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Generating Evidence for the Perioperative Care of Patients Undergoing Elective Colorectal Surgery

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Abstract

Background and Aims

The concept of 'Enhanced Recovery After Surgery' (ERAS) pathways was introduced almost a quarter of a century ago, consisting of a series of nine interventions. More recent ERAS pathways have included significantly greater numbers of interventions, some of which have been based on variable quality evidence. The aim of this thesis was to identify interventions which are controversial or where new literature may alter their evidence base, then to systematically evaluate this evidence in order to analyse their efficacy as part of a perioperative multimodal intervention.

Methods

The aims of this thesis were investigated by four meta-analyses conducted according to Cochrane Collaboration methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The topics for these meta-analyses were mechanical bowel preparation (MBP), oral antibiotic (OAB) preparation, goal-directed fluid therapy (GDFT) and intravenous lidocaine (IVL) infusion in the perioperative management of patients undergoing elective colorectal surgery.

Results

The role of MBP versus no bowel preparation in elective colorectal surgery was evaluated in a meta-analysis of 36 studies (21,568 patients). In the most comprehensive analysis performed to date, MBP was not associated with a significant difference in any clinical outcome measure examined and as such should not be routinely administered prior to elective colorectal surgery.

A meta-analysis concerning the role of OAB preparation, both with and without MBP, was conducted including 40 studies (74,714 patients). This demonstrated that combined MBP and OAB was associated with a significant reduction in surgical site infection (SSI), anastomotic leak, 30-day mortality, and development of ileus, with no significant difference seen in *Clostridium difficile* rates versus no preparation. Interestingly, no difference was observed in the incidence of SSI when combined MBP and OAB, and OAB alone were compared.

The role of goal-directed fluid therapy (GDFT) versus conventional fluid management was evaluated in a meta-analysis of 11 RCTs (1113 patients). No benefit was found associated with GDFT in overall morbidity, hospital length of stay (LOS), 30-day mortality, SSI, anastomotic leak, incidence of postoperative ileus, or time to return of gastrointestinal function.

Finally, the administration of perioperative IVL infusion was evaluated in a meta-analysis of 10 RCTs (610 patients). This demonstrated that IVL infusion was associated with a significant reduction in time to defecation, visual analogue scale (VAS) rated pain scores at rest at early time points, VAS score on coughing at 12 hours and hospital LOS. However, no difference was seen in the time to return of flatus, pain at rest at 48 hours, overall morphine consumption, and anastomotic leak or prolonged postoperative ileus rates.

Conclusion

This thesis has provided high-quality evidence on four components which contribute to ERAS pathways in elective colorectal surgery. This thesis has provided evidence suggesting that bowel preparation with either the combination of MBP and OAB, or OAB alone, and

perioperative IVL infusion should be considered as a potential standard of care, whereas MBP alone does not have a place due to its potentially deleterious effects and lack of clinical benefit. GDFT does not appear to have a role in low risk patients undergoing elective colorectal surgery, however further evidence is required in high-risk patient groups. This thesis has demonstrated the beneficial effects of evaluation of single components within a multimodal, complex intervention such as ERAS pathways, such that all included interventions do indeed provide 'aggregation of marginal gains' which culminate to produce a significant clinical benefit to patients.

Declaration

I certify that the work presented in this thesis is the result of original research primarily conducted by myself with the specified guidance and assistance:

- Dual abstract and full text screening as well as data extraction was conducted independently by myself and Miss Hannah Javanmard-Emamghissi for the meta-analyses examining mechanical bowel preparation (Chapter 3), oral antibiotic preparation (Chapter 4) and intravenous lidocaine (Chapter 6).
- Dual abstract and full text screening as well as data extraction was conducted independently by myself and Mr Neil Mathias for the meta-analysis concerning goal-directed fluid therapy (Chapter 5).
- Independent researcher input regarding discrepancies regarding full-text screening and data extraction was provided by Professor Dileep Lobo.
- Colorectal specialist input was provided by Mr Austin Acheson for the oral antibiotic preparation meta-analysis (Chapter 4).

Supervision of this thesis was undertaken by Professor Dileep Lobo.

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Glossary of Abbreviations

ACS	American College of Surgeons
AKI	acute kidney injury
ASA	American Society of Anesthesiologists
ASER	American Society of Enhanced Recovery
CHO	carbohydrate
CI	confidence interval
DVT	deep vein thrombosis
EBM	evidence-based medicine
ERAS	Enhanced Recovery After Surgery
GDFT	goal-directed fluid therapy
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HES	hydroxyethyl starch
KR	hazard ratio
IBD	inflammatory bowel disease
IQR	interquartile range
IVL	intravenous lidocaine
Kg	kilogram
LA	local anaesthetic
LAR	low anterior resection
LOS	length of stay
MBP	mechanical bowel preparation
MD	mean difference
MOOSE	Meta-Analyses and Systematic Review of Observational Studies

NGT	nasogastric tube
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drug
NSQIP	National Surgical Quality Improvement Program
OAB	oral antibiotic
OR	odds ratio
PE	pulmonary embolism
PEG	polyethylene glycol
PONV	postoperative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QL	quadratus lumborum
QUORUM	Quality of Reporting of Meta-Analyses
RCT	randomised controlled trial
RR	risk ratio
SD	standard deviation
SILS	single incision laparoscopic surgery
SSI	surgical site infection
TAP	transversus abdominis plane
TEA	thoracic epidural analgesia
TIVA	total intravenous anaesthesia
TOD	transoesophageal Doppler
VAS	Visual Analogue Scale
VTE	venous thromboembolism
WIC	wound infusion catheter

Publications and Presentations Arising from this Thesis

Publications

1) Rollins KE, Javanmard-Emamghissi H, Lobo DN. Impact of mechanical bowel preparation in elective colorectal surgery: a meta-analysis. World Journal of Gastroenterology (2018); 24(4): 519-536
2) Rollins KE, Javanmard Emamghissi, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: a meta-analysis. Annals of Surgery (2018); Epub ahead of print. Doi: 10.1097/SLA.0000000000003145
3) Rollins KE, Lobo DN. Oral antibiotic preparation in colorectal surgery: is there more to debate? Ann Laparosc Endosc Surg (2019); 4:30
4) Rollins KE, Mathias NC, Lobo DN. Meta-analysis of goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery. BJS Open (2019); Epub ahead of print.

Presentations

1) Rollins KE, Javanmard-Emamghissi H, Scott MJ, Lobo DN. The impact of perioperative lidocaine infusion on postoperative gastrointestinal function in elective colorectal surgery: a meta-analysis of randomised controlled trials. 7th ERAS Society World Congress, Liverpool, UK, May 2019 (Oral *Prize best abstract session)
2) Rollins KE, Mathias NC, Lobo DN. Goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery: a meta-analysis of randomised controlled trials. 7th ERAS Society World Congress, Liverpool, UK, May 2019 (Oral *Prize best abstract session *Best oral presentation)
3) Rollins KE. Oral antibiotics and bowel preparation in colorectal surgery. 7th ERAS Society World Congress, Liverpool, UK, May 2019 (Invited Lecture).
4) Rollins KE, Javanmard-Emamghissi, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: a meta-analysis. Society of Academic and Research Surgery, London, January 2019 (Oral)

5) Rollins KE, Mathias NC, Lobo DN. Goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery: a meta-analysis of randomised controlled trials. Society of Academic and Research Surgery, London, January 2019 (Oral)
6) Rollins KE. Bowel preparation in colorectal surgery. 6th ERAS Society World Congress, Stockholm, Sweden, May 2018 (Invited Lecture).
7) Rollins KE, Javanmard-Emamghissi H, Lobo DN. The role of mechanical bowel preparation in elective colorectal surgery: a meta-analysis. Society of Academic and Research Surgery, Nottingham, January 2018 (Oral)

Chapter 1 - Introduction

1.1 Colorectal Surgery

Colorectal surgery encompasses surgery of the colon, rectum and anus and is performed for a wide range of differing pathologies including colorectal cancer, inflammatory bowel disease (IBD), diverticular disease and perianal conditions. Colorectal resection is a common procedure performed globally, with a frequency of colectomy (removal of all or part of the colon) in the United Kingdom in 2015 of 25,000 (Eurostat, 2019), and in the United States of 302,400 (McDermott et al., 2006).

1.1.1 Morbidity and Mortality

Colorectal surgery is associated with a quoted incidence of morbidity of up to 35% (Alves et al., 2005, Longo et al., 2000, de Silva et al., 2011) and 30-day mortality between 1 and 16.4% (Alves et al., 2005, Longo et al., 2000, Henneman et al., 2013). Those patients who develop a complication following colorectal surgery are known to have an increased risk of mortality, requirement for reoperation (Morris et al., 2007), worsened oncological outcomes (Lu et al., 2016, Mirnezami et al., 2011), increased risk of omission of chemotherapy (Hendren et al., 2010) and poorer quality of life (Marinatou et al., 2014). The most common complications following colorectal resection are wound complications including surgical site infection (SSI), haematoma and dehiscence, other infectious issues including chest and urinary tract infection, anastomotic leak and gastrointestinal motility issues including postoperative ileus and bowel obstruction (Tevis and Kennedy, 2016). There are also a number of medical complications which may occur following colorectal surgery, including acute kidney injury (quoted incidence 10-20%) (Slagelse et al., 2019, Koerner et al., 2019),

thromboembolic events (quoted incidence 2.1%) (Alhassan et al., 2018, Nelson et al., 2015), myocardial infarction (quoted incidence 1 to 1.5%) (Moghadamyeghaneh et al., 2015b) and cerebrovascular accidents (CVA) (quoted incidence 0.5%) (Rajeev-Kumar et al., 2018), which all contribute to the incidence of mortality.

Several studies have sought to identify factors associated with an increased risk of overall complications following colorectal surgery which can be divided into patient and operative factors (Tevis and Kennedy, 2016). Patient factors include increased patient age (Alves et al., 2005, Verweij et al., 2016), comorbidities (Krarup et al., 2015, Tan et al., 2013), body composition measures including sarcopenic obesity (Huang et al., 2015a) and myosteatosis (Margadant et al., 2016) as well as low preoperative serum albumin concentrations (Hu et al., 2015, Alves et al., 2005). Operative variables include increased operative time (Ho et al., 2011), emergency rather than elective surgery (Stornes et al., 2016, de Silva et al., 2011), and intra-operative peritoneal contamination. The two most important surgery-specific postoperative complications relating to colorectal surgery are SSI and anastomotic leak. The incidence of a SSI and anastomotic leak can have a major impact upon overall hospital length of stay (LOS) (Cologne et al., 2016), readmission rates (Bliss et al., 2015) and cost of initial hospital stay (Hammond et al., 2014). Developing an SSI or anastomotic leak is associated with a large economic burden of an estimated £10,000 (Gheorghe et al., 2014) and $24,129 (Hammond et al., 2014) within the primary hospital admission, respectively. Readmission to hospital for an SSI is associated with a median cost of $12,835 in the US (Wick et al., 2011).

A range of strategies have been investigated with the aim of minimising the considerable risk of morbidity and mortality associated with colorectal surgery, such as infection

prevention bundles (Keenan et al., 2014, Tanner et al., 2015), and perioperative care strategies to address some of the potentially reversible risk factors for postoperative complications (Keenan et al., 2015, Reames et al., 2015). This reduction in complications has been one of the stated benefits associated with the application of Enhanced Recovery After Surgery (ERAS) programmes in elective colorectal surgery.

1.2 Enhanced Recovery After Surgery (ERAS) Programmes

1.2.1 Introduction of ERAS Concepts

It is now almost a quarter of a century since Henrik Kehlet and colleagues from Copenhagen proposed a paradigm shift in perioperative care that resulted in a reported two-day inpatient stay for a series of eight elderly patients (median age 78 years, range 71-88 years) undergoing laparoscopic colectomy (Bardram et al., 1995). Their reported approach was to use bundles of care throughout the patient pathway to reduce perioperative stay, morbidity and mortality. Their original bundle of interventions has become known as a fast-track or ERAS protocol (**Table 1.2.1**). It is now thought that this revolution in perioperative care is affected through attenuation of the stress response to surgery, avoiding the nausea, vomiting and ileus frequently seen with traditional care pathways. This original report was followed by a second larger series in which colectomy was completed laparoscopically in 44 of 50 consecutive patients with a median age of 81 years (Bardram et al., 2000). The conversion rate to open resection was 22 per cent. Median hospital stay in the patients who underwent laparoscopic resection was 2.5 days, bowel movement occurred within 3 days in 92% and patients were mobilised for more than 8 h daily from day 2. These remarkable results were met initially with a degree of scepticism, with doubts being raised about the generalisability and the possibility of complications after discharge and higher readmission rates.

