colorectal surgery, employing small transverse incisions, can also no longer be justified for every case. For those high risk patients in whom the use of a thoracic epidural is felt to be beneficial, appropriate postoperative management of any epidural associated hypotension is required to mitigate any potential effects on splanchnic flow.

Chapter 4 - The Effects of Thoracic Epidurals on Splanchnic Blood Flow - Two Prospective Observational Studies

4.1 Introduction

Thoracic epidurals are widely used in colorectal surgery for the provision of postoperative pain control. Their use is advocated by existing enhanced recovery protocols and has a substantial evidence base[37,52,75,120-122]. However, there is extensive circumstantial evidence that epidurals are associated with hypotension in the postoperative period. The effects of such epidural mediated hypotension on the splanchnic circulation are not fully understood. This is clearly an area of great relevance in the field of colorectal surgery due to the potential consequences of impaired colorectal anastomotic perfusion in terms of the high morbidity and mortality associated with an anastomotic leak.

The effect of thoracic epidural anaesthesia (TEA) on intestinal perfusion is not fully understood. In animal models TEA has been shown to increase gut mucosal perfusion[58,59]. However, epidural anaesthesia with bupivacaine has been shown to cause a significant decrease in the oxygen-perfusion state of colorectal anastomosis in humans, although this was not associated with anastomotic or other complications[60]. Most studies into the effect of TEA on splanchnic blood flow in patients have utilised indirect measurements such as tonometry. Gould *et al* performed an intraoperative study of 15 patients in which they directly measured inferior mesenteric artery flow and colonic serosal red cell flux. They found that the measured reduction in colonic blood flow caused by epidural block did not respond to an increase in cardiac output with fluid resuscitation, but required the use of a vasopressor to restore blood flow[61].

Gould *et al'*s findings raise significant concerns about current practice. The trend towards goal directed fluid therapy using oesophageal Doppler measurements of cardiac output in colorectal patients is called into question by the existence of new evidence that cardiac output may not correspond to colonic blood flow in the presence of TEA. This is a particular area of concern in colorectal patients with an anastomosis. Recent literature suggests that restrictive fluid regimes may reduce morbidity after colorectal resection[62]. Fluid challenges in patients with TEA induced hypotension may not only be ineffective in restoring gut blood flow but may also place them at risk of potential fluid overload with its associated morbidity.

There is a definite need for further studies to investigate the effects of TEA on splanchnic flow and also the role of intravenous fluids and vasoconstrictors in mitigating such effects. Two such studies have been devised, focussing on the effects of TEA on Superior and Inferior Mesenteric Artery (SMA and IMA) blood flow respectively.

4.2 Hypotheses and Aims

The hypotheses of these studies are that a bolus of local anaesthetic given via an epidural catheter will mediate a decrease in both SMA and IMA flow which will not be completely restored by the administration of oesophageal Doppler directed fluid therapy but will necessitate the use of vasoconstrictors.

The aims of these studies are to assess the effects of thoracic epidural on SMA and IMA blood flow and the adequacy of goal directed fluid therapy and vasoconstrictors in ameliorating such affects.

4.3 Patients and Methods

Study protocols, patient information sheets and consent forms have been attached as Appendices A-F.

4.3.1 Study Design

Two prospective observational studies:

SMA flow: A prospective observational study of patients receiving thoracic epidural anaesthesia.

IMA flow: A prospective observational study of patients undergoing left hemicolectomy receiving thoracic epidural anaesthesia.

4.3.2 Inclusion Criteria

SMA flow: Patients receiving thoracic epidurals and general anaesthetic for any surgery.

IMA flow: Patients undergoing left hemicolectomy receiving thoracic epidurals.

4.3.3 Exclusion Criteria

SMA and IMA flow: Pregnant females, patients under 18 years of age and patients unable to give informed consent were excluded from this study. Also excluded were patients in whom prolongation of anaesthesia was deemed unsafe and those classified as American Society of Anaesthesiologist (ASA) grade IV or above. ASA grade IV denotes patients with incapacitating disease which is a constant threat to life[123].

4.3.4 Recruitment

SMA flow: Patients on the waiting list for any surgery involving thoracic epidurals and a general anaesthetic were identified in outpatient clinics, at pre-assessment or on the ward. They were approached by pre-assessment clinic or ward nurses and informed about the existence of the trial. If they were happy to discuss this with a research fellow then

this occurred and they were given an information leaflet and a period of at least 24 hours to consider participation. If after this period they still wished to proceed they were consented and recruited to the study.

IMA flow: Patients on the waiting list for left hemicolectomy were identified in outpatient clinics, at pre-assessment or on the ward. They were approached by pre-assessment clinic or ward nurses and informed about the existence of the trial. If they were happy to discuss this with a research fellow then this occurred and they were given an information leaflet and a period of at least 24 hours to consider participation. If after this period they still wished to proceed they were consented and recruited to the study.

4.3.5 Epidural Catheter

SMA and IMA flow: All patients underwent insertion of a thoracic epidural catheter at T8-T11 in the anaesthetic room. Local anaesthetic was not given via the epidural catheter at this time.

4.3.6 Anaesthetic Protocol

SMA and IMA flow: Anaesthesia was induced and maintained following a standard protocol; propofol, fentanyl, and atracurium for induction of general anaesthesia, and ventilation, oxygen, air and sevoflurane for maintenance.

4.3.7 Monitoring

SMA and IMA flow: Patients were monitored with an oesophageal Doppler, arterial line, non invasive blood pressure monitoring, continuous ECG (electrocardiogram) and other standard anaesthetic monitoring equipment. Cardiac output, systolic and diastolic blood pressure and mean arterial pressure were measured throughout the procedure.

4.3.8 Measurement of Splanchnic Flow

SMA flow: Baseline measurements of SMA diameter and SMA flow were obtained using trans-abdominal Doppler ultrasound (Philips HDI 5000 Ultrasound) performed by a single Consultant Radiologist.

IMA flow: The operation proceeded as planned and the IMA was dissected out. Once dissected out baseline measurements of IMA flow were obtained using a vascular intraoperative Doppler ultrasound using a SonoSite Titan HST Transducer (Hockey Stick Transducer 10-5 MHz, 25mm broadband Linear Array Transducer, scan depth 5.1 cm).

4.3.9 Bolus of Local Anaesthetic via Epidural

SMA and IMA flow: A test dose of 5ml 0.25% bupivacaine was given for safety purposes to assess the adequacy of the positioning of the epidural catheter within the epidural space. The epidural was then started and a bolus of 0.5mg/kg (12-16ml) of 0.25% bupivacaine given via the epidural catheter. Arterial pressure was allowed to fall to a mean arterial pressure (MAP) of no less than 60mmHg. Further measurements of SMA or IMA flow were then taken in conjunction with other observations including cardiac output.

4.3.10 Oesophageal Doppler Guided Fluid Resuscitation

SMA and IMA flow: Oesophageal Doppler guided fluid resuscitation with 6% Volulyte then took place to restore cardiac output to baseline levels (with the exception of the final patient in the study who received compound sodium lactate (Hartmann's) solution due to an alteration in Hospital Trust policy). A further reading of SMA or IMA flow was then obtained.

4.3.11 Administration of Vasoconstrictors

SMA and IMA flow: If the MAP was not restored to baseline levels then up to three 0.5mg bolus doses of metaraminol were given over a 6-9 minute period to return the mean arterial pressure to the pre-epidural level. A final set of measurements including SMA or IMA flow were then taken to conclude the study and the operation would then proceed as planned.

Ethical approval for the study was granted by the Leeds East Regional Ethics Committee, subject to a 30 minute time limit for the study period.

4.3.12 Sample Size and Statistical Analysis

In view of the nature of these small observational studies no power calculation has been performed. The aim was to recruit 15 patients in each group (15 for IMA flow and 15 for SMA flow).

Data were analysed by means of a commercially available statistics package (SPSS v 20). A p-value of less than 0.05 will be taken to signify statistical significance. Categorical data will be analysed using the chi squared test or Fisher's exact test, as appropriate. Data which are not normally distributed will be analysed using the non-parametric tests: Mann-Whitney U or Wilcoxon as appropriate.

4.4 Results

Recruitment to these studies was slower than anticipated. A total of six patients were recruited to and participated in the SMA flow study. Three patients were recruited to the IMA flow study. Due to technical difficulties with the transducer the third IMA flow patient's study was abandoned. Barriers to recruitment were patients' reluctance to voluntarily extend their period of time under anaesthetic. This was

commonly perceived to be unsafe despite reassurance to the contrary in both the written and verbal information given.

It was also necessary to coordinate the same anaesthetist and radiologist's availability for each of the SMA flow participants which also reduced the potential number of participants. There was also a shift within the anaesthetic department at the time of study recruitment away from using epidurals for many patients which also impacted upon patient selection.

For each subject, vessel diameter, PSV and EDV were obtained (with the exception of subject SMA1 where there were concerns over the anatomy and correct flow readings were not possible). Measurement of volume flow was calculated as follows:

Figure 2 - Formula for the calculation of splanchnic blood flow [124]

Volume	**=**	**Cross-sectional area x**	**Mean velocity**	**x**	**60**
(ml/min)		**(cm^2)**	**(cm/sec)**		
		(Cross sectional area (cm^2): $\pi d^2/4$)		**(d: diameter)**	

In order to compare trends between subjects the volume flow rates for each individual were converted to percentages of baseline. The results obtained from both the IMA and SMA subjects studied are shown in the table below.

Table 3 - IMA and SMA flow results

Subject	% of Baseline			
	Baseline	Post Epidural	Post Fluid	Post Vasopressor
SMA1	Unobtainable	Unobtainable	Unobtainable	Unobtainable
SMA2	100	10.24	17.84	27.39
SMA3	100	78.23	NA	95.75
SMA4	100	188.87	189.59	124.81
SMA5	100	98.41	66.03	75.14
SMA6	100	102.65	143.71	109.58
IMA1	100	68.53	Unobtainable	50.76
IMA2	100	90.16	32.82	73.97

Results for SMA and IMA flow were analysed together using the Friedman test, results did not demonstrate a statistically significant change ($p=0.948$). Analysis of the SMA group independently also produced a non-significant result ($p=0.96$), whilst owing to the missing data no statistical analysis could be performed on the IMA group. Individual results for each subject will be discussed in turn.

Table 4 - Subject IMA1

Measurement (time in minutes)	BP	MAP	Oesophageal Doppler			IMA flow				
			CI	SV	FTc	IMA D	IMA PSV	IMA EDV	Flow ml/min	%
Baseline (0)	131/53	81	5.8	97	350	0.31	156.9	32.5	428.86	100
Post bolus of epidural (13)	101/38	69	3.3	68	332	0.31	109.4	20.4	293.91	68.53
Post fluid resuscitation (21)	83/58	66	5.1	115	388	U	U	U	NA	NA
post Metaraminol (25)	129/67	86	5.8	123	388	0.24	138.8	21.6	217.69	50.76

BP = blood pressure, MAP = mean arterial pressure, CI = cardiac index, SV = stroke volume, FTc = flow time corrected, IMA d = diameter of inferior mesenteric artery, IMA PSV = IMA peak systolic velocity, IMA EDV = IMA end diastolic velocity

4.4.1 Subject IMA1

Subject IMA1 was a 76 year old lady due to undergo an anterior resection of rectum for colorectal malignancy. She suffered from hypertension and hypercholesterolaemia. Her medications included bendroflumethiazide, valsartan and moxonidine. A thoracic epidural was inserted at T11-12 after several attempts due to technical difficulties experienced by the anaesthetist. This did not conform to the protocol which specified T8-11, however a higher level of insertion was not possible in this patient.

This subject was hypertensive prior to induction of general anaesthesia with a blood pressure of 160/83 mmHg. This fell following induction of general anaesthesia, to 105/74 mmHg, necessitating the administration of ephedrine. The blood pressure subsequently fell further to systolic levels below 70 mmHg and required further administration of ephedrine. It was noted and discussed that this subject's blood pressure rose as the operation proceeded and the IMA was exposed. However, this fell again once the active surgery had stopped to obtain steady state baseline readings, prior to commencing the study. A true steady state measurement could therefore not be obtained for patient safety reasons. A further dose of ephedrine was administered to restore the patient's blood pressure to her pre-induction reading of 160 mmHg systolic prior to starting the study period.

As observed in the SMA flow study this patient's MAP fell in response to a bolus of local anaesthetic given via her epidural catheter. Her MAP did not correct with the fluid bolus given to restore her cardiac output. Both the IMA PSV and EDV and calculated IMA flow fell in response to the epidural bolus. However, as it was not possible to obtain a useable trace after intravenous fluid administration, no measurement of IMA flow could be obtained. This failure to obtain a measurement was associated with a further decrease in MAP. It is of interest that following the administration of metaraminol the MAP increased back to baseline and the IMA flow measurements became obtainable once more.

Table 5 - Subject IMA2

Measurement (time in minutes)	BP	MAP	Oesophageal Doppler			IMA flow				
			CI	SV	FTc	IMAD	IMA PSV	IMA EDV	Flow ml/min	%
Baseline (0)	137/68	92	3.7	106	374	0.21	134.2	28.3	168.85	100
Bolus of epidural (5)										
Post bolus of epidural (12)	88/46	60	2.1	80	353	0.22	120.3	13.2	152.24	90.16
Post fluid resuscitation (15)	82/46	59	3	98	376	0.22	34.1	14.5	55.42	32.82
Metaraminol (17)										
post Metaraminol (22)	119/60	80	3.7	120	362	0.21	103.4	16.8	124.9	73.97

4.4.2 Subject IMA2

Subject IMA2 was a 63 year old female due to undergo a left hemicolectomy for colonic malignancy. She was otherwise well and took no medication. Her thoracic epidural was inserted at level T10-11. Her blood pressure prior to induction of general anaesthesia was 145/ mmHg but fell markedly following the induction of general anaesthesia to 75/45 mmHg. She required the administration of repeated doses of both metaraminol and ephedrine to correct this prior to the start of the study period.

During the study period the bolus of local anaesthetic via the epidural catheter was associated with a fall in MAP, falling further following fluid resuscitation. This was accompanied by a decrease in IMA flow, most markedly in the measurement taken post fluid resuscitation. This was largely corrected by the administration of metaraminol but did not return to baseline.

Table 6 - Subject SMA1

Measurement (time minutes)	BP	MAP	Oesophageal Doppler			SMA flow				
			CO	SV	FTc	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline * (0)	157/81	108	5.9	79	310	0.72	132 134 155	U U U	NA	NA
Post Bolus via epidural (7)	117/58	81	7.7	93	355	U	U	U	U	NA
Post Fluid resuscitation (13)	85/49	62	6.8	88	358	U	U	U	U	NA
Post Metaraminol (20)	151/77	105	6.5	80	341	U	U	U	U	NA

* Baseline reading was obtained following administration of epinephrine to correct hypotension induced by GA

U = unable to measure, NA = not applicable

4.4.3 Subject SMA1

Subject SMA1 was a 67 year old male who was due to undergo a nephrectomy. He did not take any antihypertensive medications but was taking aspirin and hydroxycarbamide preoperatively. A thoracic epidural catheter was inserted at level T10-T11 in the left lateral position under general anaesthesia, using a median approach and the loss of resistance technique. Following the induction of general anaesthesia (GA) it became immediately apparent that maintaining a steady haemodynamic state under anaesthesia would be problematic, as this gentleman's blood pressure became labile. Following induction of GA his blood pressure fell from 141/100 mmHg (millimetres of Mercury) to 100/45mmHg and then to 68/40 mmHg with an associated pulse rate of 56 bpm (beats per minute), necessitating the administration of ephedrine. This corrected the blood pressure to 100/64 mmHg. A further dose of ephedrine was given prior to the start of the study to restore the blood pressure to his pre-anaesthetic level. A measurement of 157/81 mmHg (MAP of 108 mmHg) was subsequently obtained.

This difficulty of maintaining a steady haemodynamic state in the absence of stimulation under general anaesthetic is a significant limitation of this study and has an impact on the baseline reading obtained. It was intended that these baseline measurements of blood pressure be obtained prior to any intervention at the beginning of the study. However, the hypotension resulting from general anaesthetic rendered it unsafe to start the study without prior intervention. The situation under general anaesthesia is clearly not an accurate reflection of the physiology in a postoperative patient on a surgical ward.

During the study period this subject's blood pressure fell in response to initiation of the local anaesthetic bolus via the epidural catheter and subsequently fell further still following the administration of the IV fluid bolus. This ongoing decrease may be attributed to the prolonged duration of the effect of the local anaesthetic. It is likely that the local

anaesthetic had not exerted its full effect by the time the post epidural readings were taken. Due to the time constraints recommended by the ethics committee it was not possible to allow a longer time period for this effect to become apparent. Despite falling further after oesophageal Doppler guided fluid therapy, this fall in MAP was corrected by administration of metaraminol.

Significant difficulties were experienced in the measurement of this subject's superior mesenteric artery blood flow. Whilst baseline readings of diameter and Peak Systolic Velocity (PSV) were obtained, a poor trace rendered an accurate End Diastolic Velocity (EDV) reading impossible. Following the administration of the bolus of local anaesthetic via the epidural catheter it was not possible to reproduce an accurate Doppler ultrasound reading of the SMA. These technical difficulties persisted after the administration of a fluid bolus and of metaraminol. The decision was taken to abandon these attempts as the time limit of 30 minutes had been reached. Intervention in terms of fluid bolus and metaraminol was deemed necessary to safely correct the subject's physiology. No conclusions can therefore be made as to the effects of this participant's hypotension on splanchnic flow.

The subject's Computed Tomography (CT) scan was subsequently examined and the technical difficulties in measurement were attributed to abnormal anatomy. The superior mesenteric artery and celiac axis were in very close proximity to one another. This made vessel identification and measurement difficult as the Doppler signals merged. The decision was made to review each participant's preoperative CT scan prior to conducting the study to delineate the anatomy.

Table 7 - Subject SMA2

Measurement (time in minutes)	BP	MAP	Oesophageal Doppler			SMA flow				
			CO	SV	FTc	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline (0)	103/60	74	3.6	50	240	0.83	4101	1072 938	82680.1	100
Post Bolus via epidural (7)	85/52	64	3.8	54	277	0.76	514	116	8467.47	10.24
Post Fluid resuscitation (9)	95/56	71	5.5	82	310	0.75	932	178	14750.75	17.84
Post Metaraminol (13)	112/68	84	4.8	70	303	0.85	1237 995	202	22648.65	27.39

4.4.4 Subject SMA2

Subject 2 was a 68 year old man, due to undergo a laparoscopic-assisted anterior resection of rectum for colorectal malignancy. He was on hormone therapy for previous prostate cancer and suffered from hypertension and hypercholesterolaemia. His medications included simvastatin, doxazosin, bendroflumethiazide and bisoprolol. A thoracic epidural was inserted at level T10-11 in the usual fashion.

This gentleman's preoperative blood pressure was 149/82mmHg with a pulse of 52bpm. As with the previous patient this individual's blood pressure also fell following induction of general anaesthesia; in this individual's case to 98/56 mmHg (MAP 68 mmHg) and heart rate of 58 bpm. This rose slightly to 110/50 mmHg (MAP 80mmHg) during epidural insertion, however his heart rate fell to 40 bpm, followed by a further fall in blood pressure to 52/42 mmHg and fall in heart rate to 33 bpm whilst in the anaesthetic room. He received 0.6 mg of atropine, 30 mg of ephedrine and 0.5 mg of metaraminol to correct the hypotension and bradycardia. His blood pressure improved to 140/82 mmHg (MAP 105 mmHg) and his heart rate improved to 70 bpm as a result, but fell again prior to the baseline readings detailed in Table 7.

The oesophageal Doppler readings obtained for this subject were extremely variable dependent on the probe's position. Their accuracy must therefore be called into question. Measurements of splanchnic flow were straightforward in this patient. The vessels were easily seen with a strong Doppler signal. However, the initial measurements of PSV and EDV appear abnormally high as compared to the other subjects. These were repeated but found to be unchanged.

This patient's physiology altered according to the hypothesis, with a fall in arterial blood pressure and MAP following the bolus of local anaesthetic via the epidural, a partial correction in MAP with intravenous fluid bolus but requiring metaraminol to restore MAP to baseline. A fall in SMA flow was observed. This was partially corrected

following the administration of intravenous fluid and improved further with metaraminol. The final measurement of SMA flow obtained had not returned to baseline. However, it should be noted that the baseline readings obtained for this subject were particularly high and may not be reliable.

Table 8 - Subject SMA3

Measurement (time in minutes)	BP	MAP	Oesophageal Doppler			SMA flow				
			CO	SV	FTc	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline (0)	113/72	85	3.2	39	233	0.640	105	15.8	1165.84	100
Post Bolus via epidural (20)	94/57	72	3.3	43	254	0.640	90.1	4.4	912.02	78.23
Post Fluid resuscitation (NA*)	-	-	-	-	-	-	-	-		
Post Metaraminol (28)	121/70	90	3.0	42	317	0.641	92.8	22.5	1116.24	95.75

*Fluid resuscitation not administered as no fall in cardiac output therefore inappropriate.

4.4.5 Subject SMA3

Subject SMA3 was a 47 year old lady. She took no regular medications and was a current smoker of 40 cigarettes per day. Her observations taken prior to theatre on the ward were normal, with an arterial blood pressure of 120/72mmHg and heart rate of 85bpm. She had a high body mass index (BMI) which made her SMA difficult to assess with Doppler ultrasound. The oesophageal Doppler was also positional. A thoracic epidural catheter was inserted at level T10/11 under general anaesthetic. Unlike previous participants she did not experience significant hypotension under general anaesthesia, indeed her blood pressure rose to 165/106 mmHg under general anaesthesia during epidural insertion. Likewise in the study she did not experience a significant drop in MAP due to the bolus of local anaesthetic given via the epidural catheter. A period of 20 minutes was allocated to allow for her MAP to fall but it was not possible to extend this time period further owing to the time constraints advised by the ethics committee. Her cardiac output also remained unchanged. Consequently she did not receive goal directed intravenous fluid therapy during the study. This lack of response led to a query over whether her epidural was working. This subject was therefore assessed postoperatively on the ward. Her epidural was working well and her pain was well controlled. The lack of effect on blood pressure and cardiac output cannot therefore be explained by a technical failure but must indicate this individual's physiological response to her thoracic epidural. It is of note that she did not become significantly hypotensive in response to the induction of general anaesthetic. Indeed, her blood pressure in the anaesthetic room was 165/106 mmHg whilst the epidural was inserted (under general anaesthesia), falling to 107/65 mmHg prior to the start of the study. She was also comparatively younger than the other subjects, aged 47, with no cardiac history or medication.

Her SMA flow fell slightly after the administration of local anaesthetic via the epidural catheter and was restored to 95.75 % of baseline by

the administration of metaraminol. It is not possible to comment on the effect of intravenous fluids on splanchnic flow in this subject as this was not indicated.

Table 9 - Subject SMA4

Measurement (time in minutes)	BP	MAP	Vigileo		SMA flow				
			CO	SVV	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline (0)	155/68	100	4.0	12	0.58	150.0	21.3	1357.76	100
Post Bolus via epidural (18)	101/52	69	3.8	8	0.69	192.5	36.1	2564.40	188.87
Post Fluid resuscitation (22)	101/40	68	4.0	7	0.61	240	53.6	2574.12	189.59
Post Metaraminol (28)	160/72	101	4.9	5	0.62	155.1	32.0	1694.60	124.81

4.4.6 Subject SMA4

Subject SMA4 was a 70 year old man with no significant medical history apart from rectal carcinoma for which he was due to undergo an abdomino-perineal resection. He took no medications. An epidural catheter was inserted at level T10-T11 with the patient awake and in the seated position. His pre epidural blood pressure was 159/95 mmHg (MAP 126 mmHg) heart rate 71bpm. On induction of general anaesthesia his blood pressure fell to 70/40mm Hg with a heart rate of 40bpm. Ephedrine 30mg was given which improved his pulse and his blood pressure to 116/64 mmHg (MAP 83 mmHg) and heart rate 51bpm. The oesophageal Doppler signal obtained for this subject was poor and consequently the anaesthetic team employed a Vigileo monitor which analysed the arterial trace from the waveform. Due to a change in the anaesthetic department policy, Volulyte was no longer available and a bolus of Hartmann's solution was given intravenously instead. Results are shown in the table above. Once again the bolus of bupivacaine given via the epidural mediated a fall in blood pressure, notably MAP, associated with a slight fall in cardiac output. However, SMA flow did not fall but increased in response to the epidural bolus and intravenous fluid, returning to baseline after the administration of 2 doses of 0.5mg of metaraminol to restore MAP to baseline. Although this subject's mean arterial pressure behaved as expected, the SMA flow did not. This was at odds with the hypothesised outcome.