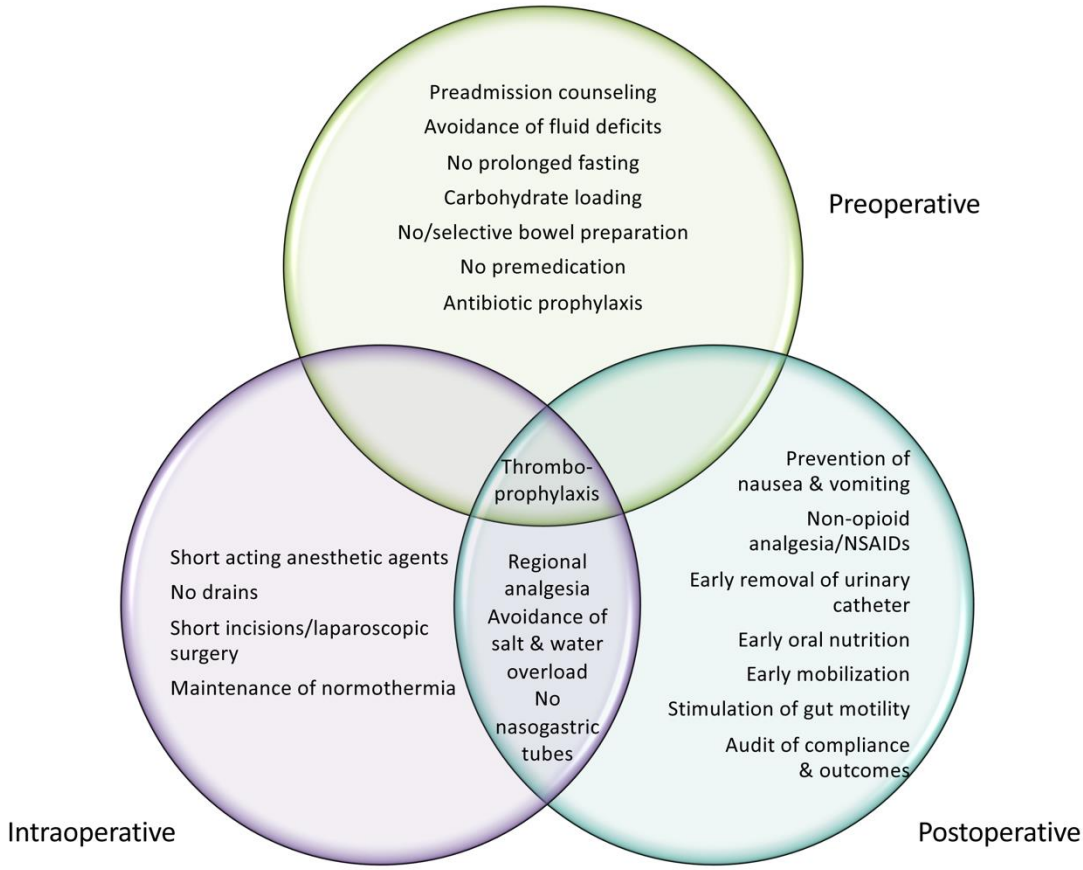
Table 1.2.1 *- Interventions advocated by Kehlet as part of the original multimodal intervention*

•Laparoscopic colonic surgery •Thoracic epidural analgesia •Avoidance of opioids •Reduced intraoperative and early postoperative fluids [median 1275 ml (650-2300 ml)] •No drains •Single dose of antibiotics •Prokinetics (Cisapride) •Removal of urinary catheter after 24 hrs •Early mobilisation

Henrik Kehlet's interpretation of the efficacy of the care bundle was that it may prove impossible to identify the contribution of each of these multimodal interventions. The combined use of epidural local anaesthesia, early oral nutrition, use of prokinetics and avoidance of nasogastric tubes (NGT) and opioids led to reduced postoperative ileus. Decreased bleeding, reduced intravenous fluids and epidural analgesia may also contribute to reduced cardiopulmonary stress (Bardram et al., 1995).

Gradual recognition of the generalisability of the interventions and transferable improvements in postoperative outcomes, led to the coinage of several terms to describe this bundle of interventions – stress-free surgery, fast-track surgery, enhanced recovery after surgery, and enhanced recovery programmes. The Enhanced Recovery After Surgery Group (later the ERAS® Society) published evidence-based guidelines for colorectal surgery in 2005 (Fearon et al., 2005) that combined a number of elements, each individually felt, to a greater or lesser extent, to reduce postoperative stress and improve outcomes (**Figure 1.2.1**). It was believed that combination of these pre-, intra- and postoperative elements would lead to a synergistic effect and improve outcomes to a greater extent than each of the individual elements.

Figure 1.2.1 *- Pre-, intra-, and post-operative components of the multimodal ERAS pathway*



The complicated series of interventions comprising an ERAS pathway gained acceptance and randomised controlled trials (RCTs) in patients undergoing colorectal surgery were performed soon after (Anderson et al., 2003, Gatt et al., 2005, Khoo et al., 2007). A meta-analysis of the first six RCTs (Varadhan et al., 2010) showed that an ERAS multimodal intervention was associated with a reduced postoperative complication rate (RR 0.53, 95% CI 0.41 to 0.69, $p<0.00001$) and hospital LOS (mean difference -2.51 days, 95% CI -3.54 to -1.47, $p<0.00001$) when compared with conventional postoperative care, without an increase in mortality (RR 0.53, 95% CI 0.09 to 3.15, $p=0.49$) or readmission rates (RR 0.80, 95% CI 0.32 to 1.98, $p=0.62$) (Varadhan et al., 2010). Although the results were remarkable, the number of individual interventions used in the RCTs ranged from 4 to 12, with the

Hawthorne effect creeping in and some interventions being used in the control group as well (Varadhan et al., 2010). The Hawthorne effect is the tendency for research participants to modify their behaviour because they know they are being observed, thus resulting in a distortion of the research findings. This led to the question of identification of the most important interventions and whether "partial ERAS" was valid, where institutions could choose interventions that suited them and were easy to implement, when compared with the more complex interventions. It also led to extrapolation of evidence primarily gathered from patients undergoing colorectal surgery to other forms of surgery, including pancreatic surgery (Lassen et al., 2012), upper gastrointestinal surgery (Mortensen et al., 2014), bariatric surgery (Thorell et al., 2016) and urology (Cerantola et al., 2013), to name a few.

1.2.2 Current Evidence for ERAS Programmes

There is a wealth of evidence published to support the practice of ERAS programmes in the field of elective colorectal surgery. Multiple studies have found a benefit in favour of ERAS in terms of hospital LOS (Thiele et al., 2015, Miller et al., 2014b), time to return of gastrointestinal function (Geltzeiler et al., 2014), overall complication rates (Greco et al., 2014) and postoperative quality of life (Wang et al., 2015). Several systematic reviews and meta-analyses have further reinforced the significant benefits associated with ERAS in patients undergoing colorectal surgery, both via open and laparoscopic approaches (Varadhan et al., 2010, Wind et al., 2006, Zhuang et al., 2013). There is also evidence of the potential benefits of an ERAS pathway in high risk patients such as elderly patients (Gonzalez-Ayora et al., 2016, Bagnall et al., 2014), those with low functional reserve (Braga et al., 2017) or those undergoing emergency surgery (Gonenc et al., 2014, Paduraru et al., 2017).

In addition to the clinical benefits associated with an ERAS pathway, there is also evidence of a cost effectiveness benefit, with several comparisons between ERAS and traditional care pathways (Roulin et al., 2013, Thiele et al., 2015) demonstrating between a €1651 to $7129 mean saving per patient benefit in favour of the ERAS pathway. This has been further analysed by a systematic review of 17 studies (Stowers et al., 2015) across a range of surgical specialities including colorectal, bariatric, gynaecological, gastric and vascular surgery, finding that ERAS pathways are 'clinically efficacious and cost effective', but highlighting a lack of long-term cost effectiveness data.

1.2.3 Impact of ERAS Compliance on Outcomes

In addition to the positive effects of undergoing colorectal surgery within an ERAS pathway, there are a number of studies in the literature which suggest a strongly positive link between increasing levels of compliance to components of the ERAS pathway and improved clinical outcomes including reduced hospital LOS and postoperative morbidity (Pedziwiatr et al., 2015, Cakir et al., 2013, Feroci et al., 2013). A prospective cohort study (Gustafsson et al., 2011) which observed clinical outcomes before and after reinforcement of an ERAS protocol in 953 patients with colorectal cancer demonstrated improved adherence was associated with reduced postoperative complications (OR 0.73; 95% CI 0.55-0.98) and the incidence of postoperative symptoms which delayed discharge (OR 0.53; 95% CI, 0.40-0.70) declined significantly. This was followed up by a study by the ERAS Compliance Group who published a multicentre study of 1509 colonic and 843 rectal resections (ERAS Compliance Group, 2015) suggesting that increasing ERAS compliance was associated with fewer surgical complications (OR 0.69, 95% CI 0.50 to 0.89, $p<0.001$) and reduced hospital LOS (OR 0.88, 95% CI 0.82 to 0.92, $p<0.001$). A multivariate analysis was conducted to assess factors predictive of worse clinical outcome from this data. Both a laparoscopic approach

(OR 0.68, 95% CI 0.62 to 0.74, p<0.001) and restrictive intravenous fluid strategy (OR 0.35, 95% CI 0.30 to 0.40, p<0.001) were associated with lower rates of postoperative complications, and laparoscopic approach (OR 0.83, 95% CI 0.79 to 0.87, p<0.001), preoperative carbohydrate drinks (OR 0.89, 95% CI 0.84 to 0.94, p=0.001) and the use of total intravenous anaesthesia (OR 0.86, 95% CI 0.81 to 0.91, p<0.001) were all associated with significantly lower hospital LOS.

1.2.4 ERAS and Long-Term Outcome

There is emerging evidence to suggest that increasing compliance to components of the ERAS pathway is also associated with improved long-term outcome. A single centre prospective observational study (Gustafsson et al., 2016) of 911 consecutive patients undergoing major colorectal cancer resection found that patients with ≥70% adherence to the ERAS interventions had a 42% reduction in the risk of 5-year cancer-specific death when compared with those with lower rates of adherence, although a higher rate of adherence, ≥ 80 and ≥ 90% did not affect survival. This is despite those with a higher adherence having an increased rate of malignant lymph nodes (N1) and reduced incidence of N2 –disease versus those with lower adherence.

The reason for this striking difference in long term survival is not entirely clear, with these studies proving evidence of association alone rather than causality. However, the principles underpinning ERAS programmes began initially with the aim of reducing surgically-induced stress during the immediate perioperative period. Evidence has been published suggesting that elevated levels of perioperative stress are associated with higher rates of local disease recurrence, possibly linked to increase release of angiogenic factors as well as suppression of T-helper 1 and Natural Killer cells (Kim et al., 2000) which act to target circulating cancer

cells and prevent metastases (Koda et al., 2003). There is evidence that several of the interventions which together make up ERAS pathways such as careful choice of anaesthetic (Iwasaki et al., 2015), use of locoregional anaesthesia (Cata et al., 2011) and laparoscopic approach (Huang et al., 2010), result in a reduction in perioperative surgical stress, which may explain the reduction in cancer-related mortality in those undergoing surgery as part of an ERAS programme, and furthermore in those with high levels of compliance. One other potential explanation relates to the goal of minimisation of surgical complications and early restoration of function which may result in reduced time to commencement of adjuvant therapy in the form of chemotherapy which may have a subsequent benefit in terms of oncological outcome. Several studies (Lohsiriwat, 2014, Shang et al., 2018) comparing time to adjuvant chemotherapy in elective colorectal surgery have demonstrated that those undergoing surgery within an ERAS pathway have a significantly shorter time when compared to those undergoing surgery within a traditional care pathway.

1.3 Components of ERAS Pathway

The components of an ERAS pathway can be divided into three distinct phases; that of pre-, intra- and post-operative interventions (**Figure 1.2.1**). The relative importance of interventions at the three different time points are not clear, however a recently published study of 2876 patients (Aarts et al., 2018) found that postoperative compliance to components of the ERAS protocol were the most difficult to achieve however they were most strongly associated with optimal recovery. At the time of writing of this introduction, the most recently published ERAS guidelines were from 2012 (Gustafsson et al., 2012b) which provide an outline of the available evidence for each individual intervention as well as an overall summary and recommendation for implementation. Subsequently, further ERAS Society guidelines have been published in 2018 (Gustafsson et al., 2018) which are

discussed in chapter 7 of this thesis, however these do not reflect the state of the literature at the time the work for this thesis was embarked upon. The 2012 guidelines (Gustafsson et al., 2012b) provide a summary of the quality of evidence available and recommendation grade based upon the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (Guyatt et al., 2008). However, this guideline was published in 2012 and subsequent to this there have been significant changes in the evidence for a number of the interventions considered as part of the ERAS pathway. This introduction seeks to provide a brief summary of the literature available for the different interventions and identify potential topics for evidence synthesis in the form of a meta-analysis which will form the remaining chapters of the thesis.

1.3.1 Preoperative Interventions

1.3.1.1 Patient counselling

This is, arguably, one of the most important elements of enhanced recovery, despite the fact that this recommendation is not supported by a large amount of evidence (Egbert et al., 1964, Gustafsson et al., 2012a, Kiecolt-Glaser et al., 1998). The importance of involving patients and their families in the process of preparing for, undergoing and recovering from major surgery cannot be underestimated. Clear instructions on what the patient can expect and what is expected from the patient helps engender a sense of responsibility and feeling of partnership amongst patients and carers. Details of the expected hospital LOS, goals to achieve during the perioperative period and factors which need to be met to achieve hospital discharge help improve clarity. A systematic review of 45 studies (Mondloch et al., 2001) found that an improved understanding and expectation of patient recovery resulted in improved healthcare outcomes. Increased co-operation on the part of the patient can only help accelerate the recovery process (Kiecolt-Glaser et al., 1998) as there is some evidence

that provision of this counselling reduces patient anxiety, improves early postoperative mobilisation (Samnani et al., 2014), post-operative pain levels and hospital LOS. This has been further reinforced by a recent Cochrane review (Powell et al., 2016) which supported the role of psychological preparation in optimising patients behavioural recovery, negative affect and postoperative pain levels. This intervention is unlikely to be associated with any negative effects in patients due to undergo elective colorectal surgery, and although evidence of its benefits are somewhat limited, this was not chosen as a topic for meta-analysis for this thesis.

1.3.1.2 Avoidance of Prolonged Fasting

Historically, patients would undergo prolonged periods of fasting prior to elective surgery due to concerns regarding the risk of pulmonary aspiration. The documented incidence of pulmonary aspiration related to general anaesthetic is low, quoted at approximately 1 in 7000 with consequent mortality estimated around 1 in 100,000 (Sakai et al., 2006). This prolonged preoperative fasting would frequently cause patients to reach the anaesthetic room in a starved state, frequently associated with electrolyte imbalance, hypoglycaemia and hypovolaemia (Falconer et al., 2014). In addition, there is evidence that prolonged preoperative starvation results in a metabolic response which leads to increased insulin resistance and an acute-phase response. However, with increasing knowledge of the adverse physiological effects of preoperative dehydration due to a better ability to measure cardiac output and oxygen delivery, there has been an evolution in preoperative fasting guidance. Contemporary guidelines produced by a range of Anaesthetic Societies (2017, Smith et al., 2011, Thiele et al., 2016) have recommended a fasting period of two hours for clear liquids and six hours for solid foods. This recommendation is based upon evidence from RCTs and meta-analyses which have demonstrated low risk of aspiration (Phillips et al., 1993), low

residual gastric volume (Maltby et al., 1986) and low patient thirst and hunger levels. This has been further reinforced by evidence from dynamic gastric ultrasound in the calculation of gastric volume. A prospective RCT (Phillips et al., 1993) demonstrated that patients who were allowed a 150ml drink of water up to 120 minutes prior to anaesthesia rather than 6 hours of preoperative fasting did not have a significantly different residual gastric volume or gastric pH, with no issues surrounding aspiration or regurgitation.

Despite contemporary guidance, there is evidence that these fasting times are often poorly adhered to (Falconer et al., 2014), and a link has been established between prolonged preoperative fasting and increased postoperative complication rates (de Amorim et al., 2015). In terms of fasting to clear fluids and solids, there is no major additional evidence to suggest these fasting times should be reconsidered in adult patients, and as such this was not chosen as a potential topic for meta-analysis for this thesis.

1.3.1.3 Carbohydrate loading

The use of preoperative carbohydrate (CHO) loading remains controversial, despite extensive basic science evidence that this intervention reduces perioperative insulin resistance which results in hyperglycaemia, poor glucose uptake and resultant glycogen storage which can lead to muscle degradation. There is some evidence that insulin resistance results in adverse clinical outcomes (Sato et al., 2010, Ljungqvist et al., 2002) including postoperative complications and mortality. A preoperative carbohydrate load has been shown to convert the metabolic state of the patient from fasting to fed (Ljungqvist and Soreide, 2003), and evidence suggests that this is safely tolerated up to two hours prior to anaesthetic. Despite this good body of evidence, the benefits associated with carbohydrate

loading in the clinical setting have not proven as conclusive (Bilku et al., 2014, Pogatschnik and Steiger, 2015, Li et al., 2012).

A recently published network meta-analysis (Amer et al., 2017) of 43 RCTs including 3110 participants undergoing elective surgical procedures compared preoperative low (10-44g) or high (45g or more) dose carbohydrate with water or placebo. This analysis demonstrated no benefit from preoperative carbohydrate loading at either dose when compared with water or placebo in terms of hospital LOS or surgical complication rate, although carbohydrate loading was associated with a small but significant reduction in hospital LOS versus fasting alone. Similar results were observed in a Cochrane review (Smith et al., 2014) of 27 RCTs involving 1976 patients who underwent elective surgical procedures including abdominal, orthopaedic, cardiac surgery and thyroidectomy. Preoperative carbohydrate treatment (defined as at least 45g of carbohydrate) in this study population was associated with a small reduction in hospital LOS (mean difference 0.30 days, 95% CI 0.56 to 0.04) although this was based upon very low-quality evidence. The authors observed no difference in postoperative complication rates when compared with either water or fasting. At present given the fairly recently conducted meta-analysis, and a lack of more recent evidence to further inform the evidence base, this would not be a useful topic for a meta-analysis for this thesis.

1.3.1.4 Bowel preparation

The use of bowel preparation, both in the form of mechanical bowel preparation (MBP) and oral antibiotic (OAB) preparation, is designed to prepare the colon prior to surgery. MBP is defined as an ‘oral preparation given prior to surgery to clear faecal material from the bowel lumen’ (McCoubrey, 2007) and OAB as the administration of oral, non-absorbable, luminal

antibiotics in order to reduce the levels of intestinal bacteria (DiPiro et al., 1985) with the aim of reduction of postoperative infectious complications. The administration of MBP and OAB is a highly controversial topic, with a wealth of studies and meta-analyses debating its role in surgery involving the colon or rectum. It was initially proposed that MBP would reduce faecal bulk and bacterial colonisation, thereby reducing SSI and anastomotic leak rates (Nichols and Condon, 1971). However, concerns have been raised that by liquefying the faeces there is an increased risk of spillage and evidence suggests that bowel preparation does not result in a gross reduction in gut microbial flora counts (Jung et al., 2010). Recent meta-analyses (Dahabreh et al., 2015, Courtney et al., 2015) have suggested that there is no role for MBP alone in the prevention of postoperative complications in elective colorectal surgery. However, the outcome of these meta-analyses are not reflected in surveys of current practice (Drummond et al., 2011, Kang et al., 2013, Shahab et al., 2014, Altman and Nelson, 2016) which have found persistently high use of mechanical bowel preparation in elective colorectal surgery. In addition, there have been several new studies (Bhattacharjee and Chakraborty, 2015, Ji et al., 2017, Chan et al., 2016, Allaix et al., 2015) which have been published on the role of mechanical bowel preparation since the last meta-analysis, hence this would be a good topic for a further meta-analysis to provide definitive evidence on the potential role of MBP in elective colorectal surgery.

OAB preparation, as an oral non-absorbable antibiotic, was first proposed by Rosenberg *et al*. (Rosenberg et al., 1971), with a study of 150 patients demonstrating that OAB was associated with a significant reduction in SSI and anastomotic leak rates. After a period of significant interest in the use of OAB, their routine administration fell from favour, with MBP alone more commonplace. In recent years there has been a rapid increase in interest in OAB administration once more (Zelhart et al., 2014), particularly due to multiple large

database studies (Klinger et al., 2017, Garfinkle et al., 2017, Kiran et al., 2015) suggesting a potential role for the combination of MBP and OAB or OAB alone in the prevention of SSI. ERAS guidelines currently recommend against the use of routine preoperative bowel preparation in colonic surgery (Gustafsson et al., 2012a), however it is recommended in patients undergoing an anterior resection with diverting stoma (Nygren et al., 2012), based upon very little evidence. ERAS guidelines currently do not mention the potential role for OAB, which is a topic very much in evolution. This fact, coupled with the multitude of recent publications on the topic made this an ideal focus for meta-analysis within this thesis, looking to strengthen the evidence base for or against OAB preparation, either alone or in combination with MBP.

1.3.1.5 Parenteral Antibiotic Prophylaxis

The administration of parenteral antibiotic prophylaxis is considered a basic standard of care in current surgical practice following a multitude of previous RCTs (Sato et al., 2009, Nygaard and Hognestad, 1980, Hagen et al., 1980) and meta-analyses (Nelson et al., 2014, Bartlett and Burton, 1983, Baum et al., 1981), which have incontrovertably proven than antibiotic prophylaxis reduces SSI. In colorectal surgery specifically, a meta-analysis of 260 RCTs (Nelson et al., 2014) which included a range of 68 different parenteral antibiotics and randomised a total of 43,451 patients provided definitive evidence of a reduction in SSI versus placebo or no treatment (RR 0.34, 95% CI 0.28 to 0.41), which was based upon high quality evidence. Given this evidence, the topic of parenteral antibiotic prophylaxis was not considered a suitable topic for meta-analysis within this thesis as it should be considered a standard of care for patients undergoing colorectal surgery. Indeed, the National Institute for Health and Care Excellence (NICE) Clinical Guideline (NICE, 2008) for the prevention and treatment of SSI recommends that antibiotic prophylaxis should be administered to patients

prior to clean-contaminated surgery which would include colorectal surgical wounds. As such, there is no requirement for any additional evidence synthesis on this topic so this has not been chosen as the topic for meta-analysis in this thesis.

1.3.1.6 Avoidance of Premedication

Historically, premedication was administered in an effort to reduce patient anxiety and pain, promote amnesia, reduce the vagal reflexes associated with intubation and reduce gastric secretions prior to surgical intervention. However, there is minimal literature available to support their routine administration. There are well documented side effects associated with premedication use, including drowsiness, cognitive impairment (Rogers et al., 2002), and amnesia. These negative effects may result in a reduced patient capacity to undertake the postoperative interventions suggested as part of an early ERAS recovery protocol such as early enteral nutrition and mobilisation. A large RCT (Maurice-Szamburski et al., 2015) including 1062 adult patients undergoing a variety of elective surgical procedures demonstrated that lorazepam premedication was associated with no difference in patient satisfaction with anaesthesia, increased the time to extubation and prolonged early cognitive recovery versus placebo or no premedication. This study has, however, come under some criticism (Heller and Koch, 2015) for its primary outcome measure of patient satisfaction rather than patient reported anxiety levels, as anxiolysis is often regarded as the main indication for premedication.