Following these four subjects results the decision was taken in conjunction with the anaesthetic team to amend the protocol. As a number of the subjects had required treatment with different vasopressors for hypotension associated with their general anaesthesia it was decided to standardise this by using an infusion of phenylephrine (0.1mg/ml) which could be manipulated throughout the study and the total dosage quantified. The bolus of metaraminol administered in during the final stage of the study protocol would be replaced with an increased rate of the phenylephrine infusion. This technique has also

been employed in a recently published study investigating epidural mediated hypotension (124). Cardiac output was measured with Vigileo monitoring which was felt to be more accurate than the oesophageal Doppler. In order to minimise error in the SMA flow Doppler measurements three readings of PSV and EDV were obtained at each of the time points for both of these individuals.

4.4.7 Subject SMA5

Subject SMA5 was a 69 year old gentleman who was due to undergo an APER for malignancy. He was hypertensive and was taking ramipril, amlodipine and indomethacin. A thoracic epidural was inserted at level T10-11 prior to induction of general anaesthesia. Unlike previous subjects he had a phenylephrine infusion in situ to help control for hypotension. It is therefore not possible to discuss individual drops in blood pressure as this was titrated to maintain a steady state. He received 6.45 ml of phenylephrine in the time period prior to the baseline readings. He required continuation of this infusion to maintain his blood pressure so this was running at a low rate throughout. He received 12.3mls from the time of his baseline reading until just prior to his bolus. He required a bolus dose of 12.6 ml. The total dose of phenylephrine over the course of the study was 18.45ml. His results are seen in table SMA5.

Table 10 - Subject SMA5

Measurement (time in minutes)	BP	MAP	Vigileo		SMA flow				
			CO	SVV	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline (0)9.38	99/66	77	4.0	5	0.61	151.9 145.1 137.6	57.1 54.9 54.9	1757.86	100
Post Bolus via epidural (4) 9.42	81/53	67	3.0	4	0.72	116.6 109.8 103.0	30.1 33.1 32.3	1729.98	98.41
Post Fluid resuscitation (8)9.46	78/53	62	3.1	6	0.64	94.7 90.2 88.7	28.6 27.8 30.8	1160.69	66.03
Post phenylephrine bolus (200ml/hr) (11)9.49	103/70	84	4.1	5	0.68	85.0 86.5 86.5	35.3 35.8 34.6	1320.84	75.14

Following the bolus of local anaesthetic down the epidural catheter there was a marked change in the EDV, and PSV and the SMA diameter, however these balanced out and SMA flow remained constant. As this gentleman was usually hypertensive the next stage of the study was commenced i.e. fluid when a MAP of 67 was reached, however, this did not correct the hypotension, indeed this worsened and was associated with a fall in splanchnic flow. It was not possible to restore cardiac output without the use of vasopressors despite continuous infusion of these throughout. More worryingly, when a bolus was given with the resultant effect of restoring cardiac output to baseline levels this only restored the SMA flow to 75% of baseline.

4.4.8 Subject SMA6

Subject SMA6 was a 59 year old gentleman due to undergo an abdomino-perineal resection of rectum for malignancy. His only other medical history was asthma for which he took but took inhaled, as required medication. He had taken inhaled salbutamol immediately prior to anaesthesia on the direction of the anaesthetist. He underwent insertion of thoracic epidural at level T10-11 under general anaesthesia. Again a phenylephrine infusion was commenced and he required 18.6 ml of this to achieve a steady state prior to the start of the study. As his blood pressure had then stabilised this was discontinued during the study until he received the bolus dose. He required a bolus of 15.7 ml to return his blood pressure to baseline levels. His results are shown in the table SMA6 below.

Table 11 - Subject SMA6

Measurement (time in minutes)	BP	MAP	Vigileo		SMA flow				
			CO	SVV	D cm	PSV cm/s	EDV cm/s	Flow mm/min	%
Baseline 0	119/68	87	4.3	6	0.50	122.7 131.0 136.0	44.5 44.5 45.7	1029.66	100
Post Bolus via epidural 4	83/50	63	3.6	9	0.49	149.2 151.4 143.2	39.7 38.5 38.5	1056.96	102.65
Post Fluid resuscitation 8	73/43	55	3.8	9	0.54	172.0 176.9 178.1	38.5 39.7 40.9	1479.71	143.71
Post phenylephrine bolus (200ml/hr) 11	121/68	87	4.2	9	0.51	142.0 148.0 148.0	38.5 37.3 38.5	1128.25	109.58

This gentleman was the second subject in the SMA flow study to exhibit an increase in PSV in response to the epidural. His SMA flow increased marginally in response to the bolus of the local anaesthetic down the epidural catheter but increased still further in response to the fluid challenge. This was seen despite the fact that he became markedly hypotensive in response to the epidural bolus and became even more so following the intravenous fluid challenge. The reasons for this are unclear.

Patient demographics have been analysed to see if there are any associations between these and the results obtained.

Table 12 - Patient demographics

Subject	Age	Sex	Epidural level	Medications	Hypotension	Splanchnic Flow
IMA1	76	F	T11-12	Bendroflumethiazide, Valsartan, Moxonidine	Yes	Decrease then not measureable
IMA2	63	F	T10-11	Nil	Yes	Decreased
SMA1	67	M	T10-11	Aspirin, Hydroxycarbamide	Yes	NA
SMA2	68	M	T10-11	Simvastatin, Doxazosin, Bendroflumethiazide, Bisoprolol	Yes	Decreased
SMA3	47	F	T10-11	Nil	No	Slight decrease
SMA4	70	M	T10-11	Nil	Yes	Increase
SMA5	69	M	T10-11	Ramipril, Amlodipine, Indomethacin	Yes	Decreased
SMA6	59	M	T10-11	Salbutamol, Seretide	Yes	Increased

4.5 Discussion

These studies have enabled the development and fine tuning of the technique of splanchnic flow measurement. The study protocol has been modified accordingly. However, significant problems were encountered with the physiological impact of general anaesthesia for the majority of these patients. Due to a number of factors meaningful discussion of the results obtained is difficult. Results were converted to percentages to better allow for comparison of trends between individual subjects and to control for intra observer error.

The two sets of results for the IMA flow study both demonstrated a decrease in flow, consistent with the hypothesis. Technical difficulties were experienced with the final IMA flow subject, such that no readings could be obtained at all. Analysis of the trends for the initial four SMA flow subjects did not provide a clear pattern in terms of their splanchnic blood flow. Indeed, each patient appeared to have a different physiological response. The first patient's results cannot be used as no readings were obtainable following epidural bolus, the second showed trends consistent with the hypothesis; a fall in splanchnic blood flow following epidural bolus, not corrected by fluids, indeed it fell further, which was restored by the administration of metaraminol. The third patient exhibited a small decrease in SMA flow in response to the epidural and the fourth patient’s response was unexpected with a rise in flow in response to the epidural which returned to baseline with metaraminol. Rather than clarify the situation, the results obtained from the following two subjects; SMA5 and SMA6, strengthen the evidence for different responses between individuals. Subject SMA5’s results were in line with the hypothesis, similar to subject SMA2. However, the results from subject SMA6 were not. He became hypotensive in response to the epidural bolus, which did not correct with intravenous fluids. This hypotension was not accompanied by a decrease in SMA flow, as hypothesized, but instead by an increase in flow. This was most marked after the fluid bolus. The mechanism for this is unclear.

As subject SMA6 had taken 200 micrograms of inhaled salbutamol just prior to induction of general anaesthesia, the potential influence of this on splanchnic blood flow should be considered. There is evidence in the literature that of cardiovascular effects at both supra therapeutic doses. Inhalation of 200 micrograms of salbutamol has been shown to have a significant effect on cardiac output and systemic vascular resistance in healthy individuals. His physiology may therefore differ from the other trial subjects. However, the other individual in whom flow increased was not asthmatic and had not taken any similar medication so this does not adequately explain the phenomenon. Three out of the five individuals who experienced a decrease in splanchnic blood flow following the epidural bolus were on antihypertensive medications. This in itself does not account for the decrease but it should be noted that both of the subjects in whom an increase in splanchnic flow was seen were not taking antihypertensive medications. Further data from future subjects are required to confirm this trend.

It is of note that the patient who did not require treatment for hypotension prior to induction also did not experience any significant hypotension as a result of the bolus of local anaesthetic via the epidural catheter. This suggests that some individuals may be more susceptible to such changes in blood pressure than others, whether from the results of general anaesthesia or from epidurals. Indeed, a recent paper by *Frey et al*[125] found that the β2 adrenergic receptor Glu 27 allele was an independent predictor of arterial hypotension and vasopressor requirements after TEA. A shorter time to critical hypotension was noted in this group after TEA both in the presence and absence of general anaesthesia.

4.5.1 Doppler Ultrasound Measurement of Splanchnic Blood Flow

The use of transcutaneous Doppler ultrasound to measure splanchnic blood flow in humans is well established. This technique was developed

and attempted in 1982 and subsequently evaluated further in a study by Qamar et al in1986[126]. The authors used transcutaneous Doppler ultrasound to measure Superior Mesenteric Artery Blood Flow (SMABF) in 21 healthy volunteers and evaluated the inter subject variability in flow measurements over the short (1hour) and long (3 weeks) term. The authors calculated the mean value of SMABF as being 517ml/min and found a mean variability of 6.8% in the short term and 8.2% in the long term in healthy volunteers. Whilst the variability is small, this would indicate that small changes in SMABF cannot be reliably attributed to any clinical effect. The authors also discussed the limitations of the technique which related to the ease of location of the vessel, the angulation of the vessel in relation to the Doppler ultrasound beam (also known as the angle of insonation) and the ease of measuring the lumen area and average velocity within the vessel. Despite these limitations Qamar et al concluded that this was a reliable technique for measuring SMA flow[126]. The same authors previously reported changes in SMABF in response to glucose but not lactulose ingestion using this technique[127].

A similar study investigating the effects of enteral and parenteral nutrition on SMABF has previously been performed in this authors institution[128]. In this study SMA flow was measured pre and post prandially on awake subjects using transcutaneous Doppler ultrasound. SMA flow measurements were performed using a multi frequency 2.5 MHz probe with real time analysis on an HDI 5000 Ultrasound system (ATL Ultrasound, Bothwell MO). During each flow measurement 3 time – velocity waveform readings and 3 cross sectional area measurements were obtained. Time velocity waveform readings measured the peak systolic velocity (PSV), mean diastolic velocity (MDV) and the time average mean velocity which was calculated by the ultrasound machine's software. This represented the mean blood flow velocity for the duration of the waveform. Cross sectional are measurements were extrapolated from the vessel diameter as measured with B mode USS in

transverse plane. All measurements were made by single radiologist in order to reduce bias.

This author's technique for SMA flow measurement was modelled on this previous study. Again a single radiologist was selected to perform all measurements in order to reduce bias. In a study published in 1996 Iwao et al found the intra observer coefficient of variation in the measurement of transcutaneous SMABF to be 9%, whereas the inter observer coefficient of variation for this technique was 18%[129]. This larger variation between different observers is the reason that the use of a single observer is mandatory. Nonetheless, variability of 10% in measurements is often expected, dictating that changes must be much greater than this to be considered significant

The equipment used in this author's study differed from the previous study by Gatt et al published in 2009[128]. In the study reported in this chapter the Doppler ultrasound machine needed to be used in the operating theatre, it was also of clinical importance that the same machine be used for all measurements. This dictated selection of a machine which was both appropriate for this purpose and consistently available. The machine used in 2009 was no longer available at the time of this author's SMA flow study. In the study by Gatt et al[128] the time averaged mean velocity measurements were also calculated by their ultrasound machine's software, once again this was unavailable at the time of this authors study. To compensate for this the primary researcher consulted with the radiologist who had previously performed the readings in the 2009 study and attended a vascular ultrasound course (Axiom ultrasound at Imperial College London). The selected methods for the calculation of SMA and IMA flow were extensively discussed with those running the course and the resident radiologists who were skilled in measuring blood flow.

Development of the IMA flow aspect of this study was based on the previous work by Gould et al[61]. The study protocol for this was designed to duplicate their findings regarding the changes in flow in response to

epidural anaesthesia, goal directed intravenous fluid therapy and vasopressors. They used a cuffed Doppler probe (Op Dop – Scimed) again no longer available at the time of this study. After discussion with Radiological and Vascular colleagues it was decided that the Vascular 'hockey stick' transducer should be used for the IMA flow measurement once the vessel had been exposed.

Figure 3 - Image of HST transducer

Reproduced with permission of United Medical Instruments, Inc.[130]

4.5.2 Limitations

Limitations surrounding the difficulties in obtaining a signal are a known issue in Doppler ultrasound measurements of blood flow. Such difficulties were present in both the SMA and IMA flow studies. These may be broadly divided into difficulties obtaining a Doppler signal and potential inaccuracies of any signal obtained. Barriers to obtaining measurements of splanchnic blood flow which were encountered in these studies were abnormal patient anatomy, poor Doppler signal due to overlying bowel gas or high body mass index and in one case a technical problem was encountered with the Doppler ultrasound machine. In subject SMA1, an anatomical variant precluded measurements of SMA flow due to merging of signals from the SMA and coeliac axis. In one subject (IMA1), no signal could be obtained at only one point in the study protocol and this was associated with a low MAP.

It is unclear whether this could be attributable to a decrease in flow, given that measurement became possible once the MAP had risen once again.

A significant number of limitations have been identified for this study, contributing to its overall failure. Whilst difficulties in obtaining Doppler signal due to overlying bowel gas or patient anatomy may be unavoidable, many of the significant weaknesses identified pertain to the lack of adequate planning, failure to conduct pilot or validation studies and failure to anticipate the problems experienced in obtaining a physiological steady state following the induction of anaesthesia, which have completely invalidated any subsequent interventions or readings. In hindsight a pilot study would have identified many of these issues and would have allowed modification of the protocol to correct for these.

This is particularly relevant with respect to the IMA flow study. A pilot study or trial of this technique would have quickly demonstrated the extreme technical difficulties involved. As the vascular probe used was not circumferential such as the one employed in the study by Gould et al a single person technique was extremely difficult to perform. This was due in part to the risk of causing unacceptable contamination to the patient, as whilst the transducer could be placed in a sterile cover the machine itself could not. With a cuffed Doppler the probe would have been fixed in place, permitting a single person technique and minimising human error. With the two person technique employed, significant coordination was required between the individual holding the probe and the one operating the Doppler ultrasound machine. Whilst the same team were present for all IMA flow cases, this need for coordination between the two operators is likely to have significantly affected the validity of the measurements. Although the transducer's hockey stick design maintained a constant angle to the vessel, the exact position of the along the vessel had to be marked manually throughout the 30 minute study period. The depth of the vessel inside

the abdomen and the minimal access techniques with small incisions also made the manoeuvrability of the probe somewhat difficult for the operator.

This is of clinical relevance owing to the nature of the technique of Doppler ultrasound. The technique utilises the Doppler effect; this is the change in frequency of a wave for an observer moving relative to the source of a wave. The received frequency is higher on approach, identical at the point of passing by and lower during recession. Doppler ultrasound uses this effect by transmitting and receiving the ultrasound signal to calculate velocity. Interpretation of the result is dependent on Cos θ (Cosine of the angle between ultrasound beam and flow direction), known as the angle of insonation. The percentage error in velocity measurement is dependent on this angle of insonation and increases exponentially when Cos θ is greater than 60 degrees. Any results obtained may vary depending on the probe position, angle of insonation and the individual performing the technique.

The conduction of a validation study would have demonstrated whether or not this was a sufficiently reliable method of measurement. Due to the limitations described above, it is highly likely that this is not the case. Without such a study it can only be postulated that this technique lacks validity and hence results obtained may not be interpreted with any reliability. Had this technique been shown to lack validity, efforts to secure funding for a cuffed Doppler could have been made.

Whilst the technique of SMA flow measurement had previously been performed in the author's institution, specific validation studies were not performed. This was attributable in part to the time constraints imposed by the local REC allowing 30 minutes. Although the technique has been well validated over a long period of time this lack of any validation study has significantly damaged the reliability of any data obtained. The availability of rates of intra observer variability would have facilitated the interpretation of the data, permitting analysis as to what percentage

change in blood flow would be likely to have significance and could be reasonably attributed to an actual change in the patient's physiology. In addition to the lack of validation studies to evaluate intra observer variability, this study lacked continued readings over a steady state to observe any physiological fluctuations in flow not due to the interventions given. This would have allowed the calculation of variability coefficients over time. It is unfortunate that these were not built into the study design, weakening the value of the results obtained. This was contemplated but felt that it would not be ethically permitted under general anaesthesia and there was insufficient time to do so. In hindsight the extent to which this study is weakened by the lack of such validation and steady state observation has been so significant that it any results observed are not reliable and are not open to any meaningful interpretation.

Failure to anticipate the magnitude of the effects of the induction of general anaesthesia on the physiology of each subject has significantly weakened this study. Significant problems were encountered with the physiological impact of the induction of general anaesthesia for the majority of these patients. Five of the six initial participants studied (SMA1,SMA2, SMA4, IMA1 and IMA2) required treatment for hypotension following induction of general anaesthesia, prior to the start of the study. It is of interest that this profound effect was not reported by Gould et al in their study on IMA flow. Again a pilot study would have identified this issue and facilitated the fine tuning of technique developed in this study. The use of different vasopressors in this study, further impacts upon the validity of the results obtained. The modification of the protocol by standardising the vasopressor therapy used will minimise but not obviate this issue. The use of an infusion of 0.1mg/ml phenylepherine, titrated to control the blood pressure after induction of general anaesthesia with documentation of total volumes infused overall and at the start and end of the study has been adopted. This offered a more scientific way to quantify vasopressor requirements

for each individual whilst still allowing for a bolus of vasopressor at the appropriate time points.

The modification of the study protocol to include 3 separate measurements of vessel diameter and flow strengthened the results, however this occurred during the study, rather than being specified at the beginning. The previous study conducted in the author's institution employed software to obtain these readings. Initially the time constraint and lack of familiarity with the technique made three sets of manual observations at each time point difficult to obtain, however as the study progressed this became easier. Once again the fact that these were not done from the start weakened this study. This could have been avoided by a pilot study to evaluate the technique.

This investigation into the effects of thoracic epidurals on splanchnic blood flow could be improved in a number of ways. As previously discussed, the conduction of pilot studies for each of the techniques would have identified the issues encountered in the conduction of this study. In effect these studies have served as a pilot study as they have led to the discontinuation of the technique for measuring IMA flow and modification of the technique for the measurement of SMA flow and a standardised anaesthetic technique to combat the physiological effects of general anaesthesia. What is lacking at present and would serve to strengthen the SMA flow studies would be a validation study to assess the intra observer variability and the variability coefficients over time. Such data would facilitate a more meaningful interpretation of the data and make the study more robust.

Further changes which could improve this study would be the use of bespoke software to obtain and process splanchnic flow measurements and the availability of more advanced technology such as the use of a cuffed Doppler flowometer. Another factor which might improve the study would be an extension of the time limit set by the REC. There were concerns that the full magnitude of the effect of the epidural bolus

had not been seen by the time that the goal directed fluid therapy was given. However, this was not deemed to be appropriate due to the extension of time under general anaesthesia, perceived as risky by both patients and the ethics committee.

The single greatest confounding factor identified in these studies was the effect of general anaesthesia on the patient's physiology. Whilst steps have been taken to combat this they do not alter the fact that this is an artificial situation which cannot be satisfactorily related to the postoperative situation on a surgical ward. In an ideal situation, splanchnic blood flow in the postoperative patient with an epidural would be measured to investigate the effects of hypotension and the way in which this is managed. This is clearly not feasible for a number of reasons, including difficulty with imaging vessels in the postoperative setting and the ethical considerations of subjecting a postoperative patient with an anastomosis to hypotension.

At the time of study design it was not considered feasible to perform this investigation on conscious patients in the anaesthetic room. This was largely due to the use of oesophageal Doppler measurement of cardiac output which is invasive and unpleasant and consequently not performed in conscious patients. During the course of the study a significant development was made. This was the use of the Vigileo which calculated the cardiac output from the waveform obtained from the arterial line. Arterial lines are commonly used in non anaesthetised patients in an intensive care setting. The availability of this alternative technique for the measurement of cardiac output obviates the need for this study to be performed under general anaesthesia. Whilst an investigation into IMA flow would likely not be achievable, SMA flow has been successfully managed in awake patients.

A future study where the effects of thoracic epidural anaesthesia could be studied in preoperative patients in the anaesthetic room would provide a much more scientific means of measuring the effects of epidural bolus, goal directed fluid therapy and vasopressor on SMA flow.

Thoracic epidurals are frequently inserted while patients are awake. Baseline readings of SMA flow could be obtained following the insertion of the thoracic epidural but prior to the administration of the local anaesthetic bolus. A further reading could be obtained following the epidural bolus and indeed if continuous monitoring were available the effects of the bolus on both Blood Pressure, cardiac output and and SMA flow could be monitored. The blood pressure would then be allowed to fall until it reached a predetermined MAP, something not always possible in the conducted study due to time constraints. Further measurements would be taken and goal directed fluid therapy administered, whilst monitoring the effects on SMA flow. Once the patient had been adequately filled a vasopressor would be administered if required and the effects of this on SMA flow further evaluated. This study would not be limited by the effects of general anaesthesia. The lack of general anaesthesia would also be likely to remove the requirement for the time limit imposed by the ethics committee, which would facilitate the conduction of validation studies and allow measurement of variability coefficients over time, making the study more robust. Results obtained should therefore offer greater reliability as well as being more applicable to the postoperative patient's physiology and should grant a more meaningful insight into the effects of thoracic epidurals on splanchnic blood flow.

4.6 Conclusion

The data obtained from these studies does not yield any firm conclusion regarding the effect of thoracic epidurals on splanchnic blood flow. It would appear that the effect of thoracic epidurals on SMA flow is not standards, but varies between individuals. This may differ from the effect on IMA flow but these studies have insufficient power to prove this. The recent publication by Frey *et al* has found a significant genetic component in the occurrence of epidural mediated hypotension. This may also have an impact upon the effects of thoracic epidurals on splanchnic blood flow.

Both of these studies were limited by the physiological changes brought about by the induction of general anaesthesia and the requirement for pharmacological intervention to treat the resultant hypotension. This has led to development and fine tuning of the research technique. The study design is not representative of the postoperative situation on the ward, due to the confounding effects of general anaesthesia. However, there are many potential limitations to the measurement of splanchnic blood flow in the postoperative setting. Surrogate measures of flow would be required, and some of these techniques, such as trans-abdominal Doppler measurement might be difficult to perform in the Postoperative setting. There are also ethical considerations regarding the manipulation of thoracic epidurals in patients with postoperative pain. Further observational studies are required to clarify any effect of TEA on both SMA and IMA flow. Avenues for future research could include the use of a cuffed Doppler for the measurement of IMA flow, to lend greater accuracy to this technique. The replication of this SMA flow study in awake, preoperative awake patients would also be of value as this would remove the confounding element of general anaesthetic.