Recent RCT evidence (Jeon et al., 2018) has suggested a potential benefit for midazolam premedication, finding a significant reduction in haemodynamic instability as well as an analgesic effect as measured by the surgical pleth index during induction of anaesthesia. This is also supported by evidence suggesting that midazolam administration is associated

with faster induction of anaesthetic and reduced anaesthetic requirement (Koh et al., 2017, Kim et al., 2017b). A meta-analysis conducted in the field of day-case surgery (Mijderwijk et al., 2016) found that benzodiazepine premedication was associated with a significant increase in time to recovery but no difference in anxiety or psychological outcome following surgery, however this study is not hugely applicable to the area of elective colorectal surgery. The routine administration of premedication is currently not considered a standard of care in all surgical specialities and is not specific to ERAS, hence this topic was not chosen for evidence synthesis for this thesis.

1.3.2 Intraoperative Interventions

1.3.2.1 Mid-thoracic Epidural Analgesia

The use of mid-thoracic epidurals have previously been shown to decrease hospital LOS, promote gastrointestinal function and minimise opiate requirement without effecting the incidence of anastomotic dehiscence (Liu et al., 2014, Carli et al., 2001, Lai et al., 2013). The use of epidurals however is invasive, associated with epidural-induced hypotension and a small risk of serious side effects. With the increasing popularity of laparoscopic over open surgery, which in itself is associated with a decreased hospital LOS, earlier promotion of gastrointestinal function and minimised opiate requirement, the use of a routine mid-thoracic epidural as has been questioned (Eto et al., 2017, Hubner et al., 2015). In addition, the rates of non-functional epidural are estimated between approximately 20 and 30% (Gleicher et al., 2017, Hermanides et al., 2012), with studies suggesting that non-functioning epidural analgesia is an independent predictor of postoperative complications.

Increasing interest is now being shown in the use of local anaesthetic techniques such a wound infusion catheters (WIC) and transverse abdominis plane (TAP) block, particularly

in open surgery, with studies suggesting these techniques to be safe and provide adequate analgesia (Boulind et al., 2013, Fustran et al., 2015). Increasing high quality evidence has supported the use of TAP blocks, particularly in the field of laparoscopic colorectal surgery (Kim et al., 2017a, Pirrera et al., 2018), with equivalent postoperative pain levels and benefits in terms of ileus rates cost effectiveness. Similarly, a recent meta-analysis (Mungroop et al., 2018) of 29 RCTs (2059 patients) demonstrated continuous wound infiltration using preperitoneal wound catheters to be an effective pain modality in abdominal surgery, with improved patient satisfaction, incidence of hypotension and levels of opioid consumption versus thoracic epidural. This topic, in combination with the use of non-opioid analgesic regimes is one which is currently controversial and a topic in flux and as such should be considered as a potential topic for meta-analysis.

1.3.2.2 Short-Acting Anaesthetic Agents

The principles of the administration of anaesthetic in patients undergoing an ERAS pathway mirror other components of the pathway, aiming to minimising complications and optimise the patient's ability to achieve the early postoperative goals, including early mobility and enteral nutrition. A widely utilised approach involves the use of short acting anaesthetics with the intention of achieving anaesthesia without the hangover effects of longer acting anaesthetic agents (Kehlet and Dahl, 2003, Baldini and Fawcett, 2015). In these circumstances, induction of anaesthesia is frequently achieved by administration of propofol followed by the administration of short-acting opioids such as fentanyl or remifentanil. There is variation in individual clinical practice, however many anaesthetists then use volatile inhaled anaesthetic in the form of sevoflurane or desflurane in oxygen-enriched air (Martin and Grocott, 2015). This combination of opioid-sparing analgesics and short acting volatile agents facilitates effective rapid recovery from anaesthetic with minimal adverse

effects in the postoperative setting. Total intravenous anaesthesia (TIVA) has been proposed for its reduction in postoperative nausea and vomiting (PONV) (Lee et al., 2015, Kumar et al., 2014), which significantly impairs the patients' abilities to achieve early nutritional and mobility goals. There has recently been some emerging evidence to support potentially superior oncological outcomes in terms of recurrence-free survival and overall survival in those patients undergoing cancer surgery who receive TIVA versus inhaled anaesthetic (Soltanizadeh et al., 2017, Yap et al., 2019, Jun et al., 2017, Wigmore et al., 2016), however the evidence for this is currently not well established and some studies have found no difference in survival(Yan et al., 2018, Oh et al., 2018).

However, there is not currently definitive evidence to support one strategy over the other. A consensus statement has recently been published surrounding anaesthetic practices in patients undergoing gastrointestinal surgery as part of an ERAS pathway (Feldheiser et al., 2016). The use of laparoscopy, when possible, is one of the key component of ERAS pathways. The process of abdominal insufflation in order to achieve laparoscopic colorectal surgery results in reduced venous return and impaired respiratory function. There is evidence to support the use of neuromuscular blockage during laparoscopy to facilitate lower insufflation pressures (Bruintjes et al., 2017), and this should be considered for all laparoscopic cases to facilitate renal and mesenteric blood flow as well as optimise cardiac output. There have been no major changes in the evidence for short acting anaesthetic agents and as such this topic was not chosen for evidence synthesis as part of this thesis.

1.3.2.3 Maintenance of Normothermia

The occurrence of intra-operative hypothermia, defined as a temperature below 36°C, is well known to be associated with a range of perioperative complications. Temperature

disturbance can cause a disorder of the clotting cascade, resulting in increased bleeding and transfusion requirement, increased cardiovascular stress levels, an increased risk of SSI, increased risk of intraoperative coronary events and prolonged action of several anaesthetic drugs (Horosz and Malec-Milewska, 2013, Frank et al., 1993, Putzu et al., 2007, Insler and Sessler, 2006). Given the clear benefits to maintenance of normothermia and no evidence to suggest any negative effects, this topic is not suitable for further evidence synthesis.

1.3.2.4 Minimally Invasive Surgery

There is excellent evidence in the form of both RCTs and meta-analyses (Veenhof et al., 2012, Zhuang et al., 2015, Vlug et al., 2011) that where possible, laparoscopic surgery, is associated with improved short term outcomes including a reduced hospital LOS, post-operative pain level and morbidity. In terms of longer term oncological outcomes, an international multicentre RCT (Bonjer et al., 2015) examined rates of regional recurrence in a total of 1044 patients undergoing laparoscopic versus open surgery for rectal adenocarcinoma. This study found that at 3 year follow up, the locoregional recurrence rates were 5% for both intervention groups, with all-cause disease-free survival of 74.8% in the laparoscopic group and 70.8% in the open group (difference, 4%; 95% CI, -1.9 to 9.9). Overall survival rates were 86.7% in the laparoscopic group and 83.6% in the open group (difference, 3.1%; 95% CI, -1.6 to 7.8). When long term outcomes of colonic malignancy were examined, meta-analyses have found equivalent long term outcomes between laparoscopic and open colectomy in colon cancer (Athanasiou et al., 2017, Bonjer et al., 2007) as well as advanced, pT4 malignancy (Klaver et al., 2017, Feinberg et al., 2017).

There has been increasing interest in alternative methods for minimally-invasive colorectal surgery which may play a part in ERAS pathways in the future. Single-incision laparoscopic

surgery (SILS) has been considered as an alternative to standard laparoscopy, with potential cited benefits including reduced postoperative pain and superior cosmetic outcomes. A meta-analysis has recent been conducted comparing standard laparoscopy with SILS including 32 studies and a total of 3863 patients (Hoyuela et al., 2017). This demonstrated equivalent outcomes between SILS and standard laparoscopy in terms of operating time (p=0.44), conversion rate (2.0% versus 3.0%, p=0.52) and incidence of postoperative complications (14.4% versus 13.6%, p=0.10). A recent consensus statement released by the European Association for Endoscopic Surgery (EAES) (Morales-Conde et al., 2019) found a lack of high quality evidence and long-term follow up as well as increased direct costs associated with SILS and a prolonged learning curve associated with the technique. They concluded that 'wider acceptance of the procedure should be supported only after demonstration of clear benefits'.

There has also been increasing interest in the use of robotic-assisted resection over laparoscopy in colorectal resection which has been the subject of several recent meta-analyses (Zhang et al., 2016c, Trinh et al., 2014, Sun et al., 2016). Quoted advantages of robotic-assisted surgery include improved visualisation, accuracy and precision, as well as improved depth of field which may result in reduced conversion rates to open over laparoscopic surgery (Valverde et al., 2017, Trastulli et al., 2012) and improved postoperative pelvic nerve function (Xiong et al., 2015). However, this is at the cost of increased operative time and surgery-related costs (Rondelli et al., 2015). There is some evidence to support equivalent long-term oncological outcomes between robotic-assisted and laparoscopic colorectal resection (Park et al., 2018, Lim et al., 2017), however more large-scale studies and long-term follow up data are needed to provide definitive evidence to support robotic-assisted resection. Given the recent large number of up-to-date meta-

analyses comparing SILS and standard laparoscopy as well as robotic versus laparoscopy, this was not chosen as a potential topic for meta-analysis in this thesis.

1.3.2.5 Goal-directed fluid therapy (GDFT)

While healthy patients are able to tolerate a loss of 25-30% of their circulating blood volume under anaesthesia without a significant alteration in haemodynamic status, splanchnic perfusion falls appreciably with a 10-15% decrease in blood volume and this hypoperfusion of the gut frequently outlasts the period of hypovolaemia (Giglio et al., 2009). This gut hypoperfusion may result in an intramucosal acidosis (Holland et al., 2005), leading to a cascade of events that result in reduced postoperative gastrointestinal function (Filsoufi et al., 2007). Relatively small volume colloid boluses (200-250 ml) have been shown to increase stroke volume and cardiac output, improve gut perfusion (Giglio et al., 2009) and decrease gut mucosal acidosis intraoperatively.

A number of methods, including transoesophageal Doppler, lithium dilution, arterial pulse contour analysis, thoracic electrical bioimpedance, partial non-rebreathing systems and transpulmonary thermodilution techniques, have been used to measure intraoperative stroke volume and cardiac output, and thereby guide intraoperative fluid therapy (Funk et al., 2009). The most commonly utilised devices in a clinical setting are the transoesophageal Doppler and lithium dilution techniques. The commonest algorithm used is to measure stroke volume and infuse a fluid bolus of 200-250 ml over 5-10 min. A stroke volume increase of >10% following administration of this bolus indicates hypovolaemia and this indicates the need for an additional bolus. If the stroke volume increase does not exceed 10%, this suggests that the patient has an adequate circulating volume and therefore does not require any additional

fluid bolus. Variations in this methodology include monitoring of stroke volume variation and corrected flow time (FTc) (Noblett et al., 2006, Gan et al., 2002).

In terms of fluid management in patients on an ERAS pathway, GDFT has become seen as a key concept, with studies from the first decade of the 21st century demonstrating that this was associated with a significant reduction in overall hospital LOS and the incidence of postoperative complications (Pearse et al., 2005, Noblett et al., 2006). This evidence led to the technique of intraoperative GDFT being recommended as gold standard by the UK National Institute for Health and Care Excellence (NICE, 2011). However, a recent meta-analysis (Rollins and Lobo, 2016) which considered the impact of GDFT in the setting of an ERAS pathway versus traditional care pathways demonstrated that the significant benefits previously seen associated with this technology were not seen when GDFT was combined with management as part of an ERAS pathway, where aiming for a 'zero fluid balance' state may be the determining factor (Brandstrup et al., 2012). This has been further reinforced by a recent meta-analysis of 11 RCTs (Xu et al., 2018) in colorectal surgery which found no significant differences in 30-day mortality (RR 0.86, 95% CI 0.28 to 2.63, p=0.79), hospital LOS (weighted mean difference 0.22, 95% CI -0.1 to 0.55, p=0.18), although the GDFT did experience a significant reduction in overall complications (RR 0.84, 95% CI 0.71 to 0.99, p=0.04). Within the setting of an ERAS pathway, careful perioperative fluid management is key to optimising clinical outcomes, however whether GDFT is a compulsory component of this remains unclear. No meta-analyses to date have focused upon the role of GDFT in colorectal surgery alone, hence this is a potential topic for meta-analysis for this thesis.