Chapter 5 - Continuous Wound Infiltration with Local Anaesthetic *vs.* Epidurals in an Enhanced Recovery Protocol: A Randomised Controlled Trial

5.1 Introduction

Despite advances in surgical and anaesthetic techniques, major surgery is still associated with undesirable side effects such as pain, cardiopulmonary and infective complications and prolonged ileus. Enhanced Recovery after Surgery (ERAS) protocols comprise simple measures such as shortened preoperative fasting along with carbohydrate loading, use of transverse incisions wherever possible, use of epidural analgesia and avoidance of opiate based analgesics[5,6,131-133]. Good evidence now exists to show that significant reductions of hospital stay can be achieved without compromising patient safety. Clearly this has important implications not only for patient well-being but also to health care resources[41].

Epidural analgesia has been utilised in most ERAS protocols as it provides excellent pain relief and may attenuate the surgical stress response[4,52]. It employs a fine bore catheter which is placed into the lower thoracic epidural space (outer covering of the spinal cord) and through which a combination of local anaesthetic and a short acting opiate is infused. This provides 'regional analgesia' by blocking the spinal nerves which supply the abdominal wall and lower limbs[4,52]. However, epidural analgesia has a number of disadvantages. In addition to blocking the pain transmitting afferents, epidurals also block the sympathetic efferents which can result in hypotension intractable to intravenous fluids, often necessitating inotropic support on the High Dependency Unit (HDU)[61,71,121]. The placement of epidural catheters requires a considerable amount of time and despite this they carry a significant failure rate[51,134,135]. In addition, their placement is

contraindicated within 12 hours of thromboprophylaxis with low molecular weight heparin. Lastly, epidural catheters can impair sensation in the lower limbs, and this, combined with the cumbersome equipment they require, can render Postoperative mobilisation difficult. Major complications associated with the placement of epidural catheters include epidural abscess, meningitis and epidural haematoma[136]. Whilst these are rare they carry significant morbidity for those individuals affected.

Many of the trials of epidural anaesthesia compare them to patient controlled analgesia with parenteral opioids (PCA). Epidurals have been found to provide superior postoperative pain control than PCA following laparoscopic colorectal surgery, although no difference was seen in length of stay[71]. They have been shown to provide superior pain relief and higher levels of patient satisfaction in major open thoraco-abdominal surgery when compared with PCA[137]. In a study of patients undergoing laparoscopic colorectal resection in a non fast track program Taqi *et al* found them to be superior to PCA as regards swifter return of gut function and superior pain control[48]. Many of the beneficial effects of epidurals are thought to be due to their superior pain control and the avoidance of opiates.

However, advances in the field of minimally invasive surgery have called into question the necessity of epidural anaesthesia for such procedures. Levy *et al* conducted a trial comparing epidurals with PCA and Spinal anaesthesia in patients undergoing laparoscopic colorectal surgery. They concluded that many outcomes in the epidural group were inferior to spinal and PCA including length of stay and return of gut function, suggesting that either may replace epidurals in the context of an enhanced recovery programme[76].

A relatively new modality for the provision of postoperative analgesia after major abdominal surgery is the continuous infusion of local anaesthetic directly into the wound. This is done using a purpose built

multi-holed catheter (PainBuster®) which is placed into the wound by the surgeon at the end of the operation. This provides selective local analgesia and avoids the disadvantages associated with epidural catheters. Local anaesthetic wound catheters have been successfully used in a variety of surgical procedures[91,92,94,97,138]. A systematic review and meta-analysis of local anaesthetic wound infusion in colorectal surgery found a significant reduction in visual analogue scores for pain on the 1st 2nd and 3rd postoperative day which was associated with a reduction in total opioid consumption[90]. The trials included in this meta-analysis compared local anaesthetic would infiltration with placebo. Local anaesthetic wound infiltration has been shown to reduce morphine requirements in patients undergoing laparotomy via transverse left iliac fossa incisions when compared with PCA[92]. Retrospective case controlled studies have suggested that local anaesthetic wound infiltration might be of benefit when used in place of thoracic epidurals for patients undergoing abdominal surgery. Parsons et al retrospectively compared thoracic epidurals with rectus sheath catheters for patients undergoing radical cystectomy[98]. The authors reported similar outcomes in terms of postoperative pain and analgesic requirements and noted a non significant reduction in LOS. This study was of interest despite not being a randomised controlled trial as most of the existing data for wound infiltration was in comparison with morphine PCA. The authors commented on several potential advantages of rectus sheath catheters including earlier mobilisation and reduced burden on nursing and medical staff[98].

The use of local anaesthetic wound infiltration instead of epidural analgesia within an ERAS programme, now thought of as routine care, should provide a number of potential advantages. Unlike thoracic epidurals wound infiltration has no systemic autonomic effects, the requirement of postoperative intravenous fluid administered to manage hypotension should reduce. The absence of such autonomic side effects and the portability of the device should also facilitate early removal of urinary catheters, reduce nursing needs, improve mobilisation and

reduce intravenous fluid associated complications such as fluid overload and electrolyte imbalance. Cumulatively, all these advantages should accelerate postoperative recovery.

At the time of study design no clinical trial comparing the use of thoracic epidurals with local anaesthetic wound catheters in colorectal surgical patients had been published. This trial was designed to fill the gap in the literature by comparing local anaesthetic wound infiltration with thoracic epidurals in colorectal surgery patients in the context of an enhanced recovery program. Subsequently a number of studies have reached publication which compare local anaesthetic wound catheters with thoracic epidurals in patients undergoing colorectal resection.

The first such study to be published was by Bertoglio et al in 2012[139]. This multicentre randomised controlled non inferiority study conducted in Italy compared thoracic epidurals with local anaesthetic wound infiltration in patients aged 18-75 undergoing elective open colorectal resections. Patients whose ASA was ≥ 3 were excluded, as were patients with stomas. Patients in the intervention group received pre-peritoneal infusion of 2% ropivicaine via wound catheters for 72 hours postoperatively, controls received epidurals. This study was powered to 108 patients in each study group, although the trial was stopped prematurely by the data monitoring committee due to the slow accrual rate. The authors reported continuous wound infiltration as non inferior to epidural despite only recruiting 50% of their calculated sample. No significant difference was seen in morphine consumption although the authors reported lower rates of postoperative nausea and vomiting and swifter return of gut function in the wound infiltration group. It should be noted that this study was done in the setting of traditional care and not an enhanced recovery program.

In February 2013 Boulind et al published the results of their feasibility study of epidurals versus continuous wound infiltration in patients undergoing laparoscopic colorectal resection[140]. This trial was conducted

in 2 UK centres in the context of an enhanced recovery program. Exclusion criteria for this study were ASA>3, locally advanced malignancy, a palpable mass, inflammatory bowel disease, patients requiring total mesorectal excision (TME) and patients under the age of 18. This study is of interest as it assessed the feasibility of a double dummy blinding technique in which patients were allocated to active epidural and sham wound infusion or sham epidural and active wound infusion. Wound infiltration was done with a pre-peritoneal wound catheter (PainBuster®). Although designed as a feasibility study outcome measures for use in future trial were tested, including assessment of pain and quality of life. Because of the nature of design no power calculation was performed. Thirty four patients were recruited to the study and the authors concluded that the technique was both safe and feasible, recommending a larger trial.

The third such study also published in 2013 by Jouve *et al* was a prospective double blind trial comparing continuous wound infiltration with epidurals in patients undergoing open colorectal resections[141]. The primary outcome measure selected was the dynamic pain score, or pain score on movement. Patients with ASA>3, a BMI >35 or a defunctioning stoma were excluded. All patients received periumbilical midline incisions. Amongst the secondary endpoints were pain at rest, return of gut function and length of stay. The authors reported that an Independent board stopped the study after significantly lower pain scores were noted in the epidural group 24 hours postoperatively whilst length of stay was reduced in this group. Mean incision lengths were around 20 cm in both groups. Although the difference in pain scores at 24 hours was statistically significant, mean pain scores in the continuous wound infiltration group were 20mm from the afternoon of the first postoperative day and were 30mm in the morning of this day. A pain score of this magnitude, equating to 2/10 is often termed mild and may be deemed clinically acceptable. The clinical relevance of this effect is therefore unclear. Mean pain scores for the epidural group were 0, implying full epidural blockade throughout these 3 days.

The results of the above trials have been mixed, in open surgery non inferiority of wound infiltration has been claimed in one study in terms of analgesic effect[139] whilst in another epidurals were found to be superior[141]. Both of these studies employed midline incisions. No significant conclusion regarding the superiority or otherwise of wound infiltration can be extrapolated from the study in laparoscopic surgery as this was a feasibility study and not powered to a particular endpoint. Not all of the studies were conducted in the context of multimodal optimisation.

The strict criteria of these trials, for example only laparoscopic or only open incisions with no stomas simply do not reflect the majority of patients undergoing surgery. The need for a defunctioning stoma is not always clear preoperatively and therefore it is not reasonable for postoperative analgesia to be based on whether or not this is present. The distinction between laparoscopic and open surgery within an enhanced recovery program is also not clear cut, indeed in one well conducted double blind study no difference in outcome has been found between the two[22]. Laparoscopic procedures may be converted to open or laparoscopically assisted procedures may be planned. Open operations may be performed with smaller transverse incisions which are associated with less postoperative pain[28,142]. Although plans can be made for a laparoscopic resection or stoma, often this is something determined by the findings at the time of operation by which time the method of postoperative analgesia has often been determined.

This randomised controlled trial has been designed to evaluate the role of wound catheters in colorectal surgery in the context of an enhanced recovery program. It is important to the current body of literature as it evaluates the use of wound catheters in a much more generic fashion than the other studies, not focussing purely on analgesic effect but on overall recovery as determined by length of stay. This study included all patients undergoing colorectal resection within an enhanced recovery program who were deemed suitable for epidural or wound infiltration.

The pragmatic nature of this study makes it more relevant and applicable to routine practice, rather than to a single sub group of patients. Whilst it may be argued that this approach may make the study less specific or scientific, it has the advantage of being more realistic, reflecting the normal practice in a colorectal surgical unit and therefore has greater relevance than the other studies which involved either exclusively laparoscopic resections or open surgery with no stomas and large midline incisions[139-141].

5.2 Hypothesis

The hypothesis of this study was that continuous infusion of local anaesthetic directly into the wound (PainBuster®) would reduce the length of stay when compared to epidural analgesia in the setting of an ERAS programme.

5.3 Patients, Materials and Methods

5.3.1 Study Design

This was a randomised controlled study. As PainBuster® and epidural catheters require different apparatus, blinding was not deemed to be feasible. The use of sham epidurals was felt to expose patients to excess morbidity if catheters were inserted unnecessarily, or to be unrealistic if they were simply taped to the patients back. Safety concerns regarding the potential for confusion amongst ward staff regarding which intervention was a sham and which was real were also considered. It was also felt that the inability of clinicians managing these patients to determine whether or not the patient had an epidural or wound catheter would hamper clinical decisions such as how hypotension should be managed and when urinary catheters should be removed. For these reasons it was decided to conduct an unblended study and accept the bias that this might introduce.

To reduce this bias, pre-defined criteria were used to assess the primary outcome and all secondary outcomes. Ethical approval for the study was granted by the Sheffield Regional Ethics Committee.

5.3.2 Inclusion Criteria

In the author's institution, where full laparoscopic resection is not possible, a combination of laparoscopic and open techniques are used, using small transverse incisions to minimise surgical trauma. As large midline incisions are avoided wherever possible and enhanced recovery protocols adhered to, differences between laparoscopic and open surgery are minimised. Evidence exist to suggest that outcomes are comparable in the context of well conducted multimodal optimisation[22]. As it is impossible to always determine whether patients would receive a laparoscopic or minimally invasive open procedure, distinction between the two groups were felt to be somewhat artificial. For this reason all patients who were undergoing either laparoscopic or open colorectal resection were considered eligible for the study provided they were considered suitable for both thoracic epidural and PainBuster®.

5.3.3 Exclusion Criteria

Patients under 18 years of age and pregnant females were excluded. Patients undergoing an abdomino-perineal resection were excluded as they would require two incisions, one of which would not be covered by the PainBuster®. Patients unable to understand English were also excluded.

5.3.4 Recruitment

Patients who expressed interest in the study were approached in the pre-assessment clinic and given written and verbal information about the study (Appendix J). They were given a minimum of 24 hours to consider this prior to informed consent being obtained. Once consent

had been obtained patients were randomised by an independent research fellow to the epidural or PainBuster® arm using a computer generated randomisation sequence.

5.3.5 Intervention

Routine care in the author's institution involved the use of thoracic epidural anaesthesia. Thoracic epidurals (T9-T12) were sited in the anaesthetic room prior to the operation by the anaesthetist, using the loss of resistance to saline technique in the usual fashion. Local anaesthetic wound catheters were inserted at the end of the operation by the operating surgeon. For transverse incisions a single catheter was introduced from side of wound and placed between anterior and posterior sheath, or peritoneum if this was a lower abdominal incision. For small incisions a 6.5cm catheter was used, whilst a 12.5cm was used for longer incisions. Patients with midline incisions received dual 12.5cm catheters, tunnelled to lie beneath the rectus muscles or in transverses abdominis plane. The elastomeric pump of the PainBuster® was filled under aseptic technique with 270mls of 0.25% levobupivacaine (Chirocaine) or 2% ropivacaine depending on the Centres preference. This was infused at a rate of 4mls per hour for the dual catheters and 5 ml per hour for the single catheters. A bolus local anaesthetic was given down each catheter once the fascia was closed. This was 20ml of 0.5% Levobupivacaine for single catheters and 20ml of 0.25% Levobupivacaine down each catheter for dual catheters, giving a total of 40ml.

Following surgery participants were reviewed by a surgical research fellow on a twice daily basis and data pertaining to the study's endpoints were collected.

5.3.6 'Scarborough Optimisation package'

All patients were managed as per enhanced recovery principles with the 'Scarborough Optimization package', developed in this institute over the last decade. All patients underwent a thorough preoperative assessment by a pre-assessment nurse and a research fellow and received written information about their care and the type of operation they were to undergo. Opiate based analgesia was avoided in both groups and reserved only for breakthrough pain but regular non opiate analgesia was administered routinely. Patients underwent preoperative carbohydrate loading. Patients were allowed clear fluids until three hours before their operation. The night before surgery patients received a 200ml "Polycal" feed at 10 p.m. Another 200ml "Polycal" liquid feed was given three hours prior to the scheduled operation. This been shown to reduce postoperative insulin resistance, which is common after surgery and may be associated with a prolonged hospital stay.

All patients received 80% inspired oxygen during the anaesthetic and oxygen administration was continued until the patient mobilised. Oxygen was administered via mask or nasal cannula at 2 litres per minute overnight. Transverse incisions were used when deemed appropriate by the consultant operating surgeon. They are thought to be less painful and are a part of the institution's ERAS package. All patients were encouraged to eat and drink *ad libitum* after surgery and early mobilisation was encouraged in a standard manner. This involved sitting out in a chair the day after surgery, and the evening of surgery where possible. Patients were encouraged to mobilise with the aid of a physiotherapist the following day.

Figure 4 - The Scarborough Optimisation Package

Scarborough Optimisation Package

- Preoperative assessment
- Patient information
- Avoidance of opiates
- Curtailed fasting and preoperative carbohydrate loading
- High concentration of inspired oxygen
- Transverse incisions
- Avoidance of drains and nasogastric tubes
- Early reintroduction of diet and fluids
- Early mobilisation
- Regular non opiate analgesia

5.3.7 End Points

The primary end point for this study was extensively debated and discussed. As the aim of the study was to establish a possible alternative to epidural anaesthesia it could reasonably be argued that pain control should be the primary end point. A dilemma posed by this approach was that assessment of pain control is difficult. Invariably it necessitates the use of visual analogue scales which are subjective and difficult to validate. An alternative surrogate measure of pain control is opiate usage. It was decided that this should be recorded, however, it was deemed inappropriate as a primary end point because of difficulties with internal validity of usage on different wards or with different staff. The two existing trials investigating this technique selected postoperative pain scores as their primary endpoints[139,141]. The feasibility study in laparoscopic surgery lacked a primary endpoint but also evaluated pain[140]. Other similar trials have selected length of stay or time until medical fitness for discharge, recognising that whilst pain

control is important, excellent analgesia does not always reflect better recovery[76]. Improved analgesia may have clinical relevance, for example in reducing pain associated complications such as respiratory failure, atelectasis or pneumonia. It may also impact upon the patient's ability to mobilise, the preservation of intestinal function, tolerance of diet and overall recovery.

Another clinically relevant endpoint was the number of episodes of hypotension, of significance due to concerns about its management and the risk of anastomotic hypoperfusion. This was rejected as a primary endpoint after discussion with anaesthetic colleagues, as it is well known that episodes of hypotension will inevitably occur with epidurals and therefore it was felt that selection of this endpoint would potentially prejudice interpretation of results against epidurals.

Part of the concern surrounding epidural mediated hypotension relate to the risks of fluid overload from multiple fluid challenges. Fluid replacement after colorectal surgery is increasingly being recognised as being an important factor in recovery and more specifically the return of gut function[62,143]. This was felt to be unsatisfactory as a primary endpoint because of concerns regarding the potential for difficulties in managing this scientifically.

The endpoint elected by Levy et al, length of postoperative stay was selected for this study as it was felt to best represent the patients overall functional recovery, taking into account the other factors discussed. In 1958 Moore wrote that ` convalescence includes all the interlocking physical, chemical, metabolic and psychological factors commencing with the injury, or even slightly before the injury and terminating only when the individual has returned to normal physical well-being, social and economic usefulness and psychological habitus[144]. Whilst full convalescence in this regard may be difficult to assess, length of hospital stay has been used as a surrogate measure for the short term functional recovery after surgery, requiring that the patient be fit

for discharge. Functional recovery, represented by tolerance of food without nausea and regained mobility was considered the most important target of recovery in a survey of dedicated professionals[145]. Although imperfect, length of hospital stay was selected as the most clinically meaningful endpoint as it represented functional recovery.

5.3.8 Primary End Point

After lengthy consideration length of hospital stay was selected as the primary endpoint for this study. A power calculation was performed based on the institution's current mean Postoperative stay in elective patients undergoing colorectal resections of 6.8 days (SD 4.01 days). It was anticipated that this would reduce to 4 days in the intervention group. The sample size calculation was performed with Altman's nomogram assuming 0.80 Power and 0.05 significance. To use the nomogram the standardised difference was calculated by dividing the required difference (2.8 days) by the standard deviation (4.01 days) giving a figure of 0.698. A line was then drawn between these points on the nomogram giving the required sample size of 60 patients. These calculations have subsequently been checked by a Statistician (Dr Rhian Gabe senior lecturer in clinical trials HYMS). This study was designed to detect a reduction in LOS in the PainBuster® group. It was not designed as a non inferiority study and non inferiority cannot be calculated after the design of the trial as such studies require predefined parameters. Non inferiority studies also require greater power and this study would have lacked the power to provide this.

As decisions for discharge could be subjective specific discharge criteria were developed for the purposes of this study. Where patients were fit for discharge but remained an inpatient for purely social reasons this was recorded.

Figure 5 - Discharge criteria

Discharge criteria

- Good pain control with oral analgesia
- Tolerating solid food without nausea and vomiting
- No IV fluid or medication
- Independently mobile and self caring or at the same level as prior to admission
- Stable observations and blood biochemistry
- No other concerns or complications preventing discharge
- All of the above and willing to go home

5.3.9 Secondary End Points

All complications in the postoperative period were recorded. Wound infection was defined as clinical evidence of purulent discharge and erythema accompanied by microbiological (culture of microorganisms) and haematological evidence (raised white cell count). Cardiac failure was defined as the presence of clinical signs of fluid overload accompanied by radiological features on a chest X-Ray. Complications related to epidural/spinal or wound catheter were also recorded as were any other complications in the postoperative period.

Episodes of hypotension in the postoperative period were recorded. This was defined as a systolic blood pressure of less than 90 mmHg. The quantity and type of intravenous fluid administered on each Postoperative day was also recorded.

Postoperative pain was assessed objectively using the visual analogue scale for pain. Measurements were taken twice daily for as long as the epidural catheter or PainBuster® was in situ. Pain scores were measured at rest and on coughing. The total quantity and type (opiate or non-opiate) of all analgesics administered was also recorded during the period when the epidural or PainBuster® was *in situ.* The

postoperative stress response was assessed using SIRS criteria (Appendix K) and C-reactive protein.

Postoperative mobility was assessed as time until patients were able to transfer from a seated to a standing position whilst aided and unaided, duration of time spent out of bed on each postoperative day and maximum walking distance with assistance on a daily basis. In addition, assessment of mobilisation was carried out by the physiotherapists who recorded this in the patient notes. All patients were given a pedometer to wear to measure the number of steps taken. Pedometer readings were taken twice a day. Pedometers have been previously validated as an objective measurement of mobility. Return of gut function was measured and was defined by the tolerance of ≥ 80% of the prescribed nutritional requirement.

Figure 6 - Secondary Endpoints

Secondary endpoints

- **Postoperative complications**
  Wound infection
  Cardiac failure
  Complications related to epidural/spinal
- **Hypotension**
- **Time for insertion of epidural or PainBuster®**
- **Postoperative pain**
  At rest
  On coughing
- **Analgesia requirement**
  Opioid
  Non opioid
- **Postoperative IV fluids**
- **Stress response**
  SIRS
  CRP
- **Mobility**
- **Gut function**

5.3.10 Statistical Analysis

Data were analysed by means of a commercially available statistics package (SPSS v 20). A p-value of less than 0.05 was taken to signify statistical significance. Categorical data were analysed using the chi squared test or Fisher's exact test, as appropriate. The Shapiro-Wilk test was used to assess for normal distribution. Data which were not normally distributed were analysed using the non-parametric tests: Mann-Whitney U or Wilcoxon Signed-Rank test as appropriate.

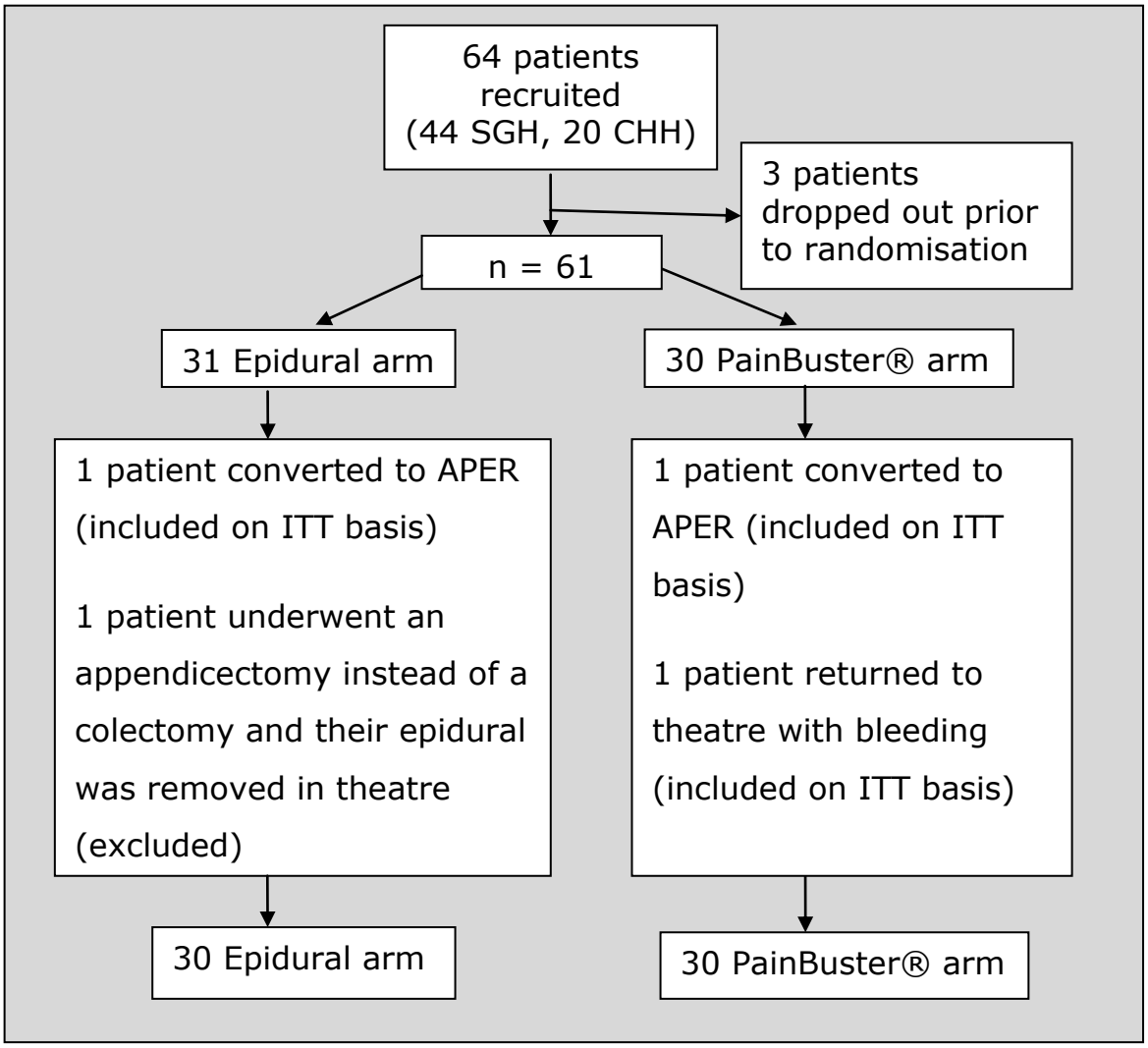
5.3.11 Ethical Approval

Ethical approval for the study was granted by the Sheffield Regional Ethics Committee. The study was also approved by Hull Research and Development.

5.4 Results

Figure 11 shows the participant flow diagram for this study. Recruitment was conducted across 2 sites: Scarborough General Hospital and Castle Hill Hospital. A total of 64 patients were recruited; 44 in Scarborough Hospital and 20 in Castle Hill Hospital, 3 of whom dropped out prior to randomisation. One patient in the epidural arm was due to undergo a right hemicolectomy, however this was converted to an appendicectomy due to operative findings. Her epidural was no longer felt to be appropriate and was removed in theatre. There are no postoperative data for this patient. One patient due to undergo an anterior resection in the PainBuster® arm and one in the epidural arm were converted to an APER intraperatively meaning that they both had two wounds. Their data have been included on an intention to treat basis. One patient in the PainBuster® arm experienced postoperative haemorrhage necessitating return to theatre for laparotomy. Her data have been included on an intention to treat basis.

Figure 7 - CONSORT diagram



5.4.1 Demographics

The demographics of the patients and surgical details of the patients are shown in Table 26.

Table 13 - Demographics

	Epidural	PainBuster®	p value
Age (years)	68.4 ± 11.2	66 ± 10	0.381
Sex Male/Female	21/9	19/11	0.584
ASA	2.3 ± 0.66	2.5 ± 0.57	0.243
Possum score	30.9 ± 4.97	31.0 ± 4.51	0.912
Approach Laparoscopic/Open	20/10	19/11	0.787
Length of incision (cm)	15.8 ± 5.14	12.6 ± 5.35	**0.019**
Incision type (midline/ transverse)	16/14	14/16	0.606

Values are presented as mean ± SD (standard deviation) or absolute values

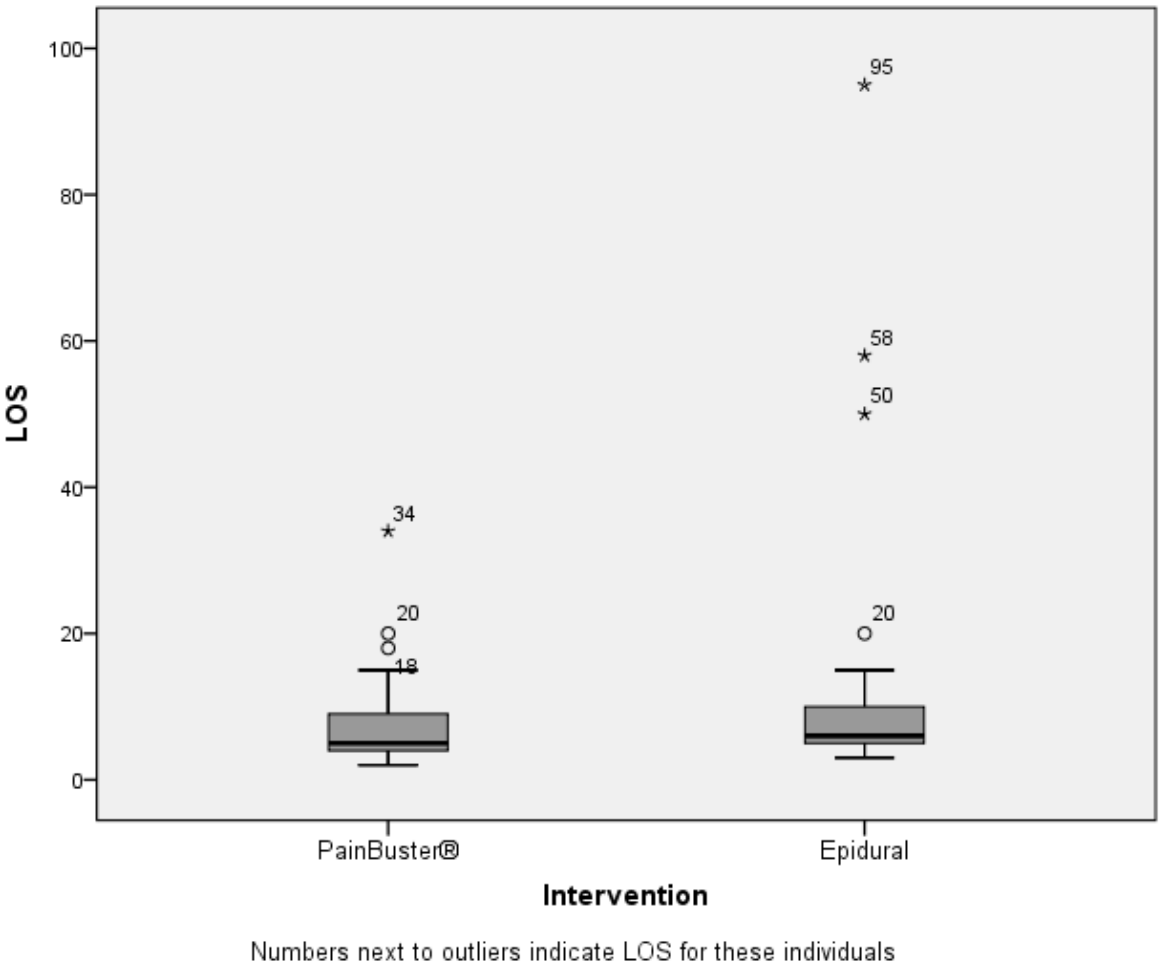
ASA = American Society of Anaesthesiologists; POSSUM = Physiological and operative severity score for the enumeration of mortality and morbidity

There was a statistically significant difference between wound lengths between the two groups (p=0.019 independent samples t-test), with longer incisions in the epidural group. The other variables were similar for both. Incision length was determined by the surgical team performing the operation and should be dictated by operative access requirements. However, surgeons and anaesthetists were not blind to the analgesic technique employed so it is not possible to tell whether this may have affected wound length or if this is purely coincidental.

5.4.2 Primary Endpoint: Length of Hospital Stay

Results for length of stay are displayed in Figure 12. There was no significant difference between length of stay between the epidural and PainBuster® groups. There was however a trend towards a shorter length of stay in the PainBuster® group. The median length of stay in the PainBuster® group was 5 Postoperative days (Inter-quartile range 4-9) while in the epidural group it was 6 (Inter-quartile range 5-10). There were no statistically significant differences between the length of stay of the two groups (p=0.08 Mann-Whitney U Test).

Figure 8 - Graph comparing length of stay between Epidural and PainBuster® groups



Non parametric tests were used as the data were not normally distributed. Some patients had significantly prolonged lengths of hospital stay, the longest was 95 days.

5.4.3 Secondary Endpoints

5.4.3.1 Postoperative Complications

The incidence of septic complications and organ dysfunction for the two groups are detailed in Tables 27 and 28 respectively. There were no significant differences between the groups (chi-squared test). The table details the total number of complications as opposed to the total number of trial patients who experienced complications.

Table 14 - Septic complications

Septic Complications	Epidural	PainBuster®
Intra–abdominal sepsis	2	3
Wound sepsis	3	4
Line sepsis	0	0
Chest sepsis	2	0
Urinary sepsis	1	1
Total episodes (individual patients)	**8 (7*)**	**8 (4^{+})**

*One patient in the epidural group had wound and intra-abdominal sepsis.

$^{+}$Two patients in the PainBuster group had multiple septic complications; one patient had wound and intra-abdominal sepsis whilst another patient had intra-abdominal and wound sepsis.

Table 15 - Organ dysfunction

Organ dysfunction	Epidural	PainBuster®
Cardiac	2	1
Hepatic	0	1
Respiratory	4	0
Renal	3	1
Total episodes (individual patients)	**9 (6pts†)**	**3**

†Epidural: one had cardiac respiratory and renal dysfunction, one had cardiac and respiratory dysfunction

One further patient in the PainBuster® group experienced significant haemorrhage from her bowel anastomosis which necessitated return to theatre and re-laparotomy for haemorrhage control. She then went on to have an epidural because of her laparotomy wound.

There were several minor complications relating to PainBuster® use. One patient developed a small haematoma following insertion of one of the tunnelled rectus sheath catheters, this was managed conservatively. In one patient the tubing of the PainBuster® snapped when the device was dropped on the floor, necessitating removal of the PainBuster®. In another patient the clips on the tubing were accidentally fastened during the night meaning that the wound infiltration was inadvertently stopped. The patient was comfortable despite this and the PainBuster® was therefore removed. There were no cases of local anaesthetic toxicity.

In terms of epidural complications one patient was persistently hypotensive and became fluid overloaded from multiple fluid challenges despite being managed on the high dependency unit. Another patient's pain was not well controlled, requiring anaesthetic team input to bolus and reposition the catheter. Unfortunately their block was still poor

despite this. There were no cases of epidural abscess or haematoma in this study.

5.4.3.2 Hypotension

Episodes of hypotension were measured for each patient and are displayed in Table 29. Hypotension was defined as a systolic blood pressure of less than 90 mmHg. Hypotension was markedly more frequent in the epidural group on the first postoperative day with eight episodes as compared to one episode. This was statistically significant (p=0.026). There were no significant differences in episodes of hypotension thereafter.

Table 16 - Episodes of hypotension

	Epidural (n=30)	PainBuster® (n=29*)
Day 1	8	1
Day 2	1	0
Day 3	0	1

*There are no data for patient 40 who returned to theatre for haemorrhage control

5.4.3.3 Postoperative Pain

Postoperative pain was measured using a visual analogue scale 10cm in length with 'no pain' at the left side of the line and the 'worst pain imaginable' on the right hand side (Appendix K). Patients were asked to select a point along the line to represent their level of pain. The distance from left to right of their mark on the line was converted to a numerical value representing their pain score. Pain scores were obtained twice daily for the duration of the epidural or PainBuster® being *in situ*. Pain was measured at rest and on coughing. Results in Table 30 (at rest) and 31 (on coughing).

Table 17 - Postoperative pain scores at rest

Pain scores at rest					
	Intervention	**N**	**Mean**	**SD**	**p-value**
Recovery	PainBuster®	12	2.64	2.30	**0.001**
	Epidural	20	0.85	1.59	
Day 0 pm	PainBuster®	19	2.12	1.39	**0.014**
	Epidural	18	1.36	2.03	
Day 1 am	PainBuster®	27	2.03	1.51	0.411
	Epidural	27	2.74	2.29	
Day 1 pm	PainBuster®	19	1.13	1.20	**0.010**
	Epidural	18	2.81	2.42	
Day 2 am	PainBuster®	25	1.34	1.24	**0.011**
	Epidural	21	2.78	2.04	
Day 2 pm	PainBuster®	11	0.58	0.72	**0.003**
	Epidural	11	2.31	1.98	
Day 3 am	PainBuster®	13	1.52	1.21	1.000
	Epidural	12	1.68	1.57	

Table 18 - Postoperative pain scores on coughing

Pain scores on coughing					
	Intervention	**N**	**Mean**	**SD**	**p-value**
Recovery	PainBuster®	13	3.98	2.66	**0.002**
	Epidural	21	1.61	2.03	
Day 0 pm	PainBuster®	19	4.21	1.95	0.123
	Epidural	19	3.03	2.81	
Day 1 am	PainBuster®	27	3.83	2.14	0.517
	Epidural	28	4.40	2.54	
Day 1 pm	PainBuster®	19	2.82	2.41	0.057
	Epidural	19	4.57	2.67	
Day 2 am	PainBuster®	25	2.66	1.94	**0.009**
	Epidural	22	4.55	2.48	
Day 2 pm	PainBuster®	11	2.06	2.30	**0.009**
	Epidural	12	4.35	2.13	
Day 3 am	PainBuster®	13	3.04	1.96	0.801
	Epidural	13	3.12	1.84	

As can be seen from the above tables pain scores were not obtained from all patients at each of the time points. Two patients were unable to quantify their pain using this technique. They were encouraged to choose a point along the line but if they could not choose one then this was abandoned. There were particular barriers to the obtaining of pain scores. In recovery patients were often too drowsy, notably so in the PainBuster® group. This was as a result of them having received opioid analgesia for breakthrough pain. As the wound catheters were inserted at the end of the operation, the bolus of local anaesthetic given via the wound catheters did not have sufficient time to have its effect prior to the end of the general anaesthetic. This is supported by a statistically significant (Mann-Whitney U test) increase in the pain scores in recovery in the PainBuster® group both at rest (p=0.001) and on coughing (p=0.002).

Data for the Castle Hill Hospital patients were obtained by the research fellow working there. Due to time commitments he was unable to obtain evening pain scores for a number of the patients there. These patients were given a patient diary with the daily morning and evening visual analogue scales to complete. Unfortunately, without the research fellow to prompt them to complete these they were often not filled in. These data are missing for the evening (pm) readings. Data from both morning and evening readings obtained are shown in the above tables. As some of the morning and evening readings are from the same patients it was not deemed appropriate to calculate a mean pain score for each day as this could skew the results obtained.

Whilst there is a significant increase in Postoperative pain scores in the PainBuster® group in recovery, this difference is not present the following postoperative day. Indeed on Day 2 there was a statistically significant (Mann-Whitney U test) difference in pain scores once again, however on this occasion it was the epidural group who had the higher pain scores. Pain scores were significantly higher at rest on Day 1 pm ($p=0.01$) and Day 2 am ($p=0.011$) and pm ($p= 0.003$). This was also the case on coughing on Day 2 (0.009 for both am and pm scores).

Figure 9 - Mean pain scores at rest

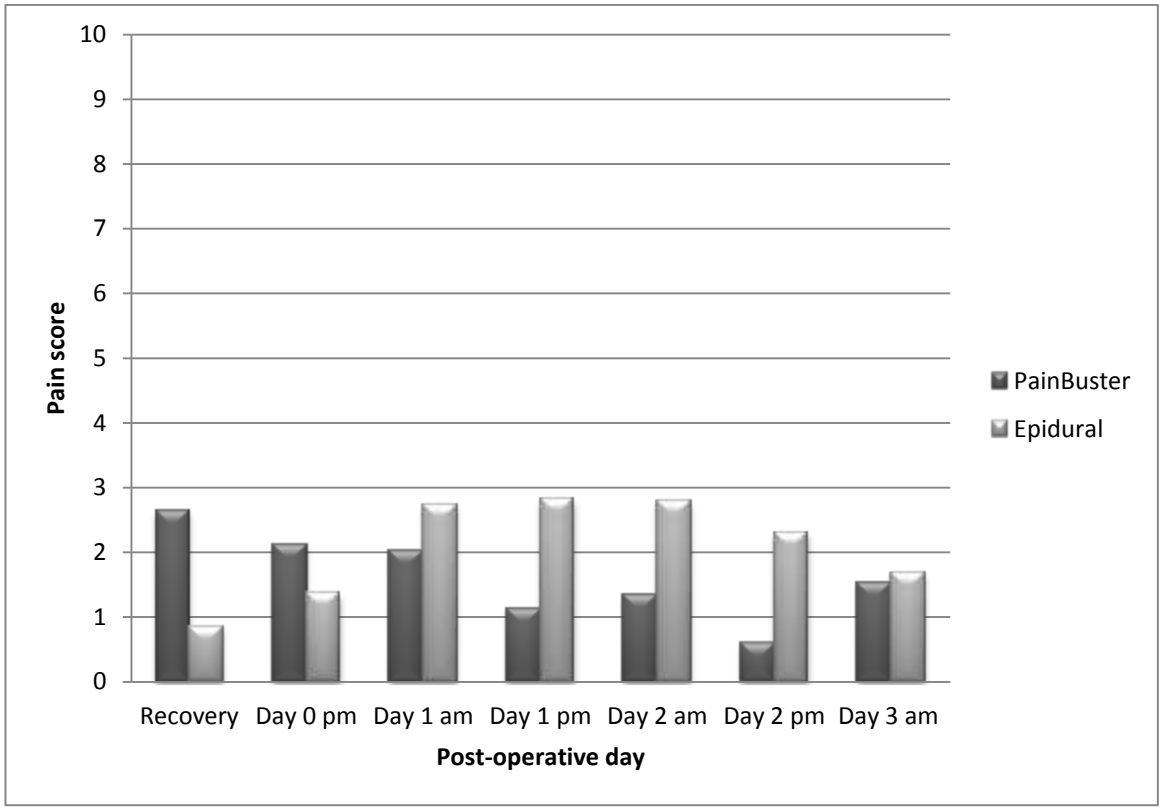
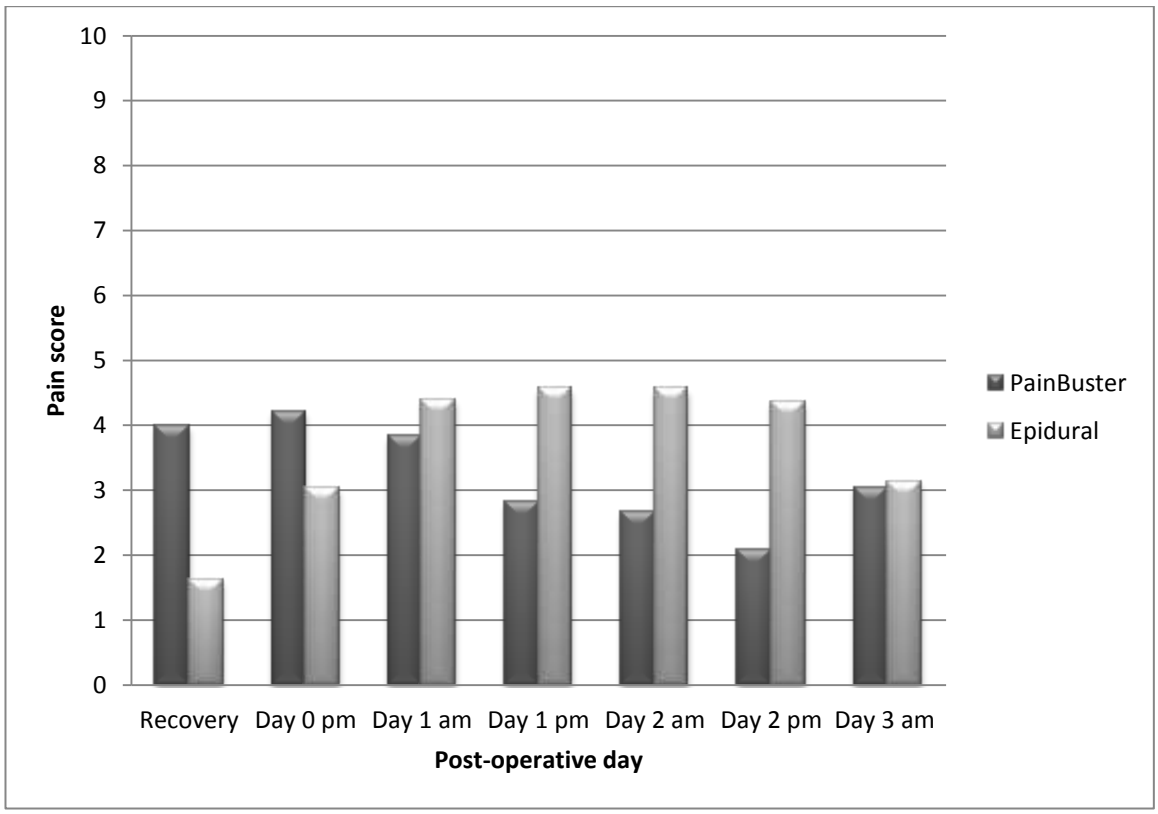


Figure 10 - Mean pain scores on coughing



Trends in pain scores at rest and on coughing are displayed in Figures 13 and 14 respectively. Patients in the epidurals group initially have decreased pain scores, however as their epidural is weaned their pain scores increase. Conversely the PainBuster® patients experience more pain immediately post surgery but this gradually improves over their postoperative course. Patients in the epidural arm frequently described feeling like they had 'gone backwards' on the second postoperative day, as they experienced more postoperative pain as their epidurals were weaned. This was not noted in the PainBuster® group whose pain improved. There is likely to be a psychological impact of perceived progress on postoperative recovery.

5.4.3.4 Analgesic Requirements

Analgesic requirements were measured on each postoperative day. Opiate analgesic requirements are displayed in Tables 32-4.

Table 19 - Mean tramadol requirements

Dose of Tramadol (mg)					
	Epidural		**PainBuster®**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Day 1	136.67	132.57	82.76	102.01	0.103
Day 2	181.67	164.78	101.72	124.27	0.070
Day 3	194.83	168.15	93.10	134.11	**0.018**
Day 4	153.45	156.94	94.64	136.31	0.135
Total dose	655.00	540.81	356.67	395.17	**0.023**

Table 20 - Mean codeine requirements

Dose of Codeine (mg)					
	Epidural		PainBuster®		p value
	Mean	SD	Mean	SD	
Day 1	8.57	45.36	12.41	47.11	0.339
Day 2	15.00	55.68	14.48	49.83	0.708
Day 3	12.86	47.21	11.38	45.65	0.940
Day 4	15.00	50.66	10.34	45.55	0.614

Table 21 - Mean morphine requirements

Dose of Morphine (mg)					
	Epidural		PainBuster®		p value
	Mean	SD	Mean	SD	
Day 1	2.68	8.22	6.32	19.87	0.725
Day 2	7.68	37.75	2.79	8.97	0.705
Day 3	1.07	4.16	.34	1.86	0.523
Day 4	0.36	1.89	.71	2.62	0.556

There was a statistically significant difference in total dose of tramadol (Mann-Whitney U test), being greater in the epidural versus the PainBuster® group. Analysis of each postoperative day showed this to be significant only on day 3. There were no statistically significant differences between the groups in terms of morphine or codeine consumption between the groups. Requirements of non opiate analgesia were also measured and are displayed in Table 35. There were no statistically significant (Mann-Whitney U test) differences in requirements of non opiate analgesia between the intervention groups.