1.3.2.6 Avoidance of Prophylactic Drainage

Routine placement of prophylactic drains should be largely avoided in abdominal surgery on the basis of good evidence that drains are frequently unnecessary, potentially harmful and uncomfortable for the patient (Wong-Lun-Hing et al., 2017, Yong and Guang, 2016, Karliczek et al., 2006). In the field of colorectal surgery, a meta-analysis of 11 RCTs (Zhang et al., 2016a) including 1803 patients found no significant difference between patients receiving prophylactic drainage in terms of overall anastomotic leakage (RR 1.14, 95% CI 0.80 to 1.62, p=0.47), clinical anastomotic leakage (RR 1.39, 95% CI 0.80 to 2.39, p=0.24), radiological anastomotic leakage (RR 0.92, 95% CI 0.56 to 1.51, p=0.74), or SSI (RR 1.19, 95% CI 0.84 to 1.69, p=0.34). In a meta-analysis focused upon prophylactic pelvic drainage versus no drainage of extraperitoneal anastomoses in rectal resection (Menahem et al., 2017), there were no differences observed in the incidence of overall mortality (0.7% versus 1.9%, p=0.90), anastomotic leakage (14.8% versus 16.7%, p=0.37) and small bowel obstruction (18.7% versus 12.67%, p=0.05). There is currently an ongoing Cochrane review focused upon this topic which is due to be published in the near future, hence the decision was made not to perform evidence synthesis on the topic.

1.3.3 Postoperative Interventions

1.3.3.1 Early Oral Nutrition

There is good evidence to support the recommendation that oral nutrition should also be commenced as early as possible following surgery resulting in a reduction in hospital LOS and is safe and well tolerated (Pragatheeswarane et al., 2014, Zhuang et al., 2013), with the exception in those patients with delayed gastric emptying. A meta-analysis focusing upon early enteral nutrition commenced within 24 hours of elective colorectal surgery versus later commencement (Zhuang et al., 2013) identified 7 RCTs which randomised 587 patients.

This comprehensive study demonstrated that early feeding was associated with a reduced hospital LOS (weighted mean difference -1.58 days, 95% CI -2.77 to-0.39, p=0.009) and the total postoperative complication rate (RR 0.70, 95% CI 0.50 to 0.98, p=0.04). The European Society for Clinical Nutrition and Metabolism (ESPEN) has produced a guideline surrounding the role of clinical nutrition in surgery (Weimann et al., 2017) which provides a strong evidence base for the importance of early enteral nutrition in patients undergoing major surgery. This states that surgery causes a major inflammatory process which leads to a metabolic stress response involving catabolism of glycogen, fat and protein, resulting in release of free fatty acids, amino acids and glucose into the circulation. In order to achieve healing and return to functional normality, nutrition is necessary to rapidly rebuild peripheral protein mass. Given the recently conducted thorough meta-analysis, and a lack of any significant additional original data, this topic was rejected as a potential choice for a meta-analysis for the thesis.

1.3.3.2 Avoidance of NGT

Historically, the routine use of prophylactic NGT in the postoperative setting was believed to reduce the incidence of aspiration pneumonia, anastomotic leak and wound dehiscence. However, there has been a wealth of high quality evidence which was summarised in a large Cochrane meta-analysis of 33 RCTs including 5240 patients (Nelson et al., 2007) which found that routine NGT insertion was associated in a delay in time to return of gastrointestinal function (men difference 0.51 days, 95% CI 0.45 to 0.56, p<0.00001), and no difference in hospital LOS (mean difference 0.53 days, 95% CI -0.39 to 1.46, p=0.26), incidence of anastomotic leak (OR 1.14, 95% CI 0.72 to 1.80, p=0.58), or wound complications (RR 0.84, 95% CI 0.61 to 1.17, p=0.30). Indeed, there is evidence from a prospective randomised case-control study that NGT insertion increases gastro-oesophageal

reflux in patients undergoing elective laparotomy (Manning et al., 2001). The avoidance of routine NGT insertion is regarded a standard of care and as such it was not chosen as a topic for meta-analysis for this thesis.

1.3.3.3 Prevention/Treatment of Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) is a common event, with a quoted incidence of vomiting of 30% and nausea of 50% (Apfel et al., 1999, Gan, 2006). Patients who develop PONV have a reduced ability to comply with the postoperative goals of an ERAS programme including early nutrition, ambulation and return of gastrointestinal function (Gupta and Soto, 2016). The presence of PONV may also contribute to dehydration, electrolyte disturbance, necessitate intravenous fluid prescription and prolong overall hospital LOS. There has been extensive published literature concerning the risk factors associated with PONV including female gender, young age, history of PONV, the use of opioids and volatile anaesthetics intraoperatively, location of surgery, use of laparoscopy and prolonged operative time (Apfel et al., 2012, Apfel et al., 2005b, Gan, 2006). The prevention of PONV is directed by the number of patient risk factors identified, with those with one or fewer factors considered low risk and those with three or more high risk. Strategies to prevent and treat PONV include pharmacological and non-pharmacological measures such as hydration, acupuncture and analgesia. When considering pharmacological measures for PONV, the site of action should be considered with a range of different agents employed as necessary (Tramer, 2001). These include serotonin 5-HT_3 antagonists such as ondansetron which act to reduce the levels of the neurotransmitter serotonin, corticosteroids such as dexamethasone, the action of which is not fully understood, dopamine D2 antagonists such as metoclopramide which block central dopamine receptors, and antihistamines which block central H_1-receptors(Weibel et al., 2017). In one study (Apfel et

al., 2005a) which examined the use of individual classes of drugs in a series of 5199 patients, the use of a single class of drug resulted in a 25% risk reduction in PONV, however when these agents were used in combination the risk reduction was further strengthened (Eberhart et al., 2002). Given the negative effects of PONV upon compliance with ERAS principles, the prevention and treatment of PONV should be routinely administered to all patients, with modifications made based upon risk. Therefore, this topic was not considered suitable for meta-analysis within this thesis.

1.3.3.4 Avoidance of Salt and Water Overload

Traditional fluid management in the perioperative setting frequently involved the infusion of large volumes of crystalloid, in order to support an adequate circulating volume to achieve reasonable end organ perfusion and tissue oxygenation (Doherty and Buggy, 2012). In this setting, weight gain of between 7 and 10kg was not uncommon and resulted in a significantly increased risk of overall morbidity and mortality (Lowell et al., 1990, Holte et al., 2003). More recent evidence has supported a U-shaped relationship between volume of postoperative fluid infused and morbidity rates (Bellamy, 2006), with a resulting aim of maintaining patients in a state of euvolaemia. The goal of maintenance of as near as possible to zero fluid balance is supported by evidence of a beneficial effect in terms of reduced overall complication rates and hospital LOS (Lobo et al., 2002, Brandstrup et al., 2012, Miller et al., 2014a). Increasing focus has also been brought upon the importance of salt balance in the postoperative setting (Lobo, 2012), with a recent move away from high-chloride-containing fluids due to a resultant hyperchloraemic acidosis due to evidence suggesting a negative impact upon clinical outcomes (Krajewski et al., 2015, Yunos et al., 2012, Lobo and Awad, 2014). There have been a flurry of publications comparing balanced crystalloid solutions versus ‘normal’ saline, many of which have concentrated on critically

unwell patients and those in an intensive care setting, which have supported the benefits of balanced electrolyte solutions (Bampoe et al., 2017, Shaw et al., 2012). There is significant evidence of the beneficially effects of aiming for zero water and salt balance, and as such this topic was not chosen as a potential topic for meta-analysis for this thesis.

1.3.3.5 Non-opioid analgesia and nonsteroidal anti-inflammatory drugs (NSAIDs)

Postoperative analgesia in ERAS pathways must be administered using a multimodal approach, with use of drugs which have different underlying mechanisms, often combining systemic analgesia and local anaesthetic techniques. Whilst opioids are a highly effective form of analgesia in the acute postoperative setting, their administration is associated with a range of negative effects including an increased risk of postoperative nausea and vomiting, delay in return of gastrointestinal function, ventilatory depression, drowsiness, pruritis, urinary retention and constipation. Despite this, a survey (Kessler et al., 2013) of administrative data from 37,301 patients undergoing a common surgical procedure between 2009 and 2010 in the United States found that 98.6% of patients received opioids in the perioperative setting, making this an ongoing major issue in the (Burton et al., 2013) perioperative care of patients undergoing surgery. In recent times an opioid epidemic has been observed in the USA (Gostin et al., 2017, Wilkerson et al., 2016), with evidence suggesting that the risk of opioid dependency after surgery in opioid naïve patients may be as high as 6.5% (Brummett et al., 2017). Hence, the need to minimise opioid use following surgery is more important than ever. There are a multitude of other systemic analgesic adjuncts which are used in elective abdominal surgery such as dexmedetomidine, ketamine, magnesium sulphate, clonidine and gabapentinoids.

The administration of NSAIDs are a key component of multimodal analgesic strategies following abdominal surgery, with evidence of analgesic, anti-inflammatory and antipyretic effects. They act by inhibition of cyclo-oxygenase, thus preventing the formation of prostaglandins which result in postoperative inflammation, activation of peripheral nociceptive nerve endings and sensitisation of the nerves of the dorsal horn of the spinal cord. There is a significant degree of variability in the administration of NSAIDs following colorectal surgery (Pommergaard et al., 2014), despite several meta-analyses which have supported their efficacy in terms of analgesia as well as a reduction in opioid-related side effects (Maund et al., 2011, Elia et al., 2005). Some evidence has suggested that the use of NSAIDs may be linked to a deleterious effect upon colorectal anastomoses (Slim et al., 2016), however meta-analyses on this topic (Bhangu et al., 2014, Burton et al., 2013) have revealed large levels of heterogeneity and bias which have somewhat limited their conclusions. More recently published studies have not suggested a link between NSAIDs and anastomotic leak rates (Kverneng Hultberg et al., 2017, Rutegard et al., 2016, Paulasir et al., 2015).

There are a range of non-opioid strategies, local anaesthetic techniques which have been suggested for the optimisation of postoperative analgesia in the setting of abdominal surgery, including rectus sheath catheters, transversus abdominis plane (TAP) block, wound infusion catheters (WIC) and intravenous lidocaine (IVL) infusion and this is a topic of huge evolution in the literature at present. There is evidence that these opioid sparing techniques result in a faster time to return of gastrointestinal function, early mobilisation and reduced hospital LOS. The use of rectus sheath catheters was initially described in the 1950s for gynaecological and general surgical procedures. They can be sited either surgically or via ultrasound-guidance and are placed via the anterior abdominal wall to the space just anterior

to the posterior leaf of the posterior rectus sheath to provide local anaesthetic blockade of the anterior division of the lower thoraco-abdominal intercostal nerves. There is evidence from case controlled and retrospective case studies that this technique is safe and can be used as an alternative to epidural in open colorectal surgery (Tudor et al., 2015, Godden et al., 2013), however the amount of published evidence is not sufficient to consider a meta-analysis on the topic at present.

TAP block works via ultrasound- or laparoscopy- guided infusion of local anaesthetic into the space between the internal oblique and transversus abdominis muscle, achieving blockade of the 7th to 11th intercostal nerves, the subcostal nerve (T12) and the ilioinguinal and iliohypogastric nerve. There has been RCT evidence to support the non-inferiority of TAP block versus thoracic epidural analgesia in patients undergoing laparoscopic colorectal surgery (Niraj et al., 2014), as well as a significant improvement in short-term opioid use and pain outcomes over placebo (Keller et al., 2014, Walter et al., 2013). In a meta-analysis (Baeriswyl et al., 2015) of 31 RCTs including a total of 1611 adult patients undergoing laparotomy, laparoscopy and caesarean section for a variety of indications, TAP block was associated with a significant reduction in IV morphine requirement at 6 (mean difference 6mg, 95% CI -7 to -4mg, $p<0.00001$) and 24 hours (mean difference 11mg, 95% CI -14 to -8mg, $p<0.00001$) postoperatively as well as postoperative pain scores on rest and movement at 6 hours, although there was no difference in the incidence of postoperative nausea and vomiting. Given the recently performed meta-analysis and lack of significant additional currently published evidence, this topic was not considered suitable for additional meta-analysis.

Postoperative wound infusion catheter (WIC) infusion of local anaesthetic into the preperitoneal space in open colorectal surgery is also supported by evidence of its safety and efficacy by several RCTs (Fustran et al., 2015, Beaussier et al., 2007) as well as some evidence of non-inferiority to epidural analgesia (Bertoglio et al., 2012). In the field of colorectal surgery specifically, there is not yet a large amount of evidence which would be suitable for evidence synthesis and as such was not chosen for meta-analysis in this thesis. However, this remains a highly interesting topic in evolution currently and as such will likely be a suitable topic in the future.