Table 22 - Mean non opiate analgesia requirements

Dose of Paracetamol (g)					
	Epidural		**PainBuster®**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Day 1	3.67	0.84	3.52	0.74	0.220
Day 2	3.50	1.14	3.41	0.91	0.382
Day 3	3.48	1.18	2.83	1.47	0.054
Day 4	2.97	1.27	2.28	1.83	0.321
Dose of Diclofenac (mg)					
	Epidural		**PainBuster®**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Day 1	21.03	45.62	36.21	59.61	0.326
Day 2	18.97	45.15	31.03	55.76	0.343
Day 3	15.52	38.04	24.14	49.32	0.495
Day 4	25.00	50.00	37.50	60.77	0.713
Dose of Ibuprofen (mg)					
	Epidural		**PainBuster®**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Day 1	137.93	374.56	224.14	459.55	0.333
Day 2	151.72	391.54	151.72	376.66	0.767
Day 3	82.76	270.01	124.14	339.81	0.670
Day 4	72.73	241.21	120.00	269.98	0.705

5.4.3.5 Postoperative Intravenous Fluids

Results are displayed in Table 36. There were no statistically significant differences between the volumes of intravenous fluid administered between the intervention groups.

Table 23 - Volumes of intravenous fluid infused

Volumes of Intravenous fluid					
Postoperative day	**Intervention**	**N**	**Mean**	**SD**	**p value**
Day1	PainBuster®	29	1554.79	1604.61	0.385
	Epidural	30	1810.77	1483.35	
Day 2	PainBuster®	27	556.70	978.84	0.956
	Epidural	30	577.27	935.59	
Day 3	PainBuster®	26	272.12	756.76	0.703
	Epidural	30	310.03	723.22	

5.4.3.6 Stress Response

Episodes of SIRS are displayed in Table 37. A difference was seen in the number of episodes of SIRS between the two interventions. There were fewer episodes of SIRS on each postoperative day and overall in the PainBuster® group as compared to the epidural group. This was not found to be statistically significant (Fishers exact test and Mann-Whitney U test). Some patients were found to have multiple episodes of SIRS. The total number of patients to have an episode of SIRS was 14 in the epidural group and 10 in the PainBuster® group whilst the total number of episodes (classed as meeting the SIRS criteria on one postoperative day) was 30 in the epidural group and 14 in the PainBuster® group.

Table 24 - Episodes of SIRS (Systemic Inflammatory Response Syndrome)

SIRS episodes	Epidural	PainBuster®	p-value
Day 1	9	6	0.547
Day 2	9	4	0.207
Day 3	7	3	0.167
Day 4	3	1	0.628
Day 5	2	0	0.508
Total episodes (patients)	30 (14)	14 (10)	(0.430)
Mean	1.035 (SD 1.43)	0.4828 (SD 0.78)	0.146

CRP values were measured preoperatively and on each postoperative day. Results are shown in Table 38. At baseline the mean CRP was 15.4 in the PainBuster® group and 14.3 in the epidural group. Thereafter the mean CRP was higher in the Epidural group. This was statistically significant (Mann-Whitney U test) on day 2 and day 4 postoperatively.

Table 25 - C- reactive Protein (CRP)

C- reactive Protein (CRP)					
	Intervention	**N**	**Mean**	**SD**	**p value**
Pre-op CRP	PainBuster®	16	15.41	18.19	0.582
	Epidural	20	14.32	25.51	
Day 1 CRP	PainBuster®	24	84.04	45.57	0.406
	Epidural	23	98.65	51.73	
Day 2 CRP	PainBuster®	19	119.42	69.55	**0.015**
	Epidural	22	197.45	113.97	
Day 3 CRP	PainBuster®	16	138.65	76.12	0.422
	Epidural	18	181.78	119.56	
Day 4 CRP	PainBuster®	14	118.36	92.72	**0.046**
	Epidural	15	194.27	113.12	
Day 5 CRP	PainBuster®	12	144.75	101.71	0.503
	Epidural	13	172.54	117.26	

5.4.3.7 Mobility

Trial patients were each issued with a pedometer and instructed in its use. Pedometer readings were obtained on each postoperative day. There was a statistically significant difference (Mann-Whitney U test) between the pedometer readings for the two groups on postoperative Day 1 and Day 2 (Table 39). There is an incomplete dataset for these results due to poor compliance with using the pedometer. A more crude measure of mobility was the time to unaided mobilisation, which was 1.93 (SD 1.33) days in PainBuster® group and 2.43 (SD 1.27) in epidural group. This was not statistically significant (p=0.064).

Table 26 - Pedometer readings

Pedometer readings					
	Intervention	**N**	**Mean**	**SD**	**p value**
Pedometer Day 1	PainBuster®	14	267.71	533.20	**0.026**
	Epidural	15	27.73	52.59	
Pedometer Day 2	PainBuster®	19	567.53	689.18	**0.002**
	Epidural	18	96.28	101.46	
Pedometer Day 3	PainBuster®	18	393.78	386.47	0.244
	Epidural	15	203.27	168.54	

5.4.3.8 Gut Function

Patients' gut function was assessed on each postoperative day. This was defined as tolerance of 80% of normal dietary intake. Return to gut function was faster in the PainBuster® group but this was not statistically significant (Mann-Whitney U test). Results for each intervention group are shown in Table 40.

Table 27 - Day of return of gut function

Day of return of gut function				
Intervention	**N**	**Mean**	**SD**	**p value**
PainBuster®	27	2.15	1.68	0.071
Epidural	25	2.80	1.53	

5.5 Discussion

The hypothesis of this study was that continuous infusion of local anaesthetic directly into the wound (PainBuster®) would reduce the length of postoperative stay compared with epidural analgesia in the

setting of an ERAS programme. The power calculation for this study was based on a reduction in length of stay of 2.8 days. A reduction of one postoperative day was seen in the Painbuster® group, 5 days compared with 6 days but this was not statistically significant. A median value was taken owing to skewed nature of the distribution, the maximum length of stay being 95 days. Analysis of the data excluding these outliers did not demonstrate a statistically significant difference. It may be that a less ambitious power calculation would demonstrate a smaller but statistically significant difference with a larger study group. Despite the non significant reduction in length of stay, the lack of difference between the groups invites the conclusion that the PainBuster® could replace successfully replace epidural analgesia in the setting of an enhanced recovery programme. However, this was not designed as a non inferiority study so a claim for non inferiority cannot be substantiated.

Whilst pain scores were not selected as the primary endpoint due to their subjective nature, Postoperative pain is an important aspect of Postoperative care. There are two separate aspects of the pain score data which are worthy of discussion. Firstly, a statistically significant difference in pain scores in recovery was seen, with lower pain scores in the epidural group than the PainBuster® group both at rest and on coughing. Mean pain scores at rest of 2.64+/-2.30, and on coughing of 3.98+/-2.66, were higher than in the patients who received epidurals, who reported little to no pain. The PainBuster® group patients also required morphine in recovery to address this. The PainBuster® is not equal to the epidural as regards immediate Postoperative pain. Reasons for this include the delay in achieving an adequate block prior to patients coming round from their general anaesthetic. The epidurals are inserted pre-procedure and started whilst the patient is still under anaesthetic. Conversely the PainBuster® is inserted at the end of the operation just prior to closing the surgical incision. A bolus of local anaesthetic is given once the wound is closed, however patients come round from the anaesthetic shortly afterwards whilst the block is still

taking full effect. There are different ways in which this issue could be addressed. Rectus sheath catheters can be inserted under ultrasound guidance by an anaesthetist prior to the start of the surgical procedure. This has been described in an observational case series of patients undergoing open radical cystectomy[98]. There are however specific limitations of this technique in colorectal patients, namely the uncertainty over the requirement for stoma formation and placement which could limit the placement of the catheters. The use of smaller transverse incisions may also not be compatible with this technique. TAP blocks and wound catheters would also not address visceral pain[146]. An alternative to the early insertion of the wound catheters is the use of an adjunct anaesthetic technique of spinal anaesthesia to cover the immediate Postoperative period. A follow-on study is currently being conducted to evaluate this.

The second finding of note is the differences in trends of pain scores for the epidural and PainBuster® groups. VAS is validated for assessing changes in pain for a number of conditions(146). As the rating of pain is dependent on the individual's experience of both extremes: 'no pain' and 'the worst pain imaginable', pain scores are likely to vary between individuals. They may be more reliable for assessing trends of pain measured at different times for a specific individual, rather than differences between individuals. Changes in pain scores over time for each patient were therefore analysed. This statistical analysis reveals a significant difference in the distributions of pain scores from recovery to day 2 ($p=0.011$ Related-Samples Friedman's two way analysis of variance by ranks) not present in the PainBuster® group ($p=0.1$). Patients in the epidural group had extremely low pain scores immediately postoperatively but these increased as time progressed. A statistically significant difference was seen within each group in terms of pain scores on coughing. For the epidural group they increased between recovery and day 2 $p=0.007$, whereas for the PainBuster® group they improved $p=0.031$. Patients in the epidural group frequently stated that

they felt that they had 'gone backwards', borne out by this statistically significant increase in their pain.

The perception of improvement in the PainBuster® group or having 'gone backwards' in the epidural group may be significant in terms of the patient's psychological recovery. There is little in the literature regarding the psychology of postoperative recovery but it is logical to assume that perceived deterioration in terms of pain scores could have a negative effect on patients' state of mind, and thereby on behaviour. State anxiety has been postulated to have an effect on Postoperative pain and recovery[148,149].

This increase in pain highlights the importance of the transition to oral analgesia whilst weaning the epidural. Similar findings have been previously reported in the literature[150]. One might argue that the epidurals were weaned too early in this study. However, ASGBI guidelines for the implementation of ERAS protocols recommend that weaning from epidural analgesia should start at 12 hours postoperatively and that they be continued for no longer than 48hours postoperatively[70]. The findings that patients in the PainBuster® arm had comparatively lower pain scores and that some patients in both groups were discharged on day 3 suggest that epidurals may not be necessary. Patient expectation is known to be an important aspect of the perception of pain. Studies exist which have used functional MRI imaging to map which areas of the brain are involved in perceiving pain[151]. Patients commonly expect pain in the Postoperative period[152]. What they may not expect is to experience virtually no pain immediately Postoperatively, followed by worsening pain over the following days. It is therefore important to manage patient expectation accordingly and to manage the epidural weaning process as smoothly as possible if an epidural is to be used. It would seem that the use of PainBuster® in this study obviates the need for this.

The statistically significant difference seen in overall tramadol requirements is consistent with the pain score findings. Patients in the epidural group required more tramadol overall, and a statistically significant difference was also observed in tramadol requirements on day 3. This increase in tramadol requirements is not in line with ERAS protocols, which advocate the avoidance of opiate analgesia where possible[70].

The return of gut function was delayed in the epidural group, although this lacks statistical significance. The preservation of gut function is a key aspect of enhanced recovery protocols, as the ability to tolerate diet and fluids is central part of recovery from colorectal surgery.

Despite the limitations associated with the use of pedometers there was a statistically significant difference in pedometer readings between the two groups. This was much higher on the first and second Postoperative days in the PainBuster® group. This may be attributable in part to the lack of need for urinary catheters and oxygen, and practical difficulties of mobilising with multiple attachments. The differences in pain scores may also be a factor for patients on day 2, as pain on coughing which equates to pain on movement may make patients feel disinclined to mobilise.

Epidurals have been shown to attenuate the postoperative stress response[153], particularly when continued for 24-48 hours postoperatively. It is therefore surprising to see a trend towards a higher incidence of SIRS in the epidural group. This was accompanied by a statistically significant increase in CRP in the epidural group over the PainBuster® group. This is in line with an increased number of septic complications in the epidural group, although this was not found to be statistically significant. It is unclear whether or not this is purely coincidental and consequently further research is warranted in order to investigate this further.

Organ dysfunction was seen more commonly in the epidural group but again this was not significant. Despite concerns about reduced Postoperative mobility increasing the potential risks of venous thromboembolism, there were no incidences of this in either group. However, the number of episodes of hypotension was significantly higher in the epidural group. This was expected as the phenomenon of epidural mediated hypotension is well documented[53,57]. Despite fluid overload occurring on one of these patients in the epidural group, who was transferred to intensive care, developed multiorgan failure and had a hospital stay of 95 days, there was no overall difference in the amount of IV fluid administered between the groups. This patient's case does however highlight surgeons' concerns regarding the management of epidural mediated hypotension and makes the case for the adoption of an alternative technique.

5.6 Limitations

This study was conducted over two hospital sites. Levobupivacaine 0.25% was used in Scarborough where the majority of patients were recruited. However, due to alterations in trust pharmacy policies, 0.2% ropivacaine, a different, slightly less potent local anaesthetic was used in Castle Hill Hospital. This does not invalidate the results obtained however, as it would reduce the efficacy and despite this there was a reduction in LOS. Subgroup analysis dividing the CHH and SGH data shows a significant decrease in LOS in the PainBuster® group for SGH but not CHH. However, this lacks sufficient power. It is possible that this may be attributable to the choice of local anaesthesia but the difference in incision lengths may also be a factor. However, if incision lengths were a true factor in determining LOS then this should be seen in the PainBuster® group as well as the epidural group; subgroup analysis shows that this is not the case.

This study was not blinded. Due to ethical considerations it was decided not to have a sham epidural arm as this would unnecessarily expose

patients to the risks inherent to epidural puncture. In retrospect it is possible that this could have been successfully accomplished without exposing patients to such risks. The feasibility study conducted by Boulind *et al* has successfully demonstrated that blinding for such a trial was possible[140]. Rather than perform an epidural puncture in the sham epidural group the authors affixed the epidural catheter to the patients back after induction of general anaesthesia. This ensured that patients did not know whether or not they had received a sham or real epidural catheter. Issues surrounding the infusion were managed by either using a syringe full of air or a covered infusion to blind ward staff to the patient's intervention.

There are a number of problems with such blinding. Lack of knowledge by the clinical team regarding the patients allocation would affect clinical decisions such as the management of any hypotension or removal of urinary catheter. It could be argued that the lack of blinding would be associated with the risk of performance bias, where knowledge of the intervention rather than the intervention per se affects outcomes. However, the use of an epidural does dictate certain aspects of management which are simply not necessary with local anaesthetic wound catheter. It is conventional to keep the urinary catheter until the epidural infusion has been discontinued, both because of the risk of urinary retention with epidural blockade, and for monitoring in the context of potential hypotension. The removal of the urinary catheter may therefore be attributed to the intervention, although this can only be performed if the clinician has knowledge of the intervention. In order to minimise performance bias, pre-defined criteria were used to by clinicians to determine length of stay.

It is unclear whether the discrepancy in incision lengths is due to this lack of blinding or is pure coincidence. This is difference is present in both the SGH and CHH datasets. Whilst it is possible that surgeons may have subconsciously minimised incision lengths in the PainBuster®

group, this may also be due to a multitude of other factors such as tumour size, patient body habitus or difficulty of procedure.

Selection bias controlled for with computer generated sequence and allocation concealment. Other elements of bias to which this study may have been at risk were detection bias as the research fellows were not blinded to which intervention the patient had received. Steps were taken to minimise this risk of bias by the use of predefined criteria for the outcome measures. Patients were also asked to complete their own pain scores and pedometer readings, although they too were not blinded to the choice of intervention.

The issue of missing data was significant in this study, over a range of endpoints such as pain scores and pedometer readings. Such missing data carries with it the risk of attrition bias and significantly affects the interpretation of the results obtained. In terms of the pedometer readings there was a significant proportion of data which was missing. However, the proportion of missing data was similar in both the groups, 14 and 15 on day 1 and 19 and 18 on day 2 respectively in the painbuster and epidural groups. Whilst a similar proportion of missing data in both groups minimises the risk of bias, this risk still exists, particularly if data in each group was missing for different reasons. For example, if patients in the PainBuster® group did not record their pedometer readings because they were not mobilising much, and those in the epidural group did not record their readings as they were mobilising a great deal then the statistically significant effect noted would not be accurate. However, it is unlikely that this was the case.

The proportions of pain score data missing at rest and on coughing were also comparable in both groups with the exception of pain scores in recovery. Rather than being attributable to random chance this is likely due to the higher morphine requirements of these patients in recovery causing sedation. This is relevant to the choice of intervention and may imply that the data obtained underestimate the pain

experienced by this group of patients at this time. There are several ways of dealing with missing data. However, imputation of the missing results was not felt to be appropriate as this could introduce further inaccuracy. The missing data may mean that the results lack sufficient power or that they may be affected by attrition bias. This renders meaningful interpretation of the results with a large proportion of missing data impossible. Consequently these are areas which merit further investigation in future studies.

The findings of two similar studies have recently been published. Bertoglio et al conducted a randomised controlled trial of local anaesthetic wound infiltration compared with epidural anaesthesia in patients undergoing open colorectal surgery[139]. They designed a non inferiority study but unfortunately did not reach the required power. Despite this the authors concluded that wound infiltration was not inferior to epidural in terms of postoperative pain. Whilst this was not in the context of multimodal optimisation their findings support those of this researcher's study.

In contrast to Bertoglio's findings and those of this researcher's study are the findings of Jouve *et al* who conducted a randomised controlled trial of continuous wound infiltration versus thoracic epidural anaesthesia in patients undergoing open colorectal surgery[141]. They reported a statistically significant increase in LOS and pain scores in the continuous wound infiltration group[141]. However, their study design differed from this trial in a number of ways. Their patients all had midline incisions and underwent open surgery, whilst participants in this trial had a variety of incisions and had had both laparoscopic and open surgery. They excluded patients with stomas, which this study did not. They also excluded patients with inflammatory bowel disease which again, this trial did not. This was a more pragmatic study, recruiting any patient undergoing elective colorectal surgery and was designed to assess whether the PainBuster ®could replace the epidural for all patients within this group. Placement of their wound catheters also

differed. For midline wounds catheters in this study, wound catheters were inserted just anterior to the posterior layer of the rectus sheath. Catheters in Jouve *et al'*s trial were placed preperitoneally. The choice of local anaesthetic used by Jouve *et al* was 0.2% ropivacaine, which had also been used in the Castle Hill Hospital site in this study. The lack of effect in both Castle Hill Hospital and the continuous wound infiltration group of Jouve *et al*'s study could be attributable in part to the choice of local anaesthetic. Further studies would be required to compare these local anaesthetics to determine if this is the case. It is reasonable to assume that the PainBuster® is more suited for use in patients with smaller transverse incisions rather than extensive midline laparotomy incisions, especially as midline incisions extending into the upper abdomen may significantly affect respiratory function.

Local anaesthetic wound infiltration is an acceptable alternative in the majority of patients. One limitation of the wound catheters alone is the increased perioperative pain in recovery. This may be negated by the use of a single shot spinal preoperatively, which has been used with success in colorectal laparoscopic resections[76]. These findings have prompted the design of a further randomised controlled trial comparing PainBuster® alone with PainBuster® and single shot spinal within the context of an enhanced recovery program. This study is currently underway in the author's institution. The primary endpoint of the new study is the postoperative stress response as measured by serum cortisol and noradrenaline levels at baseline, 60 minutes after surgical incision and 24 hours postoperatively. Length of stay, postoperative complications, hypotension, pain scores, analgesic requirements and gut function will also be assessed.

In addition to the PainBuster® versus PainBuster® and Spinal study which is currently underway this study may also inform further research using preoperatively inserted catheters to provide continuous transverses abdominis plane (TAP) block. As discussed, the higher pain scores in recovery were in part attributed to the length of time required

to establish effective TAP blockade. The concerns regarding the use of rectus sheath catheters prior to stoma formation was that these may either be damage or interfere with this. Continuous TAP infusion of local anaesthetic has been shown to be non inferior to epidural for patients undergoing laparoscopic surgery[84]. A similar study investigating the effectiveness of this technique in open colorectal surgery in the context of an enhanced recovery program would be of interest, particularly where smaller transverse incisions were employed. If such a block could be commenced prior to the start of surgery it is anticipated that problems with pain control in the immediate postoperative setting could be avoided. Alternatively a 4 quadrant preoperative TAP block could be administered prior to the start of surgery, following which the wound catheters could be inserted as usual at the end of the procedure. A trial comparing PainBuster® and preoperative TAP block with PainBuster® and single shot spinal anaesthesia would be beneficial in determining which of these two mechanisms for controlling the immediate postoperative pain would be most effective.

5.7 Conclusion

The results of this study suggest that local anaesthetic wound infiltration is an acceptable alternative to epidural in the majority of patients in the context of multimodal optimisation. As well as a trend towards reduction in length of hospital stay this technique appears to confer distinct advantages in term of postoperative mobilization and recovery. The PainBuster® group exhibited a reduced stress response, faster return to gut function, fewer opiates and earlier mobility, all of which contributed to a faster overall recovery. The use of the PainBuster® in colorectal surgery would appear to be more in keeping with the principles of enhanced recovery programs, which are designed to attenuate the stress response, preserve gut function, avoid opiates and preserve mobility. Further studies are required to evaluate the addition of spinal anaesthesia or preoperative TAP block to this

technique, in order to provide superior pain relief in the immediate postoperative setting.

Chapter 6 - Discussion

The need for colorectal surgery is on the increase. This is due in part to the increasing incidence of diseases for which treatment involves colorectal resection, such as colorectal malignancy[1]. Despite advances in surgical and anaesthetic techniques, colorectal surgery is associated with postoperative pain and stress response. Postoperative pain has been clearly implicated in the pathogenesis of postoperative complications, such as pulmonary embolus, pneumonia and myocardial ischaemia. Thoracic epidural analgesia has long been seen as the gold standard for the management of postoperative pain in major abdominal surgery, facilitating the avoidance of opiates in line with enhanced recovery after surgery (ERAS) protocols. However, despite the many advantages of epidurals, concerns also exist regarding their effects on splanchnic blood flow, particularly in the presence of epidural mediated hypotension. The trend towards minimally invasive surgery accompanied by viable alternative analgesic modalities has warranted further investigation into whether epidurals still have a role in the postoperative management of colorectal surgical patients.

This thesis has aimed to examine the evidence regarding the effects of thoracic epidurals on splanchnic blood flow, the other issues surrounding the management of colorectal patients with epidurals and to explore a potential alternative in the form of local anaesthetic wound catheters.

5.1 Thoracic Epidurals and Splanchnic Flow

The literature review conducted and detailed in Chapter 3 has highlighted the lack of good evidence as to precisely what effect thoracic epidurals have on splanchnic blood flow. Few studies on the effects of thoracic epidurals on splanchnic blood flow were identified, fewer still in human subjects. These studies utilised different modalities for measuring splanchnic flow under differing physiological

circumstances. The results were conflicting. There was some evidence of concern generated by the study by Gould *et al*, which suggested that goal directed fluid therapy as a treatment of epidural mediated hypotension did not sufficiently address the effects of the epidural blockade on inferior mesenteric artery blood flow[61]. If this is the case then clearly this has implications for postoperative management of patients with epidurals, particularly those with anastomoses. Despite the lack of other manuscripts with the same findings and indeed those with conflicting results, this was an area considered worthy of further investigation.

The need for further studies to investigate the effects of TEA on splanchnic flow and the role of intravenous fluids and vasoconstrictors in mitigating any such effects led to the development of two prospective observational studies. Two such studies were devised by this researcher, focussing on the effects of TEA on Superior and Inferior Mesenteric Artery (SMA and IMA) blood flow respectively. These study protocols contained similar methodology to Gould *et al*'s research[61]. The two vessels chosen for examination were the SMA and IMA. These are both important vessels in the context of colorectal surgery, although the IMA is divided in left sided colonic surgery such as anterior resection of rectum or left hemicolectomy. This renders the IMA amenable to dissection and study without causing harm to the patient. However, as this vessel is sacrificed during resection it does not contribute to anastomotic perfusion in left sided colonic surgery. It is arguable that selecting the marginal artery of Drummond for study following resection and anastomosis would be more representative of the postoperative situation. In view of Gould *et al*'s findings it would not be ethical to subject a newly formed anastomosis to a potential reduction in blood flow. As Gould *et al*'s work also linked IMA flow to colonic serosal red cell flux, which is thought to equate to mucosal blood flow, this vessel was selected for further study. Lundberg *et al* had found a similar reduction in blood flow in the SMA in response to thoracic epidurals[102]. The SMA was also selected for study but as this was more easily

amenable to trans-abdominal Doppler ultrasound measurement this technique was chosen for the second study.

The hypotension which was observed following induction of general anaesthesia in both the SMA and IMA flow studies conducted by this researcher led to the modification of the study protocols. Only 1 of the 8 subjects studied did not experience this. The manuscript by Gould *et al* does not specify whether their subjects experienced any hypotension as a result of general anaesthesia, and if so how this was managed[61]. It is difficult to reconcile this lack of need for any intervention with the findings of the SMA and IMA flow studies conducted in Scarborough Hospital. The demographics of the studies seem to be similar, with a similar sex distribution and mean ages of 66 years (Gould *et al*) and 65 in this researcher's studies. The main difference was that 3 of the subjects in this researcher's study group were taking medications for hypertension, whereas Gould *et al's* subjects were not. This difference does not adequately explain these differences in response to general anaesthesia.

As discussed in Chapter 4, the results of the SMA flow study were variable. The majority of these patients demonstrated a decrease in SMA flow in response to TEA, although in some this is more pronounced following the fluid bolus. However, two individuals had a different response, with the epidural bolus being followed by an increase in SMA flow. In one individual this increased markedly following the intravenous fluid therapy whereas in the other this remained stable at almost 190% of baseline.

Gould *et al* reported statistically significant findings from their 15 patients, although the specific responses of each individual subject were not detailed in their paper[61]. It is therefore unclear whether any subjects in their study exhibited an increase in splanchnic blood flow in response to the bolus of local anaesthetic given down the epidural catheter. The two sets of results obtained from the IMA flow study replicated Gould *et al's* findings. However, technical difficulties were

encountered with the Doppler ultrasound transducer which was used for these measurements, which may have affected the results which were obtained. Further studies with a cuffed Doppler similar to that used by Gould *et al* may be more appropriate than proceeding with the current technique.

The SMA flow findings outlined in this thesis are not directly comparable to those of the study by Gould *et al*, or that by Lundberg *et al*[61,102]. Lundberg *et al* had directly measured SMA blood flow using electromagnetic flowometry. They reported a significant decrease in SMA flow following a bolus of local anaesthetic administered via the epidural catheter in their study of 9 patients. They did not assess the effect of intravenous fluid therapy in ameliorating this decrease although this improved with dopamine. Again individual responses were not discussed in this paper and they did not specify whether any individual experienced a similar increase in SMA flow. However, this is unlikely given the significance of their results with small study numbers.

Increased splanchnic blood flow in response to TEA has been previously described in the literature. Michelet *et al* reported an increase in gastric mucosal blood flow in postoperative oesophagectomy patients with TEA compared with controls[103]. Kortgen and colleagues also found an increase in hepatosplenic blood flow, as measured with indocyanine green, in patients with thoracic but not lumbar epidurals after TEA[104]. This response has not previously been reported in studies utilising Doppler ultrasound.

The variability of the results obtained in the SMA flow study is intriguing. There is no clear association between the patient demographics and their response, although both subjects who exhibited an increase in SMA flow were not taking antihypertensive medication. However, there were also patients who experienced a decrease in SMA flow who were also not taking such medication, so this does not appear to be a contributing factor. The potential effect of salbutamol on splanchnic blood flow was investigated. The therapeutic dose of 0.2mg

has been reported to cause an increase in cardiac output and a decrease in peripheral vascular resistance in healthy individuals[154], whilst a supra-therapeutic dose has been shown to cause peripheral vasodilatation manifested by an increase in forearm blood flow[155]. The potential effects of inhaled salbutamol on splanchnic blood flow are unknown. Whilst salbutamol has been shown to have these cardiovascular side effects this does not adequately explain the increase in splanchnic blood flow. The other patient who exhibited this was not taking any medications. Both patients to have had this effect were male, but so were two other SMA flow subjects whose splanchnic blood flow decreased. Age ranges were also similar, and the effect on splanchnic blood flow was not related to hypotension, as this was observed in the majority of the research participants. Recently published research by Frey *et al* has demonstrated that patients with the β2 adrenergic receptor Glu 27 allele displayed a shorter time to critical hypotension following thoracic epidural anaesthesia[125]. This effect was noticed prior to and following the induction of general anaesthesia. Their findings show that some individuals are more susceptible to epidural mediated hypotension than others and that expression of the β2 adrenergic receptor Glu 27 allele was an independent predictor of both arterial hypotension and vasopressor requirements following TEA[125]. This may explain the variability seen in this researcher's studies in terms of hypotension in response to TEA and general anaesthesia, especially the absence of the anticipated hypotension in one of the subjects. It is possible that the effect of TEA on splanchnic blood flow also has a genetic component, but this is beyond the scope of these studies.

There were several limitations to the splanchnic blood flow studies described by this researcher. As previously discussed it was necessary to modify the study protocols to allow the appropriate management of the physiological response to general anaesthesia. This has now been standardised, so that vasopressor requirements can be quantified whilst maintaining patient safety. The study published by Frey *et al* also

details the use of a phenylephrine infusion to address this issue[125]. Aside from these physiological problems encountered in this researcher's studies, there were also a number of limitations during the study period itself. Limitations of Doppler ultrasound were noted both with obtaining a signal and ensuring the accuracy and repeatability of this signal. Throughout the course of the studies a variety of difficulties were encountered in the measurement of splanchnic blood flow. These included aberrant anatomy, which precluded isolation of the signal from the SMA from the nearby celiac axis. On several occasions the Doppler signal was poor, due to overlying bowel gas or patient body mass index, although this did not altogether preclude measurement. In the case of one subject a technical problem was encountered with the Doppler ultrasound machine which led to the study being abandoned as no useable results could be obtained.

Practical difficulties were encountered in the measurement of IMA blood flow. The necessity, in order to maintain asepsis, for a two person technique and the resultant coordination required did make this study less robust. The technical aspects of transducer manipulation within the abdominal cavity would be simplified by the use of a cuffed Doppler probe. This is likely to improve the reliability of the readings obtained. In order to address the potential variability of results the protocol was modified to obtain three sets of readings of splanchnic flow at each time point. This was employed for the two most recent subjects in the study.

The results of the splanchnic flow studies described in Chapter 4 were limited by the physiological response to general anaesthesia. Whilst the results raise concerns about the management of epidural mediated hypotension, they are not representative of the postoperative situation on the ward. The ideal study would be one in which the blood flow at the anastomosis could be monitored on the ward in the postoperative setting. The fact that this has not been described in the literature is a reflection of the numerous practical and ethical considerations that such a study would entail.

There are a number of ways in which splanchnic blood flow may be measured. The most direct is with the use of an invasive probe such as the electromagnetic flowometry described by Lundberg *et al*[102]. This is not feasible in the postoperative setting. Neither is measurement with a cuffed Doppler as both of these techniques would involve further surgery to remove the probe. Trans-abdominal Doppler ultrasound is technically possible postoperatively, but is likely to be associated with pain and views may be limited by bowel gas or residual intraperitoneal air. Contrast enhanced ultrasound, using fluorescent micro bubbles may be a potential avenue for future research as this would offer enhanced views in the postoperative setting. There are practical implications for this as it would not be ethical to deliberately cause hypotension in a patient with a recently fashioned bowel anastomosis, nor to manipulate epidural anaesthesia for study purposes if doing so caused otherwise avoidable pain.

Surrogate measures of splanchnic blood flow include gastric tonometry and near infra-red spectroscopy using indocyanine green[104,114]. There are limitations to both of these techniques. Whilst gastric tonometry is a simple and relatively non-invasive technique for measuring mucosal perfusion, controversies exist regarding its use. These include the potential need for gastric acid suppression and the actual measurement medium used. Saline has been shown to yield erroneous pCO_2 values and results may depend both on the type of medium and type of blood gas machine used[114]. The use of contrast enhanced near infra-red spectroscopy in conjunction with indocyanine green (ICG) may yield quantitative measures of blood flow. It has been used to measure muscle, cardiac and cerebral blood flow[156]. As IGC is cleared from the systemic circulation by the liver, a bolus of ICG must be given each time flow is measured. As this takes approximately 10-20 minutes, measurements may only be taken infrequently so as to avoid erroneous results[156]. These techniques would not be well suited for use in studies examining the effects of epidural bolus, fluid and vasopressors on splanchnic blood flow, where changes in physiology occur more rapidly.

A potential future study could utilise trans-abdominal Doppler ultrasound to measure SMA flow in preoperative surgical patients with thoracic epidurals. This would be more ethically sound than a postoperative study. This was not considered at the time of initial study design due to the need for oesophageal Doppler monitoring to measure cardiac output. The adoption of the Vigileo to calculate this from the arterial line waveform would now facilitate measurement of this in conscious patients. Baseline readings could be taken prior to bolus of local anaesthetic via the epidural catheter, following epidural, following intravenous fluids and following a vasopressor, such as a phenylephrine infusion. This would remove the confounding factor of the general anaesthetic. This was considered in the design process but rejected due to the requirement for oesophageal Doppler guided fluid therapy. The recent change in practice from using an oesophageal Doppler to the use of the Vigileo monitor, which interprets the arterial waveform, would now make this possible. This could provide a viable avenue for future research.

The results of the splanchnic flow literature review and the splanchnic flow studies are inconclusive. Concerns exist regarding epidural mediated hypotension and the possible association of a reduction in splanchnic flow and anastomotic leakage. No association of this nature has been proven[60]; indeed it would appear that the response in terms of gut blood flow would be variable. However, the potential risk of anastomotic leakage is not the only concern.

6.2 Postoperative Management of Thoracic Epidurals

Hypotension as a physiological side effect of thoracic epidural anaesthesia is well documented[53,57,125]. The mechanism for this is vasodilatation and decrease in venous return[53], producing functional hypovolaemia[57]. The degree of hypotension has been shown to be associated with the level of anaesthetic block[53] and lower pain scores[54]. Rates of hypotension associated with epidural blockade are variable in

the literature, ranging from 2.2% to 56%[54,55]. What is demonstrated by this researcher's splanchnic flow studies and in the literature is that this hypotension does not correct with intravenous fluid alone but requires the use of vasopressors[61,99,125]. This is of clinical concern as patients are often managed on a surgical ward by junior doctors who are trained to treat hypotension with intravenous fluid challenges. Whilst this may be ineffective it may also place patients at risk of fluid overload.

Junior doctors' knowledge of fluid balance has been a topic of repeated concern in the literature[157,158]. Fluid prescribing is often left to the most junior medical staff and may be poorly managed[159]. A systematic survey of medical textbooks found them to be inadequate in providing information about fluid balance and prescribing[159]. Fluid prescribing remains an area of concern amongst both consultants[160] and many Foundation trainees alike[161-163]. The topic of junior doctors' knowledge of epidurals and the management of epidural mediated hypotension has not been previously discussed in the literature.

Accurate postoperative fluid management is a key aspect of postoperative care[164] and inappropriate fluid management is associated with morbidity in postoperative patients[165]. Whilst there is no literature on the training of junior doctors about the management of epidurals, concerns over their knowledge on fluid balance are prevalent[157,158,166]. The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients set out clear protocols for the assessment of oliguria and for fluid therapy, advocating a thorough postoperative assessment of fluid balance[167].

Recent National Institute for Clinical Excellence (NICE) guidance also does not deal with epidurals but recommends that an understanding of fluid physiology and pathophysiology is required prior to prescribing intravenous fluids[168]. They advocate a balance but do not specifically mention epidurals and their potential effects on blood pressure. The Scottish Intercollegiate Guidelines Network (SIGN) have issued SIGN

guideline 77, entitled Postoperative management in adults, which does mention epidurals in the context of hypotension[169]. This guideline recommends that hypotensive patients with epidurals should be assessed to exclude a fluid deficit, but that excessive administration to well perfused, hypotensive patients with epidural anaesthesia should be avoided, as this may cause fluid overload which may only manifest after cessation of the epidural[169]. This guideline further states that when junior doctors have difficulty in managing a patient, they have a duty of care to discuss the patient with a senior colleague[169]. As well as being taught about fluid balance and the potential pitfalls in patients with epidurals, emphasis was placed on the importance of seeking help from senior colleagues. As Lobo *et al* have reported that whilst Senior House Officers were significantly more confident about fluid balance than their junior colleagues, their level of knowledge was the same[158].

Given the underlying mechanism of hypotension in patients with epidurals, repeated fluid challenges may neither be appropriate nor effective. Postoperative fluid overload has been associated with a higher incidence of Postoperative complications and mortality[164]. A more restrictive fluid regimen has been shown to reduce the incidence of Postoperative cardiopulmonary and tissue healing complications[170]. Despite this patients with epidurals are often administered a fluid challenge as initial treatment of their hypotension. The postoperative destination of colorectal patients with epidurals is likely to influence the way in which hypotension is assessed and managed. There is a clear need for recommendations regarding who should manage such patients and when medical or nursing staff should escalate care.

In view of these concerns about potential management problems in patients with epidurals, a shift of opinion amongst surgical and anaesthetic staff away from the use of epidurals for the majority of colorectal surgical patients was seen at a local level. There is a trend in the literature towards moving away from epidurals for laparoscopic surgery[74] and their role in open surgery requires further investigation.

6.3 Local Anaesthetic Wound Catheters - An Alternative to Thoracic Epidurals

The role of epidurals in laparoscopic colorectal patients has been called into question, whilst the situation for open surgery is unclear. Open procedures may denote large midline laparotomies but may equally entail minimally invasive open surgery employing small transverse incisions. It is unclear whether the laparoscope confers additional advantages in colorectal surgery[21], consequently alternative techniques should be explored for colorectal surgery as a whole.

The safety and efficacy of local anaesthetic wound catheters have been demonstrated in a number of randomised trials both within and outside of colorectal surgery[91,92,94,97,138]. At the time of study design no randomised controlled trial of epidurals versus local anaesthetic wound catheter had been described in the literature. A prospective randomised controlled study was designed by this researcher, in order to investigate the role of such wound catheters within an ERAS programme, with a view to their utility as a potential alternative to thoracic epidurals. The findings of this trial would suggest that the PainBuster® is at least equivalent to epidurals in colorectal patients in terms of the primary endpoint of length of stay. A trend towards decreased length of stay was observed in the PainBuster® group.

This was a pragmatic study, designed to evaluate the effectiveness of the existing technique of continuous wound infiltration with local anaesthetic in an enhanced recovery setting and to compare this with epidurals. Data from individuals in whom there were unexpected surgical outcomes, such as conversion to abdomino-perineal resection or postoperative haemorrhage necessitating a return to theatre, were included on an intention to treat basis. The study was conducted in two separate institutions, Scarborough General Hospital (SGH) and Castle Hill Hospital (CHH). The PainBuster® was in use in both of these and patients were easily randomised to either this intervention or to an

epidural. However, the local anaesthetic solution used in the PainBuster® differed between the two hospitals, partially as a result of pharmacy policy and in part due to the preferences of the anaesthetic department. This was discussed at the time and the decision was taken to continue, as both local anaesthetic solutions were in routine use, rather than stop the study in CHH.

Statistical analysis of the two hospital sites has shown a difference in results in terms of length of stay, pain scores and analgesic requirements in that there are significant differences in SGH but not CHH. It is unclear whether this could be due to the different local anaesthetic agents used. This could be assessed by future studies in CHH with either a higher concentration of ropivacaine, or with an alternate local anaesthetic if this could be approved by the anaesthetic department and hospital pharmacy.

The other potential confounding factor encountered in this trial was the discrepancy in incision lengths between the epidural and PainBuster® groups. This was present across both sites but was statistically significant both in SGH, and overall. Due to the nature of the trial, blinding was not deemed appropriate, meaning that operating surgeons were aware of which technique would be employed. This was unavoidable as the PainBuster® had to be inserted at the end of the operation. There are a variety of factors which could have influenced incision length, including patient body habitus, tumour bulk and difficulty of operative procedure. This could not have been anticipated preoperatively and was impossible to control for. It is conceivable that surgeons may have subconsciously made more effort to minimise the incision length in the PainBuster® group, or this could be purely coincidental.

Despite the non significant difference in LOS, the PainBuster would seem to confer advantages for patients in terms of improved mobilisation, reduced pain scores after the day of surgery and a swifter return to gut function. There were fewer barriers to mobilisation in the

PainBuster® group. Patients with the PainBuster® could have their urinary catheter removed when it was deemed clinically appropriate, rather than waiting for their epidural to be weaned. They had the additional advantage of localised analgesia and did not suffer from any effects on their lower limbs as some of those patients in the epidural group did. The device itself could be carried in a small bag over the patient's shoulder, as opposed to the epidural pump which required mains power and was attached to a drip stand. The pedometer readings obtained in the study reflect this. However, there were a number of practical issues with the pedometers in this patient group which affected the compliance. The pedometer is a validated tool for assessing mobilisation and is usually worn at the hip on the waist band of clothing. However, not all patients were fully dressed in their usual clothes on each postoperative day. For those patients who mobilised whilst wearing a hospital gown, there was no appropriate place to attach the pedometer. There were also several occasions on which devices became contaminated, due to leaking wound dressings or stoma bags, and were subsequently discarded. Some patients also forgot to wear them. Consequently the pedometer data are incomplete which may affect the validity of the results obtained.

Epidural anaesthesia was clearly superior to PainBuster® in controlling immediate postoperative pain. This is an area which clearly needs to be addressed. Reasons for this include the fact that the PainBuster® does not have an effect on visceral pain, only wound pain, whereas the epidural block is more complete. The epidural was also started at the start of surgery whilst the PainBuster® was inserted at the end. This may have allowed insufficient time for the local anaesthetic block to exert its full effect. There are different ways in which this pain could be addressed. The catheters could be inserted preoperatively under ultrasound guidance as described by Parsons *et al*[98]. In their case series they described no difference between epidural and wound catheter for patients undergoing radical cystectomy, and they found pain scores to be the same between the epidural and wound catheter group[98].

However, this would not be effective with transverse incisions and might impede stoma formation in open surgery or port site placement in laparoscopic surgery. Alternative techniques would include a preoperative TAP block or the use of spinal anaesthesia in conjunction with the PainBuster®.

The return of gut function is an important part of postoperative recovery. This was slower in the epidural group, although not statistically significant; a finding also reported by Levy *et al* in their randomised controlled trial comparing epidurals with spinal anaesthesia and PCA[76]. Rather than measure this as time to first flatus or bowel movement, a more functional measure, based on the time to tolerance of 80% of normal diet for a 48 hour period was selected. This has previously been validated in Scarborough Hospital and described in the literature[171].

Overall postoperative recovery involves a complex interplay of factors. Improved postoperative pain is likely to contribute to improved mobility which in turn reduces the need for bed rest, reducing the risk of thromboembolic and respiratory complications. Gut function is an important prognostic indicator and is preserved by the early reintroduction of diet. Patients with less pain who require fewer opiates may therefore have an improvement in their gut function. The ability to tolerate normal diet and fluids reduces the requirement for intravenous fluids. The absence of hypotension in the postoperative period reduces the requirement for intravenous fluids still further, thus preventing fluid overload and its' attendant morbidity. This interplay can be seen in the results of the trial. The patients in the PainBuster® group displayed improved mobility, faster return of gut function and improved postoperative pain scores on day two. This was accompanied by a significant reduction in their tramadol requirements, which may also have had a positive impact on gut function.

Little is known about the psychological aspects of recovery from colorectal surgery. This study has provided anecdotal evidence

regarding the way in which patients' perceptions of pain may influence their view of their recovery process. Patients in the epidural group frequently commented that they felt they had 'gone backwards' as their epidural was weaned and their pain worsened. Patients' perceptions of pain are influenced by their previous experience of pain[150] and patient dissatisfaction with the process of weaning epidurals has been reported in the literature[150]. This problem was not encountered in the PainBuster® group. Indeed they showed a significant improvement in pain scores, in part due to the high levels of pain in the immediate postoperative period. Whilst these higher pain scores need to be addressed there must be a psychological advantage to the perception of improvement. Further research into this area of recovery may be of future interest.

There may still be an indication for the use of thoracic epidural anaesthesia in some colorectal surgical patients. Jouve *et al* reported an increased length of stay and higher pain scores in patients with continuous wound infiltration as compared to epidurals in patients undergoing open colorectal surgery[141]. Their study design differed from this researcher's randomised controlled trial described in Chapter 5 of this thesis. Jouve *et al's* patient group all received midline incisions and their wound catheters were placed preperitoneally. In this researcher's trial, patients received a variety of laparoscopic and open approaches, involving both midline and transverse incisions. It is likely that epidurals are more appropriate for patients with large midline incisions, as these have been shown to be associated with higher levels of postoperative pain and greater impairment of respiratory function[172].

However, another randomised controlled trial of continuous preperitoneal local anaesthetic wound infiltration versus epidurals in open colorectal surgery published conflicting results to those of Jouve *et al.* Once again their study involved open colorectal resections through midline incisions without defunctioning stomas. This study concluded that local anaesthetic wound infiltration was non inferior to epidural in

terms of postoperative pain control. Unfortunately this study was cut short and therefore did not achieve the required sample size. This was also in the setting of traditional care and not an enhanced recovery program. Nonetheless the results suggest that local anaesthetic wound infiltration remains a viable option for this patient group.

6.4 Conclusion

Postoperative recovery should be viewed as a whole, without undue focus on any one aspect of care, and should employ multimodal strategies designed to achieve the best outcomes. ERAS protocols are intended to be dynamic, adapting with new evidence of which interventions are effective and which are not[173]. It would appear that in the presence of small incisions and minimally invasive surgery that epidurals may no longer be warranted. The PainBuster® or generic local anaesthetic wound catheters offer a viable alternative and may confer advantages in terms of both earlier, easier mobilisation, and the preservation of normal physiology. This is in line with the underpinning principle of ERAS; to minimise the effects of surgery and to preserve normal function.

Thoracic epidurals are known to confer benefits in terms of the reduction of pulmonary complications in high risk patients[35]. If used, they must be managed appropriately, by staff trained in their management. Care must be taken to avoid both fluid overload and under filling in these patients, for whilst harm has not been proven, the nature of the effects of thoracic epidurals on splanchnic flow remain unclear. Novel applications for epidurals in other aspects of surgery may exist, for example in patients with pancreatitis or sepsis, where sympathetic blockade may be desirable, as animal models have shown some benefit[59,107,108] . However, for the majority of patients undergoing colorectal surgery who receive small incisions they are not necessary. Continuous local anaesthetic wound infiltration with the PainBuster® offers one way forward, but other potential alternatives, such as TAP

blocks and spinal anaesthesia, should also be explored. As is frequently the case, there is no single solution that fits all. Rather, a selective decision should be made based on all available modalities in order to select the best care for each individual in this group of patients.

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Appendix A - An investigation into the effects of thoracic epidurals on superior mesenteric artery blood flow. A prospective observational study – Study Protocol

An investigation into the effects of thoracic epidurals on superior mesenteric artery blood flow.

A prospective observational study.

Protocol

Version 1.1
Date 3/6/11

Authors: Miss E Richards, Prof J Macfie, Dr I Tring (Consultant Anaesthetist)

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TABLE OF CONTENTS

1. INTRODUCTION

Thoracic epidurals are widely used in colorectal surgery for the provision of Postoperative pain control. Their use is advocated by existing enhanced recovery protocols and has a substantial evidence base[1-6]. However, there is extensive circumstantial evidence that epidurals are associated with hypotension in the Postoperative period. The effects of such epidural mediated hypotension on the splanchnic circulation are not fully understood. This is clearly an area of great relevance in the field of colorectal surgery due to the potential consequences of impaired colorectal anastomotic perfusion in terms of the high morbidity and mortality associated with an anastomotic leak.