Perioperative IVL infusion is currently gaining increasing interest in the field of colorectal surgery due to its documented analgesic and anti-inflammatory properties. A meta-analysis (Ventham et al., 2015) of 14 RCTs comparing IVL versus placebo following laparoscopic abdominal surgery found IVL to be associated with significantly lower opiate requirements, reduced nausea and vomiting and a shorter time to return of normal diet. However, this meta-analysis included a range of surgical specialities and purely focused upon laparoscopic rather than open surgery. Subsequent to this meta-analysis, there have been several RCTs published in the field of colorectal surgery (Ho et al., 2018, Ahn et al., 2015, Dewinter et al., 2018) which make this an ideal topic for evidence synthesis and will be considered by meta-analysis as part of this thesis.

1.3.3.6 Early Removal of Urinary Catheters

ERAS guidelines state that the urinary catheter should be removed at the earliest possible opportunity following surgery, and that this can be removed regardless of the usage or duration of thoracic epidural (Basse et al., 2000). Recently published evidence suggests that early removal of the urinary catheter in line with ERAS guidelines reduced both the

incidence of urinary tract infection (RR 0.20, 95% CI 0.07 to 0.58, p=0.003) as well as overall hospital LOS (RR 0.73, 95% CI 0.66 to 0.82, p<0.0001 for colonic surgery and RR 0.54, 95% CI 0.49 to 0.59, p<0.001 for rectal surgery) (Okrainec et al., 2017). Research has previously examined the role of routine transurethral versus suprapubic urinary catheter insertion, with evidence from abdominal (Baan et al., 2003) as well as gynaecological surgery (Healy et al., 2012) that neither route is clearly superior. The increased rate of infective complications associated with the transurethral route is offset by the increase in catheter-related complications associated with the suprapubic route. There is sufficient evidence that early removal of urinary catheters is beneficial and as such this was not chosen as a topic for meta-analysis in this thesis.

1.3.3.7 Thromboprophylaxis

Current ERAS guidelines recommend the administration of thromboprophylaxis in an extended regimen, for 28 days in patients with cancer. The evidence for this intervention is not yet clear (Fagarasanu et al., 2016). A recent clinical review (Sammour et al., 2016) found level one evidence to support combined mechanical and chemical thromboprophyaxis for 7-10 days following colorectal cancer surgery, however in the extended setting there is only evidence to support a reduction in asymptomatic, screening detected DVT only, with no difference observed in symptomatic DVT, symptomatic PE or VTE-related death (Kakkar et al., 2010, Bergqvist et al., 2002). There is a significant degree of variability in nationally published guidelines, likely as a result of unclear evidence. The American Society of Clinical Oncology guidelines published in 2015 (Lyman et al., 2015) states that extended prophylaxis should be considered for major abdominal or pelvic cancer surgery in those patients who have high risk features, whereas the National Institute for Health and Care Excellence recommend 28 day extended prophylaxis after major cancer surgery in the abdomen or pelvis

(Hill and Treasure, 2010). The event rates for total pulmonary embolism or symptomatic venous thromboembolism, are low, even in colorectal cancer, such that a large body of RCT evidence would need to be produced to significantly change the outcome of previous analysis of the topic. Hence, this topic was not chosen as a topic for meta-analysis for this thesis.

1.3.3.8 Early Mobilisation

Early mobilisation as an individual factor has not been extensively investigated however given evidence to suggest beneficial effects in terms of time to return of gastrointestinal function, as well as the reduction in pulmonary and venous thromboembolic complications, this is a variable which has been accepted without large amounts of high-quality evidence. The inability to mobilise following elective colorectal surgery may also be a reflection of PONV, post-surgical morbidity, poor postoperative pain control, continuous dependence on intravenous fluids or lack of patient motivation, This raises the issue whether the superior clinical outcomes associated with early mobilisation are due to the effects of the intervention, or rather whether those with poorer clinical outcomes are less likely to mobilise. Several studies have demonstrated beneficial effects of early mobilisation in colorectal surgery (Lee et al., 2011, Delaney et al., 2003, Raue et al., 2004), however these frequently included an intervention combined with nutritional support and as such it is difficult to discern which intervention is responsible for the beneficial effect or indeed whether these act synergistically.

1.3.3.9 Stimulation of Gut Motility

ERAS guidelines frequently include the option to administer alvimopam as a stimulant of gastrointestinal function, which acts as a peripheral opioid antagonist, although this is not regarded as a compulsory component of ERAS. There is contradictory evidence in the

literature for the role of alvimopam in colorectal resection, with several studies demonstrating a benefit in terms of hospital LOS and lower rates of complications (Steele et al., 2018, Al-Mazrou et al., 2018a, Xu et al., 2016, Vaughan-Shaw et al., 2012), yet others demonstrating no significant difference in clinical outcomes (Keller et al., 2016). In one study focusing upon the administration of alvimopam in the setting of an ERAS pathway in 660 patients (Adam et al., 2016), this found shorter time to return of bowel function by 0.6 days and reduced incidence of postoperative ileus (OR 0.23, p=0.0002). The most comprehensive literature to date on open abdominal surgery in an ERAS setting is represented by a meta-analysis of nine RCTs which found a significant acceleration in time to gastrointestinal recovery, hospital LOS and postoperative ileus. However, this included patients undergoing a range of abdominal surgeries including bowel resection, simple and radical hysterectomy and radical cystectomy which may exert a significant level of bias upon the results. In laparoscopic gastrointestinal surgery, a meta-analysis (Nguyen et al., 2015) was conducted of five studies which demonstrated a 75% relative risk reduction in the incidence of postoperative ileus, however no difference was observed in readmission rates or hospital LOS. Given the relatively recent meta-analyses on the topic and a paucity of high-quality data including RCTs subsequent to these, as well as the fact that alvimopam is not currently available in the UK, this topic was not chosen for meta-analysis for this thesis.

1.4 Application of Perioperative Factors

Many of the perioperative factors covered have become accepted as dogma without adequate evidence of their efficacy, and in some cases some evidence to suggest that they are not beneficial at all, or even deleterious to outcomes. The quality of evidence level and recommendation grade for each recommendation are stated within the ERAS guidelines.

However, on a day-to-day practice level this is likely lost, and the components of the ERAS multimodal intervention are regarded as compulsory components, irrespective of the evidence for their use. Additional RCT evidence is needed for a number of the complex interventions considered as part of an ERAS pathway in order to prove their individual efficacy.

Multiple interventions have been promoted for inclusion in ERAS pathways since their inception which have now become established as perioperative dogma, however with changes and advances in the conduct of elective surgery, some of these well-established beliefs may no longer be relevant to modern practice. Multiple aspects of the ERAS pathway now have become so entrenched in modern perioperative surgical practice, some without substantial evidence for their benefit, that it would be extremely difficult to exclude these ERAS-based interventions from the control group. David Brailsford, the previous Performance Director for Team Sky, describes a concept of 'the aggregation of marginal gains' which he describes as 'the 1 percent margin for improvement in everything that you do'. By improving performance in a multitude of different areas by 1 percent, these small gains would add up to a marked improvement. The same is true of ERAS pathways, where small gains over a select number of clinical factors may result in a significant improvement in clinical outcome for the patient. In addition, ERAS by its very definition is a complex multimodal intervention, and as such it would be impossible to investigate each individual aspect of the programme, even with a cluster RCT. Should such a trial be attempted, a Hawthorne effect would also be expected within the control group which could not be controlled for. All these complex issues result in a difficult to analyse intervention, thus many of the aspects of the ERAS pathway have been accepted without good evidence and cannot be distinguished individually as part of the intervention. In addition, the compliance

with aspects of the ERAS pathway are unreliably assessed, and again given the complex multimodal intervention that this represents, it is difficult to assess the role that each component has, both independently and synergistically upon the overall outcome.

1.5 Aims and Summary

1.5.1 Aims

The aim of this thesis was, therefore, to investigate four of the interventions proposed for perioperative care in elective colorectal surgery and considered as part of the ERAS Guidelines, in order to establish the current state of evidence for their efficacy. After reviewing the evidence to date as part of this introduction, four topics were chosen due to either publication of evidence which may affect the evidence base for their role, or due to a gap in the evidence available on the topic which may inform further perioperative care procedures. The topics chosen for this were;

- mechanical bowel preparation
- oral antibiotic preparation, with or without mechanical bowel preparation
- goal-directed fluid therapy and
- perioperative intravenous lidocaine infusion.

Chapter 2 - Methodology

2.1 PRISMA Methodology

Evidence synthesis within this thesis has been undertaken using contemporary methodology and relies, for the most part, on meta-analysis for estimation of treatment effects. All meta-analyses included within this thesis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2010) and as such, the generic methodology applied to all studies is described within this chapter, with a separate methods section within each individual chapter giving details of the methodology relevant to each particular study. The PRISMA statement superseded the previous 'Quality of Reporting of Meta-Analyses' (QUORUM) Guideline published in 1996 (Moher et al., 1999), with the aim of addressing suboptimal reporting of meta-analysis studies following several studies which identified poor quality of reporting of these kinds of studies (Sacks et al., 1987, Sacks et al., 1996). The PRISMA statement is a 27-item checklist of details designed to be included in the reporting of any systematic review analysis, covering the title, abstract, introduction, methods, results and discussion (Table 2.1). It is required by many journals as part of the submission process to ensure that systematic reviews and meta-analyses have been comprehensively conducted and their reporting is complete. This detail allows the reader of a study to assess the strengths and weaknesses of the reviews methodology and make conclusions regarding the validity of the conclusions, as with any other form of research. In addition to the PRISMA guideline, which is predominantly used for studies including RCTs, there also exists the 'Meta-Analysis of Observational Studies in Epidemiology' (MOOSE) group which is tailored more specifically to those systematic reviews focusing upon observational studies. The methodology for each meta-analysis was

Table 2.1 *– Checklist of Items When Reporting a Systematic Review or Meta-Analysis from the PRISMA Guidelines (Moher et al., 2010)*

Section/Topic	Item #	Checklist Item
Title		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
Abstract		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
Methods		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g. PICOS, length of follow up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, including rationale.
Information Sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and last date searched.

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g. risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of inconsistency (e.g. I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see item 15).
Additional Analyses	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see item 16]).
Discussion		
Summary of Evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review level (e.g. incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders in the systematic review.

conducted according to the Cochrane Handbook for Systematic Reviews of Interventions Handbook (Cochrane Collaboration, 2011).

2.2 Search Strategy

A search of the PubMed, MEDLINE, Google™ Scholar and Cochrane Library databases was performed to identify full-text studies evaluating the clinical question for each individual chapter according to the pre-determined search strategy identified in the study plan. These search strategies were designed using Boolean operators (AND, OR and NOT) to pull together groups of concepts such as the healthcare condition being considered, the intervention and control groups and the study design and methodology being included. Search filters built into the individual search databases were not used as there has been substantial concern raised regarding the validity and accuracy of these techniques.

A decision was made regarding the dates for inclusion of studies and universally throughout the thesis no language restrictions were placed upon studies eligible for inclusion. In the instance that a manuscript was only available in a foreign language, the manuscript was fully translated with the aim of inclusion. The decision whether to impose limitations upon the search dictated by the time frame of publication is highly variable within the literature. This is most appropriate when an intervention did not exist prior to a certain date so limitation of the literature will not have an impact on sourcing relevant studies. There is an argument that if an intervention has changed or evolved significantly over time then older trials and reports may not be reporting comparable interventions. Similarly, there is inconsistency in reviews regarding placing language restrictions upon searches, although this is best avoided as it results in a limitation in the number of studies included. However, translation can be difficult

and incorrect interpretation of text and results may result in incorrect data being included in the meta-analysis and skewing the results. Inclusion and exclusion criteria were clearly established prior to the conduct of the literature search. The results and conclusion of any meta-analysis are hugely dependent upon the inclusion and exclusion criteria chosen. Study investigators should be knowledgeable in the topic of the meta-analysis to ensure that a relevant clinical question is being asked of an appropriate study population, and any relevant pre-planned and specified analyses are appropriately undertaken. The primary and secondary outcome measures were also clearly established at the outset of the study, as well as any pre-planned subgroup analyses, and data extraction tools designed ahead of data collection

In all studies included within this thesis, only studies which examined adult patients aged over 18 years were included, and those conducted within the field of colorectal surgery. In addition, all studies had to be conducted within the area of elective surgery, with any study including patients undergoing emergency surgery excluded. The bibliographies of all studies that met the inclusion criteria were then hand searched for any additional suitable articles and relevant conference abstracts to ensure study inclusion was as complete as possible.

2.3 Selection of Articles

Following the exclusion of initial studies on the basis of article title and abstract by two independent researchers, the remaining full-text articles were screened in detail for inclusion. If any studies in which the inclusion criteria were not clear, the article was thoroughly reviewed with the second reviewer, and any discrepancies or disagreement resolved by a third, independent researcher. The process of review and exclusion of all articles identified by the literature search was carefully recorded by both individuals conducting the search

process, with note made of which stage each paper was excluded at and the precise reasoning for exclusion of the paper. This data was then used to construct a PRISMA diagram which is available for all meta-analyses included within this thesis.

2.3.1 Study Methodology

Prior to the conduct of a systematic review and meta-analysis, consideration should be given to the nature of the study methodology eligible for inclusion. In order to achieve the best quality conclusions, RCTs alone should be included which report on all patients included within the study, analysed on the basis of an intention-to-treat principle, including a blinding process and an objective outcome measure. However, in many review topics there is insufficient evidence from RCTs to be able to draw meaningful conclusions, therefore the decision to include observational studies may be taken. A critical examination (Shrier et al., 2007) of the process of including observational studies in addition to evidence from RCTs suggests that the advantages of including both types of study methodology could outweigh the disadvantages in many study questions and that 'observational studies should not be excluded a priori'. This is further reinforced by several systematic reviews of meta-analyses of RCTs and meta-analyses of either cohort or case-control studies assessing the same intervention (Concato et al., 2000, Golder et al., 2011) which found that the results of well-designed observational studies, whether cohort or case-control, do not systematically overestimate the effect size of treatment when compared with the results of RCTs. In two chapters within this meta-analysis, those concerning the role of pre-operative OAB and MBP in elective colorectal surgery, the decision was made to include observational studies due to the recent large numbers of publications on the topic which may significantly adjust the balance of the evidence. In the case of the oral antibiotic chapter, this was mostly in the format of database studies. This was due to a paucity of evidence available based upon RCTs,

with much of the up to date evidence arising from database studies, most notably the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). Significant note was made in the discussion of this study to the inherent weaknesses that this introduces to the meta-analysis. In addition, separate, pre-planned meta-analyses were conducted on evidence arising just from RCTs and just from cohort studies to examine any difference in results according to the quality of evidence assessed.

2.3.2 Time of Publication

With the large number of studies published on a monthly basis adding to the evidence base of many medical practices, there are frequently multiple 'Epub ahead of print' articles available prior to formal paper publication which may be suitable for inclusion within the review. There is no standardised process for the inclusion or not of these papers, however given they have been published electronically, by definition they have been through the thorough peer review process and accepted for publication by the relevant journal. It is therefore important to include these papers within the review in order for the review to represent the most up to date analysis of the literature available, and this strategy was adopted for all meta-analyses included within the thesis.

2.3.3 Abstract Versus Full Text Articles

The inclusion of studies which have been published in the format of an abstract alone is controversial, for example in the format of conference proceedings. It may take some time for research findings to be translated from abstract format through to eventual peer reviewed publication. It is not uncommon for insufficient detail to be included within the abstracts for a decision to be made regarding inclusion or not into the review, therefore it may be

appropriate to approach the study authors to verify details of the data prior to inclusion. If this process has been pursued, details should be given of this within the paper, as this has not been peer reviewed and therefore may subject the review to a degree of bias. A systematic review of 11 studies (Scherer et al., 1994) investigated a total of 2391 published abstracts from a range of medical specialities and examined the rate of conversion to full publication within two years from the date of abstract publication. The average rate of full publication within two years of the abstract was just 51% (95% CI 45% to 57%), and when evidence from RCTs alone was considered, this publication rate remained just 50%. This question has recently been reanalysed by a Cochrane Collaboration systematic review (Scherer et al., 2018) which combined data from 425 reports and demonstrated a full publication rate of 37.3% from conference abstract, with almost a third of these on data from RCTs. This study also found that this high non-publication rate had not changed significantly over time. This suggests that the inclusion of full publication alone is likely to exclude a large number of potentially relevant studies which have been published in abstract form alone.

If the study has not been through the peer review process necessary for formal publication, or indeed may have been deemed ineligible for publication, inclusion of this may result in a systematic bias which may detract from the results of other, more thoroughly designed and conducted studies. However, there may be an element of publication bias introduced by excluding these studies as papers with a negative finding are less likely to be published, thus further emphasising a potential treatment effect which is not truly there. A study of 218 RCT proposals submitted to a hospital ethics committee between 1979 and 1988 demonstrated that those studies which found statistically significant results, as defined by a p value <0.05, were significantly more likely to be published that those with no statistically significant

result (hazard ratio (HR) 2.32, 95% CI 1.47 to 3.66, p=0.0003) (Stern and Simes, 1997). Furthermore, there is evidence suggesting that trials which demonstrate a statistically significant result have a significantly shorter time to publication than those which have a non-significant result (3.5 years versus 6.1 years, p<0.001) (Song et al., 2017).

2.4 Data Extraction

Study data were dual extracted from the studies by both the thesis author and an independent researcher, with the outputs then compared to ensure maximal accuracy for each of the meta-analyses conducted as part of this thesis. The primary and secondary outcome measures were clearly established at the outset of the study, as well as any pre-planned subgroup analyses, and data extraction tools designed ahead of data collection. Data were also collated on pre-defined patient demographics, surgical variables and intra- and post-operative outcomes.

2.4.1 Handling of Missing Raw Data

If data necessary for the conduct of the meta-analysis were not available from the manuscript the corresponding author was approached to obtain this via the corresponding author email address on the manuscript. This approach was made via three separate emails over a six-week period with the aim of ensuring data collection was as complete as possible. This was particularly an issue for inclusion of continuous variables when median and interquartile range (IQR) data were frequently provided but are not suitable for inclusion within the meta-analysis. If the authors did not provide the necessary data, the technique described by Hozo *et al.* (Hozo et al., 2005) was used to estimate the mean and standard deviation from the

median and interquartile range (IQR). This technique uses the following formulae to calculate the mean and standard deviation dependent upon the sample size:

Table 2.4.1 *– Calculation of mean and standard deviation data from median and range data dependent upon sample size*

Sample Size	n≤15	15<n≤25	25<n≤70	70<n
Estimate of Mean	=(a+2m+b)/4	=(a+2m+b)/4	=median	=median
Estimate of Standard Deviation	$=1/12[((a-2m+b)^2/4)+(b-a)^2]$	=range/4	=range/4	=range/6

M=median; a= smallest value (minimum); b= largest value (maximum); n= sample size

Another issue surrounding inclusion of raw data from studies is when data is provided in graphical format in the manuscript with no mention made of the numerical data. Where data were only available in graphical format and the authors did not respond to the request for raw data as detailed above, this was extracted in either direct or indirect form using plotdigitizer (www.plotdigitizer.sourceforge.net) This technique is well described in the literature and more accurate than manual estimation from images.

2.4.2 Assessment of the Risk of Bias from Included Studies

The results of a systematic review and meta-analysis should always be interpreted in light of the analysis of quality of studies included – the quality of the synthesis conducted and therefore the strength of the conclusions drawn is a direct reflection of the quality of the evidence assessed. Bias is defined as 'a systematic error, or deviation from the truth, in results or inferences' (Cochrane Collaboration, 2011), which can result in either an under-

or over-estimation of the true intervention effect. Differing risk of bias within studies included within a meta-analysis can be at least partially responsible for differing results in studies seemingly investigating the same study question. This can therefore result in increased heterogeneity within the meta-analysis, which is explored in further detail in this chapter.

There are generally regarded to be five key types of bias which can affect the validity of a RCT, the first being selection bias which describes a systematic difference between the baseline characteristics of the intervention and control groups. The second is performance bias which is a systematic difference in the overall care provided to the intervention and control groups other than the intervention itself. Attrition bias is a systematic difference in participant withdrawal or crossover between the two groups, and detection bias a difference in how the outcome measure was determined between the two groups. Finally, reporting bias describes the presence of systematic differences between reported and unreported findings, usually relating to the increased tendency to report 'positive' findings from a study rather than negative ones.

There are a number of described methods used for the assessment of risk of bias of included studies, with a recently published systematic review of the literature (Page et al., 2018) identifying 18 tools designed for this purpose. These include the Cochrane Collaboration tool for assessing bias (Higgins et al., 2011), the Jadad Score (Jadad et al., 1996), and the Newcastle-Ottawa tool (specific to case control studies) (Wells et al., 2016). However, there is a significant lack of consistency in the tool used to assess the risk of bias and quality of included studies as well as the inclusion of this data within published systematic reviews. There is also evidence that risk of bias assessments are hugely variable in the literature, with

a systematic review of systematic reviews (Jordan et al., 2017) finding large discrepancies in how risk of bias was assessed and reported between individual studies.

In order to consider the risk of bias included within the meta-analyses in this thesis, the Cochrane Collaboration tool (Higgins et al., 2011) for assessing bias from RevMan 5.3 was employed. This analysis focuses upon six-specific domains which allow estimation of the effect of the five sources of bias described above. These domains are; random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). The Cochrane Handbook (Cochrane Collaboration, 2011) provides a list of criteria for judging the risk of bias as either low, high or unclear risk for each individual domain and these criteria were used for all risk of bias assessments throughout the thesis. The decision to employ this tool rather than the alternatives was based upon a body of literature which identified reasonable rates of concordance in risk of bias assessment and high levels of assessor satisfaction (Savovic et al., 2014). Although there are a number of identified weaknesses of this tool (Armijo-Olivo et al., 2014, Hartling et al., 2013), this appears to be true of all methods for assessment of risk of bias and as Cochrane Collaboration methodology was employed throughout this thesis the decision was taken to use this tool preferentially. The risk of bias was assessed by a single assessor throughout the study and this judgement was made based upon data presented within the manuscript. Where insufficient data was presented within the paper to make a judgement, this was recorded as 'unclear risk', rather than contacting the authors for further detail which has not been through the peer-review process.

2.5 Statistical Analysis

Data extracted from the included studies were entered into the RevMan 5.3 software program (Cochrane Collaboration, 2014). The process of meta-analysis utilises two basic principles, firstly the calculation of a summary statistic from the raw data for each individual study, typically a risk or odds ratio (OR) for dichotomous data or mean difference for continuous data. The second stage then calculates a pooled intervention effect from the weighted average of the individual study intervention effects, so it is not merely a simple sum of all the results of studies included, but an aggregation of the results dictated by the precision of the results included. The precision of a study is estimated from the variance of the study data analysed, with studies with a high level of variance given a reduced weighting in the final meta-analysis. The standard analysis for estimates of intervention effects across individual studies employs a fixed-effects model which assume that all studies estimate exactly the same intervention effect, however it is possible to employ a random-effects model. These models do not assume that each individual study estimates exactly the same intervention effect but more that they are an estimation of an effect with a similar distribution.

Throughout the thesis, dichotomous variables were analysed using the Mantel-Haenszel random effects model and continuous variables were analysed using the inverse-variance random effects model. Random effects models were chosen for analysis as this does not make the assumption that all studies included within the meta-analysis were based upon the same study population and therefore estimate the same intervention effect, rather than fixed-effect models. Data were used to construct forest plots, with a p value <0.05 on two tailed testing indicating a statistically significant difference which is used to reduce the risk of type one error, which is the rejection of a true null hypothesis, otherwise described as a false negative.

When the Hozo technique (Hozo et al., 2005) had been used to estimate mean and standard deviation (SD) data from studies included to inform continuous data analysis, two separate meta-analyses were conducted; one including the estimated data and one excluding this data to assess for any bias this built into the analysis.