The effect of thoracic epidural anaesthesia (TEA) on intestinal perfusion is not fully understood. In animal models TEA has been shown to increase gut mucosal perfusion[7,8]. However, epidural anaesthesia with bupivacaine has been shown to cause a significant decrease in the oxygen-perfusion state of colorectal anastomosis in humans, although this was not associated with anastomotic or other complications[9]. Most studies into the effect of TEA on splanchnic blood flow in patients have utilised indirect measurements such as tonometry. *Gould et al* performed an intraoperative study of 15 patients in which they directly measured inferior mesenteric artery flow and colonic serosal red cell flux. They found that the measured reduction in colonic blood flow caused by epidural block did not respond to an increase in cardiac output with fluid resuscitation, but required the use of a vasopressor to restore blood flow[10].

Gould et al's findings raise significant concerns about current practice. The trend towards goal directed fluid therapy using oesophageal Doppler measurements of cardiac output in colorectal patients is called into question by the existence of new

evidence that cardiac output may not correspond to colonic blood flow in the presence of TEA. This is a particular area of concern in colorectal patients with an anastomosis. Recent literature suggests that restrictive fluid regimes may reduce morbidity after colorectal resection[11]. Fluid challenges in patients with TEA induced hypotension may not only be ineffective in restoring gut blood flow but may also place them at risk of potential fluid overload with its associated morbidity.

There is a definite need for further studies to investigate the effects of TEA on splanchnic flow and also the role of intravenous fluids and vasoconstrictors in mitigating such effects. We have devised two such studies, focussing on the effects of TEA on both superior and inferior mesenteric artery flow (IMA and SMA).

2. HYPOTHESIS

We hypothesise that a bolus of local anaesthetic given via an epidural catheter will mediate a decrease in Superior Mesenteric Artery (SMA) flow which will not be completely restored by giving oesophageal Doppler directed fluid therapy but will necessitate the use of vasoconstrictors.

3. AIMS

To assess the effects of thoracic epidural on SMA flow and the adequacy of goal directed fluid therapy and vasoconstrictors in ameliorating such affects.

4. PATIENTS, MATERIALS AND METHODS

4.1. Study Design

A prospective observational study of SMA flow in patients receiving thoracic epidural anaesthesia.

4.2. Inclusion Criteria

Patients receiving thoracic epidurals and general anaesthetic for any surgery.

4.3. Exclusion Criteria

Pregnant females.

Patients under 18 years of age.

Patients unable to give informed consent.

Patients in whom prolongation of anaesthesia is deemed unsafe.

4.4. Methodology

4.4.1. Recruitment

Patients on the waiting list for any surgery involving thoracic epidurals and a general anaesthetic will be identified in outpatient clinics, at pre-assessment or on the ward. They will be seen in the pre-assessment clinic or on the ward and informed about the existence of the trial. If they are interested they will be given an information leaflet. Once they have had a chance to consider this they will be consented and recruited to the study.

4.4.2. Epidural catheter

All patients will receive a thoracic epidural catheter at T8-T11 in the anaesthetic room, however local anaesthetic will not be given at this time.

4.4.3. Anaesthetic protocol

Anaesthesia will be induced and maintained following a standard protocol; propofol, fentanyl, atracurium for induction, and ventilation, oxygen, air and sevoflurane for maintenance.

4.4.4. Monitoring

Patients will be monitored with an oesophageal Doppler and other standard anaesthetic monitoring equipment. Measurements of cardiac output, systolic and diastolic blood pressure and mean arterial pressure will be measured throughout the procedure.

4.4.5. Measurement of SMA flow

Baseline measurements of SMA flow will be obtained using trans-abdominal Doppler ultrasound performed by a radiologist.

4.4.6. Bolus of local anaesthetic via epidural

The epidural will then be started and a bolus of 0.5mg/kg (12-16ml) of 0.25% bupivacaine given via the epidural catheter. Arterial pressure will then be allowed to fall to a mean arterial pressure (MAP) of 60. Further measurements of SMA flow will be taken in conjunction with other observations including cardiac output.

4.4.7. Oesophageal Doppler guided fluid resuscitation

Oesophageal Doppler guided fluid resuscitation with 6% Volulyte will then take place to restore cardiac output to baseline levels. A further reading of SMA flow will then be taken.

4.4.8. Administration of vasoconstrictors

If the MAP is not back to baseline levels then up to three 0.5mg bolus doses of metaraminol will be given over a 6-9 minute period to return the mean arterial pressure to the pre-epidural level. A final set of measurements including SMA flow will be taken and the operation can then proceed as planned.

5. SAMPLE SIZE AND STATISTICAL ANALYSIS

As these are small observational studies no power calculation has been performed. We aim to recruit 15 patients in each group (15 for IMA flow and 15 for SMA flow).

Data will be analysed by means of a commercially available statistics package (SPSS v 20). A p-value of less than 0.05 will be taken to signify statistical significance. Categorical data will be analysed using the chi squared test or Fishers exact test, as appropriate. Data which are not normally distributed will be analysed using the non-parametric tests, Mann Whitney U or Wilcoxon as appropriate.

6. ETHICS

Approval will be sought from an ethical committee. Application will be made using the IRAS (Integrated Research Application System) website. The study will also be registered on the national register for randomised clinical trials.

7. DATA STORAGE

Electronic data will be stored on a personal computer in the Research Fellows' office in Scarborough Hospital. This is password protected, and part of the hospital system. It is protected both by anti-virus and firewall software, as with all trust computers. Only the named investigators will have access to patients' data. Furthermore, data will also be stored on a case report form (Appendix). These will be securely filed in the Surgical Research Fellows' office in Scarborough Hospital. This office is protected by a coded lock and general hospital security services. Data will be stored for a period of five years.

8. COSTS

This study has no resource implications for the Trust. All the interventions and monitoring are already part of standard care for patients receiving thoracic epidurals and general anaesthesia. The use of Doppler ultrasound probes is not routine for this purpose however they are available for use within the Trust and no further monitoring equipment need be purchased for the purposes of these studies.

9. REFERENCES

1 Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for Postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD001893. DOI: 10.1002/14651858.CD001893

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4 Levy BF, Tilney HS, Dowson HM, Rockall TA. A systematic review of Postoperative analgesia following laparoscopic colorectal surgery. *Colorectal Dis*.2010;12(1):5-15.

5 Gendall KA, Kennedy RR, Watson AJ, Frizelle FA. The effect of epidural analgesia on Postoperative outcome after colorectal surgery. *Colorectal Dis*.2007;9(7):584-600.

6 Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg.2008;143(10):990-1000.

7 Sielenkämper AW, Eicker K, Van Aken H. Thoracic epidural anaesthesia increases mucosal perfusion in ileum of rats. *Anesthesiology*.2000; 93(3):844-51.

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9 Sala C, García-Granero E, Molina MJ, García JV, Lledo S. Effect of epidural anaesthesia on colorectal anastomosis: a tonometric assessment. *Dis Colon Rectum*.1997;40(8):958-61.

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Appendix B - An investigation into the effects of thoracic epidurals on superior mesenteric artery blood flow. A prospective observational study – Patient information sheet

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
Woodlands Drive
Scarborough
North Yorkshire
YO12 6QL

Tel: 01723 368111

An investigation into the effects of thoracic epidurals on SMA flow.

PATIENT INFORMATION SHEET (Version 1.3, Date 06/09/2011)

Thank you for showing an interest in this study. Firstly we would like to make clear that **you do not have to take part in this study and that choosing not to take part will not affect your care in any way.** Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask us if there is anything that is unclear or if you would like additional information. We will be happy to answer any queries you may have. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Major surgery is associated with pain. To overcome this, patients receive something called 'epidural analgesia'. This involves placing a fine catheter (tube) into the spine and this then numbs the patients from waist downwards. There is a lot of evidence supporting the use of epidurals for patients having bowel surgery, however, epidurals can sometimes cause low blood pressure on the ward after the surgery. This is normally treated by giving fluid into a vein and sometimes by giving a medicine to help raise the blood pressure. The exact effect that this low blood pressure has on the blood supply to the bowel is not fully understood.

The purpose of this study is to find out exactly what effect the epidural has on the blood flow to the bowel, and also what happens when fluids and medicines are given to treat the low blood pressure.

Why have I been chosen?

All patients having a general anaesthetic and an epidural in Scarborough Hospital are being asked to take part in this study.

Do I have to take part?

No, taking part in the research is entirely voluntary. It is up to you to decide whether or not to take part.

If you agree to take part, you will be asked to sign a consent form when you get admitted for your operation. **You can still withdraw from the study at any time after you have consented without giving any reason and this will not affect the standard of care you receive.**

What will happen to me if I take part?

The difference to your care between taking part in the study and not being in the study is that if you take part in the study we will take measurements of the blood flow in the artery. Each measurement will take a few minutes. We will take a measurement of the blood flow before and after starting the epidural, after giving fluid into a vein and after giving a medicine to increase the blood pressure (if needed). We will allow a maximum of 30 minutes for taking these measurements but it should take much less time than this – around 10 or 15 minutes. If measurements take longer than 30 minutes the study will be abandoned.

If you agree to take part, you will have your epidural placed as planned and have a general anaesthetic as planned, the only difference from your normal care will be that the local anaesthetic drug used in the epidural will not be started straight away.

Once you are asleep you will have standard monitoring of your heart rate, blood pressure and a special tube placed in your gullet which measures how well your heart is pumping. This is used as standard in major surgery and is only a temporary thing whilst you are sleeping.

Before you go on to have your surgery, and once you are asleep, we will take some measurements using a Doppler probe (a type of ultrasound probe similar to what pregnant women have). The probe will be put on your tummy, with some cold jelly, and used to scan of one of the blood vessels which supply the gut, to measure the blood flow.

The local anaesthetic medicine in the epidural will then be given which normally causes the blood pressure to fall. This will be closely monitored (and happens normally with an epidural). Once it has fallen, another measurement of the blood flow to the gut will be taken and then you will be given fluid into a vein to help bring the blood pressure back up. Again, this is a normal part of your care it is just that we are measuring what happens when this happens.

Sometimes giving fluid is not quite enough to bring the blood pressure back to what is was before, when this happens it is normal to give some medicine to help. We will take one set of measurements before this medicine is given and a further one after it has worked.

Once these measurements have been taken the study will end and your operation will continue as planned.

What are the possible disadvantages and risks of taking part?

Taking the measurements will make the time you spend asleep a little longer. **This will be discussed with your surgeon and anaesthetist before hand and if they have any concerns will not include you in our study. We have limited this extra time to 30 minutes. If measurements take longer than 30 minutes the study will be abandoned.**

Our Consultant Anaesthetist has advised that this is safe for patients who are less than ASA 4. This is a score of your general health and fitness and if you are less than ASA 4 then you may have some health problems but they are not considered too serious. ASA 4 means that a patient has serious health problems which are thought to constantly put their life at some risk. If this is thought to apply to you then we will not include you in the study, or indeed approach you for the study.

What are the possible benefits of taking part?

The study will not directly help you, but the information we get might help improve the way we look after people having surgery and epidurals in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researcher (Miss Eleanor Richards or Mr. Irfan Kabir), or your consultant, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital's PALS service (01723 342434).

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Scarborough and North East Yorkshire Healthcare NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept absolutely confidential. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised people from within this Trust or by the Research & Development Department that monitors research within this Trust, to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen to the results of the research study?

We intend to publish the results of the research in peer-reviewed medical journals. You will not be identified in any of these publications.

Who is organising and funding the research?

The Sponsor of this research is Scarborough and North East Yorkshire Healthcare NHS Trust. The Combined Gastroenterology Research Fund is providing the funding. The doctors involved in this research are not being paid anything extra for including and looking after you in the study.

Who has reviewed the study?

This study was reviewed by, and given a favourable ethical opinion for conduct in the NHS, by an appropriate Research Ethics Committee. It has been given Trust research governance approval by the Scarborough Area Research & Development Committee.

Contact Details:

If you have any questions, or would like to speak to a member of the research team, please feel free to contact:

Miss. Eleanor Rhiannon Richards/ Mr Irfan Kabir

Surgical Research Fellows

Scarborough Hospital

Tel: 01723368111 Ext 5324

Appendix C - An investigation into the effects of thoracic epidurals on superior mesenteric artery blood flow. A prospective observational study – Consent form

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
Woodlands Drive
Scarborough
North Yorkshire
YO12 6QL

Tel: 01723 368111

PATIENT CONSENT FORM

(Version 1.1 Date 03/06/2011)

Title of Project: **An investigation into the effects of thoracic epidurals on SMA flow.**

1. I confirm that I have read and understand the information sheet dated ..... for the above study and have had the opportunity to ask questions. ☐

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

3. I understand that sections of any of my medical notes may be looked at by responsible individuals within the Trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my notes. ☐

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

_____	_____	_____
Name of Patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Appendix D - An investigation into the effects of thoracic epidurals on inferior mesenteric artery blood flow. A prospective observational study - Study Protocol

An investigation into the effects of thoracic epidurals on inferior mesenteric artery blood flow.

A prospective observational study.

Protocol

Version 1.1
Date 3/6/11

Authors: Miss E Richards, Prof J Macfie, Dr I Tring (Consultant Anaesthetist)

Principle Investigator: Prof John MacFie MD FRCS

Research Fellows: Miss. Eleanor Rhiannon Richards BM, MRCS
Mr. Irfan Kabir MBBS, MRCS

Combined Gastroenterology Research Unit

Scarborough Hospital

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10. INTRODUCTION

Thoracic epidurals are widely used in colorectal surgery for the provision of Postoperative pain control. Their use is advocated by existing enhanced recovery protocols and has a substantial evidence base[1-6]. However, there is extensive circumstantial evidence that epidurals are associated with hypotension in the Postoperative period. The effects of such epidural mediated hypotension on the splanchnic circulation are not fully understood. This is clearly an area of great relevance in the field of colorectal surgery due to the potential consequences of impaired colorectal anastomotic perfusion in terms of the high morbidity and mortality associated with an anastomotic leak.

The effect of thoracic epidural anaesthesia (TEA) on intestinal perfusion is not fully understood. In animal models TEA has been shown to increase gut mucosal perfusion[7,8]. However, epidural anaesthesia with bupivacaine has been shown to cause a significant decrease in the oxygen-perfusion state of colorectal anastomosis in humans, although this was not associated with anastomotic or other complications[9]. Most studies into the effect of TEA on splanchnic blood flow in patients have utilised indirect measurements such as tonometry. *Gould et al* performed an intraoperative study of 15 patients in which they directly measured inferior mesenteric artery flow and colonic serosal red cell flux. They found that the measured reduction in colonic blood flow caused by epidural block did not respond to an increase in cardiac output with fluid resuscitation, but required the use of a vasopressor to restore blood flow[10].

Gould et al's findings raise significant concerns about current practice. The trend towards goal directed fluid therapy using oesophageal Doppler measurements of

cardiac output in colorectal patients is called into question by the existence of new evidence that cardiac output may not correspond to colonic blood flow in the presence of TEA. This is a particular area of concern in colorectal patients with an anastomosis. Recent literature suggests that restrictive fluid regimes may reduce morbidity after colorectal resection[11]. Fluid challenges in patients with TEA induced hypotension may not only be ineffective in restoring gut blood flow but may also place them at risk of potential fluid overload with its associated morbidity.

There is a definite need for further studies to investigate the effects of TEA on splanchnic flow and also the role of intravenous fluids and vasoconstrictors in mitigating such effects. We have therefore devised the following study to assess the effects of TEA on inferior mesenteric artery (IMA) flow.

11. HYPOTHESIS

We hypothesise that a bolus of local anaesthetic given via an epidural catheter will mediate a decrease in IMA flow which will not be completely restored by giving oesophageal Doppler directed fluid therapy but will necessitate the use of vasoconstrictors.

12. AIMS

To assess the effects of thoracic epidural on IMA flow and the adequacy of goal directed fluid therapy and vasoconstrictors in ameliorating such affects

13. PATIENTS, MATERIALS AND METHODS

13.1. Study Design

A prospective observational study of patients undergoing left hemicolectomy receiving thoracic epidural anaesthesia.

13.2. Inclusion Criteria:

Patients undergoing left hemicolectomy receiving thoracic epidurals.

13.3. Exclusion Criteria

Pregnant females.

Patients under 18 years of age.

Patients unable to give informed consent.

Patients in whom prolongation of anaesthesia is deemed unsafe.

13.4. Methodology

13.4.1. Recruitment

Patients on the waiting list for left hemicolectomy will be identified in outpatient clinics and at pre-assessment. They will be seen in the pre-assessment clinic and informed about the existence of the trial. If they are interested they will be given an information leaflet. Once they have had a chance to consider this they will be consented and recruited to the study.

13.4.2. Epidural catheter

All patients will receive a thoracic epidural catheter at T8-T11 in the anaesthetic room, however local anaesthetic will not be given at this time.

13.4.3. Anaesthetic protocol

Anaesthesia will be induced and maintained following a standard protocol; propofol, fentanyl, atracurium for induction, and ventilation, oxygen, air and sevoflurane for maintenance.

13.4.4. Monitoring

Patients will be monitored with an oesophageal Doppler and other standard anaesthetic monitoring equipment. Measurements of cardiac output, systolic and diastolic blood pressure and mean arterial pressure will be measured throughout the procedure.

13.4.5. Exposure of the IMA

The operation will proceed as planned and the IMA will be dissected out. Once dissected out baseline measurements will be taken using a vascular intraoperative Doppler probe.

13.4.6. Bolus of local anaesthetic via epidural:

The epidural will then be started and a bolus of 0.5mg/kg (12-16ml) of 0.25% bupivacaine given via the epidural catheter. Arterial pressure will then be allowed to fall to a mean arterial pressure (MAP) of 60. Further measurements of IMA flow will be taken in conjunction with other observations including cardiac output.

13.4.7. Oesophageal Doppler guided fluid resuscitation:

Oesophageal Doppler guided fluid resuscitation with 6% Volulyte will then take place to restore cardiac output to baseline levels. A further reading of IMA flow will then be taken.

13.4.8. Administration of vasoconstrictors:

If the MAP is not back to baseline levels then up to three 0.5mg bolus doses of metaraminol will be given over a 6-9 minute period to return the mean arterial pressure to the pre-epidural level. A final set of measurements including IMA flow will then be taken. The operation will then proceed as usual.

14. SAMPLE SIZE AND STATISTICAL ANALYSIS

As these are small observational studies no power calculation has been performed. We aim to recruit 15 patients.

Data will be analysed by means of a commercially available statistics package (SPSS v 11.5). A p-value of less than 0.05 will be taken to signify statistical significance. Categorical data will be analysed using the chi squared test or Fishers exact test, as appropriate. Data which are not normally distributed will be analysed using the non-parametric tests, Mann Whitney U or Wilcoxon as appropriate.

15. ETHICS

Approval will be sought from an ethical committee. Application will be made using the IRAS (Integrated Research Application System) website. The study will also be registered on the national register for randomised clinical trials.

16. DATA STORAGE

Electronic data will be stored on a personal computer in the Research Fellows' office in Scarborough Hospital. This is password protected, and part of the hospital

system. It is protected both by anti-virus and firewall software, as with all trust computers. Only the named investigators will have access to patients' data. Furthermore, data will also be stored on a case report form (Appendix). These will be securely filed in the Surgical Research Fellows' office in Scarborough Hospital. This office is protected by a coded lock and general hospital security services. Data will be stored for a period of five years.

17. COSTS

This study has no resource implications for the Trust. All the interventions and monitoring are already part of standard care for patients receiving thoracic epidurals and general anaesthesia. The use of Doppler ultrasound probes is not routine for this purpose however they are available for use within the Trust and no further monitoring equipment need be purchased for the purposes of these studies.

18. REFERENCES

12 Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for Postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD001893. DOI: 10.1002/14651858.CD001893

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Appendix E - An investigation into the effects of thoracic epidurals on inferior mesenteric artery blood flow. A prospective observational study – Patient information sheet

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
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Tel: 01723 368111

An investigation into the effects of thoracic epidurals on IMA flow.

PATIENT INFORMATION SHEET (Version 1.3, Date 06/09/2011)

Thank you for showing an interest in this study. Firstly we would like to make clear that **you do not have to take part in this study and that choosing not to take part will not affect your care in any way.** Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask us if there is anything that is unclear or if you would like additional information. We will be happy to answer any queries you may have. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Major surgery is associated with pain. To overcome this, patients receive something called 'epidural analgesia'. This involves placing a fine catheter (tube) into the spine and this then numbs the patients from waist downwards. There is a lot of evidence supporting the use of epidurals for patients having bowel surgery, however, epidurals can sometimes cause low blood pressure on the ward after the surgery. This is normally treated by giving fluid into a vein and sometimes by giving a medicine to help raise the blood pressure. The exact effect that this low blood pressure has on the blood supply to the bowel is not fully understood.

The purpose of this study is to find out exactly what effect the epidural has on the blood flow to the bowel, and also what happens when fluids and medicines are given to treat the low blood pressure.

Why have I been chosen?

All patients having a left hemicolectomy (surgery to remove part of the left side of their large bowel) in Scarborough Hospital are being asked to take part in this study.

Do I have to take part?

No, taking part in the research is entirely voluntary. It is up to you to decide whether or not to take part.

If you agree to take part, you will be asked to sign a consent form when you get admitted for your operation. **You can still withdraw from the study at any time after you have consented without giving any reason and this will not affect the standard of care you receive.**

What will happen to me if I take part?

The difference to your care between taking part in the study and not being in the study is that if you take part in the study we will take measurements of the blood flow in the artery. Each measurement will take a few minutes. We will take a measurement of the blood flow before and after starting the epidural, after giving fluid into a vein and after giving a medicine to increase the blood pressure (if needed). We will allow a maximum of 30 minutes for taking these measurements but it should take much less time than this – around 10 or 15 minutes. If measurements take longer than 30 minutes the study will be abandoned.

If you agree to take part, you will have your epidural placed as planned and have a general anaesthetic as planned, the only difference from your normal care will be that the local anaesthetic drug used in the epidural will not be started straight away.

Once you are asleep you will have standard monitoring of your heart rate, blood pressure and a special tube placed in your gullet which measures how well your heart is pumping. This is used as standard in major surgery and is only a temporary thing whilst you are sleeping.

Your operation will proceed as planned up until the point where we need to tie off and divide the blood vessels of that part of the bowel. Before we do this we will take a measurement of the blood flow in the blood vessel supplying that bit of bowel with a special type of ultrasound probe (similar to what pregnant women have) that is placed directly on the blood vessel.

The local anaesthetic medicine in the epidural will then be given which normally causes the blood pressure to fall. This will be closely monitored (and happens normally with an epidural). Once it has fallen, another measurement of the blood flow to the bowel will be taken and then you will be given fluid into a vein to help bring the blood pressure back up. Again, this is a normal part of your care it is just that we are measuring what happens when this happens.

Sometimes giving fluid is not quite enough to bring the blood pressure back to what is was to start with, when this happens it is normal to give some medicine to help. We will take one set of measurements before this medicine is given and a further one after it has worked.

Once these measurements have been taken the study will end and your operation will continue as planned.

What are the possible disadvantages and risks of taking part?

Taking the measurements will make the time you spend asleep a little longer. To make sure this is safe for you we will discuss this with your surgeon and anaesthetist before hand and if they have any concerns will not include you in our study. **This will be discussed with your surgeon and anaesthetist before hand and if they have any concerns will not include you in our study. We have limited this extra time to 30 minutes. If measurements take longer than 30 minutes the study will be abandoned.**

Our Consultant Anaesthetist has advised that this is safe for patients who are less than ASA 4. This is a score of your general health and fitness and if you are less than ASA 4 then you may have some health problems but they are not considered too serious. ASA 4 means that a patient has serious health problems which are thought to constantly put their life at some risk. If this is thought to apply to you then we will not include you in the study, or indeed approach you for the study.

What are the possible benefits of taking part?

The study will not directly help you, but the information we get might help improve the way we look after people having surgery and epidurals in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researcher (Miss Eleanor Richards or Mr. Irfan Kabir), or your consultant, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital's PALS service (01723 342434).

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Scarborough and North East Yorkshire Healthcare NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept absolutely confidential. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised people from within this Trust or by the Research & Development Department that monitors research within this Trust, to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen to the results of the research study?

We intend to publish the results of the research in peer-reviewed medical journals. You will not be identified in any of these publications.

Who is organising and funding the research?

The Sponsor of this research is Scarborough and North East Yorkshire Healthcare NHS Trust. The Combined Gastroenterology Research Fund is providing the funding. The doctors involved in this research are not being paid anything extra for including and looking after you in the study.

Who has reviewed the study?

This study was reviewed by, and given a favourable ethical opinion for conduct in the NHS, by an appropriate Research Ethics Committee. It has been given Trust research governance approval by the Scarborough Area Research & Development Committee.

Contact Details:

If you have any questions, or would like to speak to a member of the research team, please feel free to contact:

Miss. Eleanor Rhiannon Richards/ Mr Irfan Kabir

Surgical Research Fellows

Scarborough Hospital

Tel: 01723368111 Ext 5324

Appendix F - An investigation into the effects of thoracic epidurals on inferior mesenteric artery blood flow. A prospective observational study –Consent form

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
Woodlands Drive
Scarborough
North Yorkshire
YO12 6QL

Tel: 01723 368111

PATIENT CONSENT FORM

(Version 1.1 Date 03/06/2011)

Title of Project: **An investigation into the effects of thoracic epidurals on IMA flow.**

1. I confirm that I have read and understand the information sheet dated ..... for the above study and have had the opportunity to ask questions. ☐

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

3. I understand that sections of any of my medical notes may be looked at by responsible individuals within the Trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my notes. ☐

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

_____	_____	_____
Name of Patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Appendix G – Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol: A randomised controlled trial: Protocol

Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol

A randomised controlled trial

Protocol

Version 1.2
Date 3/9/10

Principle Investigator: Prof John MacFie MD FRCS

Research Fellows: Miss. Eleanor Rhiannon Richards BM, MRCS
Mr. Irfan Kabir MBBS, MRCS

Combined Gastroenterology Research Unit
Scarborough Hospital
YO12 6QL

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1. INTRODUCTION

Despite advances in surgical and anaesthetic techniques, major surgery is still associated with undesirable side effects such as pain, cardiopulmonary and infective complications and prolonged ileus. Enhanced Recovery after Surgery (ERAS) protocols comprise of simple measures such as shortened preoperative fasting along with carbohydrate loading, use of transverse incisions wherever possible, use of epidural analgesia and avoidance of opiate based analgesics [1-5]. Good evidence now exists to show that significant reductions of hospital stay can be achieved without compromising patient safety. Clearly this has important implications not only for patient well-being but also to health care resources [6].

Epidural analgesia is an important component of ERAS protocols and has been included in most of the published studies. It employs a fine bore catheter which is placed into the lower thoracic epidural space (outer covering of the spinal cord) and through which a combination of local anaesthetic and a short acting opiate is infused. This provides ‘regional analgesia’ by blocking the spinal nerves which supply the abdominal wall and lower limbs [7-8]. However, epidural analgesia has a number of disadvantages. In addition to blocking the pain transmitting afferents, epidurals also block the sympathetic efferents which can result in hypotension intractable to intravenous fluids, often necessitating inotropic support on the high dependency unit (HDU) [9-11]. The placement of epidural catheters requires a considerable amount of time and despite this they carry a significant failure rate [12-14]. In addition, their placement is contraindicated within 12 hours of thromboprophylaxis with low molecular weight heparin. Lastly, epidural catheters can impair sensation in the lower limbs, and this, combined with the cumbersome equipment they require can render Postoperative mobilisation difficult. Major

complications associated with the placement of epidural catheters include epidural abscess, meningitis and epidural haematoma [15]. Whilst these are rare they carry significant morbidity for those individuals affected.

A relatively new modality for the provision of Postoperative analgesia after major abdominal surgery is the continuous infusion of local anaesthetic directly into the wound. This is done through purpose built multi-holed catheter (PainBuster®) which is placed into the wound by the surgeon at the end of the operation. This provides selective local analgesia and avoids the disadvantages associated with epidural catheters. Its safety and efficacy have been demonstrated in a number of randomised trials both within and outside of colorectal surgery [16-20]. However, these have shown only modest improvement in terms of length of stay. No previous randomised trial has investigated the role of such wound catheters in conjunction with an ERAS programme. Their inclusion within an ERAS programme, instead of epidurals, should provide a number of potential advantages. The PainBuster® apparatus comprises of a simple catheter connected to a self administering elastomeric balloon pump. Since it does not cause hypotension, the requirement of Postoperative intravenous fluid should reduce. These features should facilitate early removal of urinary catheters, reduce nursing needs, facilitate mobilisation and reduce intravenous fluid associated complications such as fluid overload and electrolyte imbalance. Cumulatively, all these advantages should accelerate the Postoperative recovery.

2. HYPOTHESIS

The hypothesis of this study is that continuous infusion of local anaesthetic directly into the wound (PainBuster®) can replace epidural analgesia in the setting of an ERAS programme.

3. PATIENTS, MATERIALS, AND METHODS

3.1 Study Design

This will be a randomised controlled study. As PainBuster® and epidural catheters require different apparatus, blinding will not be possible. However, to reduce bias, pre-defined criteria will be used to assess the primary outcome and all secondary outcomes.

3.2 Inclusion criteria

All patients who are undergoing either laparoscopic or open colorectal resection will be considered eligible for the study.

3.3 Exclusion Criteria

Patients under 18 years of age

pregnant females

Patients undergoing an abdomino-perineal resection

Patients unable to understand English

3.4 Perioperative management (The Scarborough Optimization Package)

All patients will be managed using the principles of ERAS using the ten point 'Scarborough Optimization package' which has been developed in this institute over the last decade. Briefly, this comprises:

3.4.1 Preoperative assessment

All patients will undergo a thorough preoperative assessment by a pre-assessment nurse and a research fellow. At this stage (approximately 2 weeks before surgery) the details of the protocol will also be discussed and patients will be invited to participate in the study.

3.4.2 Patient Information

All patients will be offered written information about their care and the type of operation they are about to undergo. In addition, they will be offered written information about the research project, should they so wish (see appendix 1).

3.4.3 Analgesia

Opiate based analgesia will be avoided in both groups and reserved only for breakthrough pain. There is ample evidence in the literature demonstrating that both adequate analgesia and the avoidance of opiates, pre and postoperatively are associated with amelioration of the catabolic response to trauma and surgery.

3.4.4 Overnight fasting and preoperative carbohydrate loading

The administration of preoperative carbohydrate has been shown to reduce Postoperative insulin resistance, which is common after surgery and may be associated with a prolonged hospital stay. Patients are allowed clear fluids until three hours before the operation. The night before surgery patients receive a 200ml “Polycal” feed at 10 p.m. Another 200ml “Polycal” liquid feed is given three hours prior to the scheduled operation.

3.4.5 High concentration of inspired Oxygen

Patients will receive 80% inspired Oxygen during the anaesthetic and oxygen administration will continue until the patient mobilises. Oxygen will be administered via mask or nasal cannula at 2L/minute overnight.

3.4.6 Transverse incision

Transverse incisions will be used when deemed appropriate by the consultant operating surgeon. These are thought to be less painful and are a part of our ERAS package.

3.4.7 Early reintroduction of diet and fluid

All patients are encouraged to eat and drink *ad libitum* after surgery.

3.4.8 Encouraged mobilisation

All patients are encouraged to mobilise in a standard manner. This involves sitting out in chair the day after surgery and mobilising with the aid of a physiotherapist the day after that.

3.4.9 Postoperative Analgesia

Non-opiate analgesia is administered routinely with opiates analgesia reserved only for breakthrough pain where possible.

4. END POINTS

The primary end point for this study has been extensively debated and discussed. As we are seeking to establish a possible alternative to epidural anaesthesia then it could be reasonably argued that pain control should be our primary end point. The dilemma with this is that assessment of pain control is difficult. Invariably it necessitates the use of visual analogue scales which are subjective and difficult to validate. An alternative surrogate measure of pain control is opiate usage. We will record this but deemed it inappropriate as a primary end point because of difficulties with internal validity of usage on different wards or with different staff. An alternative would be episodes of hypotension. We decided against this, after

discussion with anaesthetic colleagues, because episodes of hypotension will inevitably occur with epidurals (this well known) and therefore we felt this would potentially prejudice interpretation of results against epidurals.

Fluid replacement after colorectal surgery is increasingly being recognised as being an important factor in recovery and more specifically the return of gut function [20-21]. However, this was felt to be unsatisfactory as a primary endpoint because of concerns regarding the difficulties with managing this scientifically. It has therefore been decided to measure length of hospital stay as our primary endpoint. As decisions for discharge may be subjective we have developed specific discharge criteria for the purposes of this study. Where patients are fit for discharge and remain an inpatient for purely social reasons this will be recorded.

4.1 Primary end point: The primary end point to which this study is powered is length of hospital stay or time to fitness for discharge in those cases where patients remain as inpatients for purely social reasons. As this may be subjective, set discharge criteria have been defined. Patients will be assessed against these criteria on each Postoperative day. In those cases where patients remain an inpatient for purely social reason this will be documented.

Discharge Criteria:

1. **Good pain control with oral analgesia.**
2. **Tolerating solid food without nausea and vomiting.**
3. **No IV fluid or medication.**

4. **Independently mobile and self caring or at the same level as prior to admission.**

5. **Stable observations and blood biochemistry.**

6. **No other concerns or complications preventing discharge.**

7. **All of the above and willing to go home.**

4.2 Secondary end points: The secondary end points are:

4.2.1 Postoperative complications

All complications in the Postoperative period will be recorded. Particular emphasis will be given to:

- Wound infection: this will be defined as clinical evidence of purulent discharge and erythema accompanied by microbiological (culture of microorganisms) and haematological evidence (raised white cell count)

- Cardiac failure: This will be defined as the presence of clinical signs of fluid overload accompanied by radiological features on a chest X-Ray.

- Complications related to epidural/spinal

- Adequacy of deep vein thrombosis prophylaxis

4.2.2 Episodes of hypotension in the Postoperative period

This will be defined as a systolic blood pressure of less than 90 mmHg.

4.2.3 Postoperative pain

This will be assessed objectively using the visual analogue scale for pain. Measurements will be taken twice a day for as long as

the epidural catheter or PainBuster® is in situ. Pain scores will be measured at rest and on coughing.

4.2.4 Amount of Postoperative IV fluid administered

This will be documented on each Postoperative day.

4.2.5 Body composition

Body composition (Fat Mass, Fat Free Mass, Extracellular Fluid Volume, Intracellular Fluid Volume, and Total Body Water) will be determined using a bioelectrical impedence analysis (BIA) machine, specifically the “Bodystat” machine. Tests will be performed daily until the epidural or PainBuster® has been removed.

4.2.6 Postoperative analgesic requirement

The total quantity and type (opiate or non-opiate) of all analgesics administered during the period when epidurals or PainBuster® was in situ will be recorded.

4.2.7 Postoperative stress response

This will be assessed using

SIRS criteria (see appendix)

C reactive protein

Indirect calorimetry on alternate days at a fixed time.

4.2.8 Anaesthetic time required

The time taken in minutes for insertion of epidural or wound catheter will be recorded in each group.

4.2.9 Postoperative mobility

Postoperative mobility will be assessed as time until sit to stand aided and unaided, duration of time spent out of bed on each Postoperative day and maximum walking distance with assistance on a daily basis. In addition, assessment of mobilisation will be carried out by the physiotherapists who will record this in patient notes.

All patients will be given pedometer to wear which will count the number of steps taken. Pedometer readings will be taken twice a day. Pedometers have been previously validated as an objective measurement of mobility.

4.2.10 Day of return of gut function

Return of gut function will be defined by the tolerance of >/= 80% of the prescribed nutritional requirement. This will be assessed by a dietician.

5. SAMPLE SIZE AND Statistical analysis

This study is powered to detect a difference in length of stay of 2.8 Postoperative days. Our current data (unpublished) shows that the mean Postoperative stay in elective patients undergoing colorectal resections is 6.8 days (SD 4.01 days). We anticipate that this will reduce to 4 days in the intervention group. We will need a

sample size of 60 patients (30 in each group) to detect this drop (power 80 % and significance of 0.05).

Data will be analysed on an intention-to-treat basis. A power calculation will be performed to identify the number of patients required in each experimental group to provide statistical significance. Data will be analysed by means of a commercially available statistics package (SPSS v 19). A p-value of less than 0.05 will be taken to signify statistical significance. Categorical data will be analysed using the chi squared test or Fishers exact test, as appropriate. Data which are not normally distributed will be analysed using the non-parametric tests, Mann Whitney U or Wilkoxon as appropriate.

6. Ethics

Approval will be sought from an ethical committee. Application will be made using the IRAS (Integrated Research Application System) website. The study will also be registered on the national register for randomised clinical trials.

7. Data STORAGE

Electronic data will be stored on a personal computer in the Research Fellows' office in Scarborough Hospital. This is password protected, and part of the hospital system. It is protected both by anti-virus and firewall software, as with all trust computers. Only the named investigators will have access to patients' data.

Furthermore, data will also be stored on a case report form (Appendix). These will be securely filed in the Surgical Research Fellows' office in Scarborough Hospital. This office is protected by a coded lock and general hospital security services. Data will be stored.

9. COSTS

The study has no cost implications for the Trust. Both epidurals and PainBuster® are used in the Trust. The Bodystat and Indirect calorimetry machines which will be used to measure the body composition and Postoperative metabolic response

respectively have already been purchased by the Scarborough Combined Gastroenterology Fund (registered charity) and have been used extensively. There are no additional blood tests required for the purpose of this study. Pedometers will be purchased for the purpose of this study by the Scarborough Combined Gastroenterology Fund.

Appendix H - Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol: A randomised controlled trial - Patient information sheet

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
Woodlands Drive
Scarborough
North Yorkshire
YO12 6QL

Tel: 01723 368111

Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol: A randomised controlled trial

PATIENT INFORMATION SHEET (Version 1.1, Date 03/09/2010)

Thank you for showing an interest in this study. Before you decide whether or not you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask us if there is anything that is unclear or if you would like additional information. We will be happy to answer any queries you may have. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Major surgery is associated with pain. To overcome this, patients receive something called 'epidural analgesia'. This involves placing a fine catheter (tube) into the spine and this then numbs the patients from waist downwards. However this has a number of disadvantages such as low blood pressure, reduced mobility and requirements of large volumes of intravenous fluids. All this can lead to complications and delay recovery.

An alternative to this method of providing pain relief is to continuously infiltrate the surgical wound itself with local anaesthetic. This is done using a purpose built catheter (PainBuster®) and has already been shown to be safe in a number of scientific studies.

The purpose of this study is to find out whether the use of PainBuster® can replace epidurals and therefore avoid the complications associated with epidurals.

We want to find out whether or not using this device means people need to stay in hospital for less time after surgery.

Why have I been chosen?

All patients having elective colorectal (bowel) surgery in Scarborough Hospital are being asked to take part in this study.

Do I have to take part?

Taking part in the research is entirely voluntary. It is up to you to decide whether or not to take part.

If you agree to take part, you will be asked to sign a consent form when you get admitted for your operation. You can still withdraw from the study after you have consented without giving any reason and this will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part, you will be allocated randomly (like the toss of a coin) to one of two groups. One group will receive pain relief using the epidural catheter while the other will receive pain relief using the PainBuster® system. The remaining care that patients receive in both the groups will be exactly identical. Both groups will be given additional pain relief as may be required by them so that they are not in any pain.

For the purpose of this research we would require a few extra things from you. Firstly, you will be asked to fill in your pain level on a pain scoring chart. Secondly we will assess your body composition (amount of fluid, fat and protein) before and after surgery. This involves connecting the patient to a special equipment using wires (as when we take a tracing of your heart). The test takes less than a minute to perform. Thirdly, we will be providing you with pedometers to wear. These are small plastic devices worn on your clothing which measure the number of steps one takes and gives us an accurate assessment of how much you are walking.

What are the possible disadvantages and risks of taking part?

We do not feel that there are any disadvantages or risks to taking part in this study. PainBuster® has already been shown to be safe in a number of studies and epidurals are already in widespread use. If postoperative pain relief is not adequate in either of the groups they will receive extra painkillers as necessary.

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information we get might help improve the treatment of people having colorectal surgery.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researcher (Miss Eleanor Richards or Mr. Irfan Kabir), or your consultant, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital's PALS service (01723 342434).

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Scarborough and North East Yorkshire Healthcare NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept absolutely confidential. If you join the study, some parts of your medical records and the data collected for the study may be looked at by authorised people from within this Trust or by the Research & Development Department that monitors research within this Trust, to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen to the results of the research study?

We intend to publish the results of the research in peer-reviewed medical journals. You will not be identified in any of these publications.

Who is organising and funding the research?

The Sponsor of this research is Scarborough and North East Yorkshire Healthcare NHS Trust. The Combined Gastroenterology Research Fund is providing the funding. The doctors involved in this research are not being paid anything extra for including and looking after you in the study.

Who has reviewed the study?

This study was reviewed by, and given a favourable ethical opinion for conduct in the NHS, by an appropriate Research Ethics Committee. It has been given Trust research governance approval by the Scarborough Area Research & Development Committee.

Contact Details:

If you have any questions, or would like to speak to a member of the research team, please feel free to contact:

Miss. Eleanor Rhiannon Richards/ Mr Irfan Kabir

Surgical Research Fellows

Scarborough Hospital

Tel: 01723368111 Ext 5324

Appendix I - Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol: A randomised controlled trial: Data collection sheet

Scarborough and North East Yorkshire Healthcare NHS
NHS Trust

Scarborough Hospital
Woodlands Drive
Scarborough
North Yorkshire
YO12 6QL

Tel: 01723 368111

Continuous wound infiltration with local anaesthetic *vs.* epidurals in an enhanced recovery protocol: A randomised controlled trial

Patient record form (Version 1.1, Date 03/09/2010)

Sex:

Diagnosis:

Staging: T N M Duke's:

Procedure: Stoma: Y/N

Date of Admission: Ward: Consultant:

Date of surgery: Date of discharge:

Anaesthetic time (time for insertion of epidural / PainBuster):

Type of incision: Transverse/ Midline/ Paramedian/ Upper midline/Lower midline

Length of incision:

ASA grade:

POSSUM SCORE (Version 1.1, Date 03/09/2010)

	Score			
	1	2	3	8
Age (years)	≥60	61-70	≥71	
Cardiac signs	Normal	Drugs	Oedema/Warfarin/Cardiomegally	JVP Cardiomegally
ECG	Normal		AF Controlled Rate 60-90	MI Abnormal ECG
Respiratory	Normal	SOBOE Mild COPD	SOB stairs Mod COPD	SOB rest RR 30 Fibrosis
Blood pressure (systolic)	110-130	100-109 131-170	90-99 >170	<90
Heart rate	50-80	81-100 40-49	101-120	≥121 <40
Glasgow coma score	15	12-14	9-11	≤8
Haemoglobin (g/100ml)	13-16	11.5-12.9 16-17	10.0-11.4 17.1-18	<10 >18
White cell count ($x10^{12}$/I)	4.1-10	10.1-20.0 3.1-4	>20 <3	
Urea (mmol/l)	<7.6	7.6-10	10.1-15	>15
Sodium (mmol/l)	>135	131-135	126-130	<126
Potassium (mmol/l)	3.5-5.0	3.2-3.4 5.1-5.3	2.9-3.1 5.4-5.9	≤2.8 ≥6.0

	Score			
	1	2	4	8
Case	Minor	Moderate	Major	Major+
Previous ops	0 or 1		2	>2
Blood loss (surg)	≤100	101-500	501-999	>1000
Peritoneal soiling	None	Minor (serous)	Local pus	Free pus/ Blood/Bowel contents
Malignancy	None	Primary	Nodal mets	Distant mets
Timing	Electi ve		<24 > 2hrs Emergency resus	< 2hrs to theatre No resus

Non opioid analgesia

	Intra-op	**dose in mg / Postoperative day**										
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Paracetamol												
Ibuprofen												
Diclofenac												

Opiate analgesia

Opiates	**Intra-op**	**dose in mg / Postoperative day**										
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Tramadol												
Morphine												
Codeine												

Criteria for Discharge

Discharge Criteria	Postoperative day											
	1	2	3	4	5	6	7	8	9	10	11	12
Oral Analgesia												
Solid diet no N&V												
No IVs												
Mobile/self caring*												
Stable obs / Bloods												
No concerns / complications												
Accepting of discharge												

* or back to preoperative level

Metabolic response

Blood tests	Pre –op	Postoperative day									
		1	2	3	4	5	6	7	8	9	10	11
CRP												
WBC												
Neutrophils												
Albumin												
Globulin												
Haemoglobin												

SIRS criterion

Temperature	>38° C or <36°C
Heart rate	>90
Respiratory rate	>20 or $PaCO_2$ <32 mm Hg(4.3)
WBC count	>12K or <4K or >10% immature forms

1 = meeting SIRS criterion; 2 = not meeting SIRS criterion.

	Postoperative day											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Temperature												
Heart rate												
RR/PaCO2												
WBC												

Episodes of hypotension

	Postoperative day											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Hypotension (BP<90 systolic)												

Septic complications

Site	Day	Clinical	Radiological	Haematological	Culture
Intra-abdominal					
Line					
Chest					
Urinary					
Wound					

Gut function YES: 1, NO: 2 * Adequate: 1, Inadequate: 2

	Postoperative day											
	1	2	3	4	5	6	7	8	9	10	11	12
Abdo distension												
Bowels opened												
Flatus												
Diarrhoea												
Vomiting												
Bowel sounds												
*Oral nutrition												

Organ dysfunction

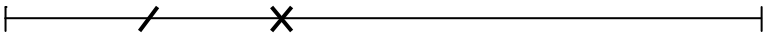
Site	Day	Clinical	Radiological	Haematological
Cardiac				
Hepatic				
Respiratory				
Renal				

Fluid balance

	Postoperative day											
	1	2	3	4	5	6	7	8	9	10	11	12
Crystalloid												
Colloid												
Oral												
Urine												
NG												
Vomit												
Stoma												

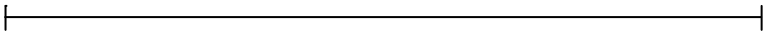
VISUAL ANALOGUE SCALE FOR PAIN

Example: / = at rest X= on coughing



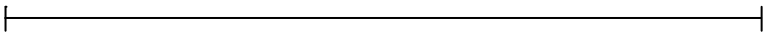
0 = No pain **10 = Worst pain ever experienced**

Recovery:



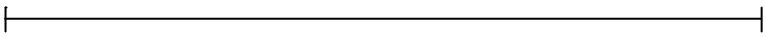
0 = No pain **10 = Worst pain ever Experienced**

Day 0 pm:



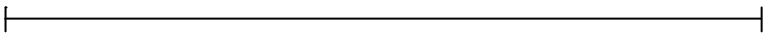
0 = No pain **10 = Worst pain ever Experienced**

Day 1 am



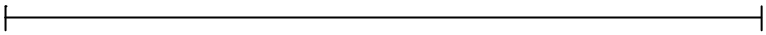
0 = No pain **10 = Worst pain ever experienced**

Day 1 pm



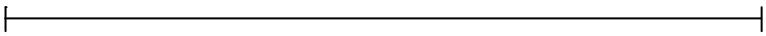
0 = No pain **10 = Worst pain ever experienced**

Day 2 am



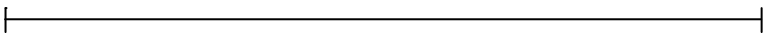
0 = No pain **10 = Worst pain ever experienced**

Day 2 pm



0 = No pain **10 = Worst pain ever experienced**

Day 3 am



0 = No pain **10 = Worst pain ever experienced**

Day 3 pm

0 = No pain **10 = Worst pain ever Experienced**

Day 4 am

0 = No pain **10 = Worst pain ever Experienced**

Day 4 pm

0 = No pain **10 = Worst pain ever experienced**