2.6 Study Heterogeneity

The combination of a range of studies, irrespective of study quality and equivalence of study inclusion criteria, will result in a degree of variability in participants, interventions and outcomes studied, termed heterogeneity. There are two forms of heterogeneity which may be incorporated as part of a systematic review or meta-analysis; that of variability in study participants, interventions and outcome measures which are considered to be clinical diversity, and that introduced by differing risk of bias within individual studies and variation in study design, termed methodological diversity. The combination of clinical and methodological diversity produces differences in study results and outcome effects, and this is termed statistical heterogeneity. Careful thought should be given to potential sources of heterogeneity in the planning stages of a meta-analysis, with identification of planned sub-group analyses prior to conduct of the meta-analysis. This can in itself be useful, as these analyses may reveal information on the impact that differing clinical or methodological approaches have upon the clinical outcome measure considered by the meta-analysis. The degree of statistical heterogeneity for an analysis can be appreciated from the Forest plot, with large degrees of overlap in the 95% confidence intervals (CI) indicating low degrees of heterogeneity, and poor overlap in CI the reverse.

Study heterogeneity and inconsistency were assessed quantitatively in the meta-analyses within this thesis using the I^2 statistic (Higgins and Thompson, 2002); with 25% or less representing low heterogeneity, 25-50% moderate and exceeding 50% high heterogeneity. This statistical test is designed 'to quantify the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results.' The figure quoted indicates what proportion of the variability in results can be attributed to heterogeneity rather than chance alone.

Within the field of surgery, the treatment and control arms are not always entirely consistent as these often represent complex interventions, in contrast to for example a drug trial where the treatment arm is a known constant. One such example is in the comparison of operative with non-operative treatment of a condition – there are a large number of factors which may influence clinical outcome measures associated with a surgical procedure, many of which cannot be appreciated in the data collection process. Similarly, in a multicentre study, there may be significant variability between the nature of supposedly equivalent treatment arms, which is further emphasised when multiple studies of this methodology are included. Pragmatism is a key concept within this field of research.

This heterogeneity can be further emphasised in clinical conditions where the precise diagnostic criteria are not well established, therefore the study population included may not be all equivalent. One good example of this within the field of surgery in the diagnosis of acute appendicitis which can be made using several differing criteria which have different sensitivities and specificities including clinical, radiological and histological diagnoses. The clinical outcome measure may also introduce some degree of heterogeneity, due to differing methods for measurement or defining this measure. One such example of this may in the

definition of failure of a particular form of intervention, nature of complications or the presence of SSI.

If a large amount of statistical heterogeneity is present within the review, there are a number of strategies suggested for investigating and minimising this effect. Data should be verified as correct from the original source data as human error may be a factor. If there is inconsistency in the direction of the effect associated with the intervention and high levels of heterogeneity, it may not be appropriate to perform a meta-analysis of the results as the analysis process may reveal a misleading result. The degree of heterogeneity will also dictate the type of analysis performed; if the results are largely homogeneous and drawn from very similar study populations, a fixed effects model can be used, whereas if the results are more heterogeneous it may be more appropriate to utilise a random effects model. It is emphasised that if the level of statistical heterogeneity is high within a meta-analysis, the reason for this degree of heterogeneity should be explored either by subgroup analyses as mentioned previously, or meta-regression. The process of meta-regression goes one step beyond that of planned subgroup analyses, examining the impact of several different study variables upon the clinical outcome measure.

2.7 Reporting of Results

Tables denoting the baseline characteristics of the study populations as well as the nature of the interventions considered by individual studies were generated to aid in the interpretation of study outcomes. A table summarising the risk of bias analysis was also generated for each meta-analysis, again to contextualise the results.

Forest plots were generated using RevMan software (Cochrane Collaboration, 2014) and quote the effect size from individual studies as a black central block with the 95% CIs demonstrated graphically by lines extending either side of the central block. Dichotomous variables were reported as risk ratios (RR) and quoted with a 95% CI and continuous variables as a mean difference again with a 95% CI. The area of the block indicates the weighting afforded to the individual study as part of the aggregated analysis of the intervention effect, with the cumulative effect size demonstrated at the bottom of the plot by a diamond and quoted in text form. The Forest plot also provides data on the number of patients analysed between groups and number of events within these groups as well as heterogeneity statistics. Forest plots should not be generated for analyses which do not include any studies and are significantly discouraged when only a single study exists for a particular outcome as suggested by the Cochrane Handbook.

2.9 Protocol Registration

In line with other contemporary research methodologies, high quality evidence synthesis also includes prospective registration of studies using the PROSPERO 'International Prospective Register of Systematic Reviews' (www.crd.york.ac.uk/prospero). The University of York established the PROSPERO database as an which currently holds the records of 10,000 planned or completed review studies, with this representing a permanent, prospective record of key review features. The aim of this resource is to reduce study duplication between different study groups, counter publication bias by including key outcomes irrespective of eventual publication status, and to increase transparency such that editors and other readers of the final review may compare the planned study protocol with the final outcome, thus protecting against selective reporting bias.

The protocols for all meta-analyses included in this thesis were prospectively registered at the outset of the conduct of the study with the PROSPERO database with the details of their registration provided in **Table 2.6.1**.

Table 2.6.1 *– Details of the PROSPERO registration of all studies included within the thesis*

Chapter Number	Study Title	PROSPERO Registration number	Accessible at:
Chapter 3	The Impact of Mechanical Bowel Preparation in Elective Colorectal Surgery	CRD42015025279 (Appendix 1)	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=25279
Chapter 4	The role of oral antibiotic preparation in elective colorectal surgery	CRD42018098950 (Appendix 2)	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=98950
Chapter 5	Goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery	CRD42018106818 (Appendix 3)	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=106818
Chapter 6	The impact of perioperative intravenous lidocaine infusion upon postoperative gastrointestinal function in elective colorectal surgery	CRD42018115916 (Appendix 4)	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=115916

2.10 Potential Alternative Methodologies

During the design of this body of work, alternative approaches to evaluating the evidence surrounding each individual ERAS intervention were considered. There are a number of other alternative approaches including the use of large population registries, institutional databases, billing and healthcare coding data as well as network meta-analysis.

2.10.1 Database-based Approaches

Large healthcare databases and registries have become ubiquitous in the medical literature. They rely on datasets defined at the time of inception and data acquisition is often through either billing data or coding data, usually collected contemporaneously. These datasets are shown to be large, but frequently have issues surrounding data linkage (Harron et al., 2014). The advantages are the richness of the datasets and the ability to subject the datasets to adjust for confounders which can allow the development of complex statistical models (Dinov, 2016). However, treatments are rarely standardised, there is variation in diagnostic coding between institutions, and in many cases the data fidelity falls short of that which would be required to establish the individual components of the ERAS protocols. The outputs of large cohort studies have been included where appropriate in the evidence synthesis throughout this thesis due to their potential strengths. However, in areas where large randomised trials exist these have been included preferentially.

2.10.2 Network Meta-Analysis

Network meta-analysis is relatively recent development in the field of evidence-based medicine, and is an approach used to compare multiple interventions simultaneously by performing a combination of direct and indirect comparisons within a network of studies

(Rouse et al., 2017). If say one study reports A *versus* B and a second study reports B *versus* C then an indirect comparison of A *versus* C can be made. There are a number of advantages to this approach and it allows for comparison of multiple studies and there have been a several recent high profile studies which have used the approach to establish effect sizes of individual components such as preoperative carbohydrate loading in elective surgery (Amer et al., 2017), a comparison of robotic, laparoscopic or open colorectal surgery (Sheng et al., 2018) and immunonutrition in gastrointestinal surgery (Song et al., 2015). However, network meta-analysis was not felt to be suitable for the topics contained within this thesis. The one chapter where multiple comparisons would add significant weight to the analysis is chapter 4 on the role of OAB with or without MBP. However, many of the comparisons did not contain sufficient evidence to be able to conduct a direct comparison using traditional meta-analysis, hence a network would not add significant merit to this.

Chapter 3 – The Impact of Mechanical Bowel Preparation in Elective Colorectal Surgery

3.1 Introduction

MBP for colorectal surgery has been surgical dogma for decades, despite increasing evidence from the 1990s refuting its benefits (Platell and Hall, 1998, Santos et al., 1994). The rationale behind the administration of MBP is that it reduces faecal bulk and, therefore, bacterial colonisation, thereby reducing the risk of postoperative complications such as anastomotic leakage and wound infection (Nichols and Condon, 1971). It may also facilitate dissection, particularly in laparoscopic surgery, and allow endoscopic evaluation. Opponents argue that in the 21st century, with rational use of oral and intravenous prophylactic antibiotics there is no longer a place for MBP. Evidence has suggested that it may cause marked fluid and electrolyte imbalance in the preoperative period, with metabolic and electrolyte disturbance being particularly pronounced in preparations involving sodium phosphate (Lieberman et al., 1996, Beloosesky et al., 2003). These changes include hyperphosphataemia, compensatory hypocalcaemia, as well as hypomagnesaemia, hypokalaemia, and elevated serum osmolality. These effects are frequently more pronounced in elderly patients and those who are dehydrated (Shapira et al., 2010). In addition to these metabolic effects, evidence has shown that the gut microbial flora load is not reduced grossly by bowel preparation (Jung et al., 2010), thus questioning its potential benefits in terms of reduction of surgical site-related complications. There is also concern that bowel preparation liquefies faeces, thereby increasing the risk of spillage and contamination intra-operatively (Mahajna et al., 2005). Its use remains controversial, particularly within the context of an ERAS program setting (Gustafsson et al., 2013, Nygren et al., 2013), and its use is now variable (Devane et al., 2017).

Meta-analyses (Dahabreh et al., 2015, Cao et al., 2012, Guenaga et al., 2011, Zhu et al., 2010, Courtney et al., 2015) have been published on MBP in elective colorectal surgery showing mixed results, with most studies demonstrating no difference in infective complications between patients receiving MBP or control treatment, although the control treatment varied significantly between the use of a rectal enema or absolutely no preparation. Similar results have been found in gynaecological (Zhang et al., 2015, Huang et al., 2015b) and urological (Deng et al., 2014, Large et al., 2012) surgery where studies have shown no benefits in visualisation, bowel handling or complication rates between patients treated with bowel preparation and those given no bowel preparation. As a result of this inconclusive evidence, practice varies significantly between countries and even surgeons in the same institution (Zmora et al., 2003b, Drummond et al., 2011). Further complicating the issue is the lack of consensus regarding the optimal method of bowel cleansing, with many different MBP regimes utilised, all of which are associated with variable compliance and side effects. There are generally regarded to by three different types of bowel preparation agents; osmotic agents such a sodium or magnesium containing agents as well as polyethylene glycol (PEG), stimulant laxatives such as bisacodyl, and those which contain a combination of the above such as Picolax and MiraLax. The mechanism of action of a stimulant laxative is to increase the force and frequency of colonic peristalsis by aiding retention of water and electrolytes within the colonic lumen mediated via prostaglandin and cyclic AMP pathways, and osmotic agents facilitate retention of fluid within the colon, with increased water retention promoting colonic peristalsis and promoting defecation.

Infective complications are amongst the leading causes of morbidity and mortality in patients undergoing colorectal surgery (McSorley et al., 2016). However, MBP is not without its own complications and the process is both time-consuming and unpleasant for patients (Jung et

al., 2007a). It has been shown to cause clinically significant dehydration (Sanders et al., 2001) and electrolyte disturbances, particularly hypocalcaemia and hypokalaemia to which the elderly are especially vulnerable (Holte et al., 2004, Shapira et al., 2010, Ezri et al., 2006). Patient satisfaction is poor for undergoing bowel preparation prior to surgery and colonoscopy, and this may necessitate an additional day preoperatively in hospital, particularly for frail elderly patients.

In the United Kingdom, the National Institution of Health and Care Excellence (NICE) does not recommend the routine use of MBP to reduce the risk of SSI (NICE, 2008) and the ERAS® Society guidelines on perioperative care of patients undergoing colonic resection (Gustafsson et al., 2013) also recommend against using preoperative bowel preparation. However, for rectal resection (Nygren et al., 2013) the recommendation, albeit weak, is to use MBP for patients undergoing anterior resection with diverting stomas with the aim of preventing a column of faeces above a left sided colonic anastomosis. In recent years further evidence has emerged from large database studies using the NSQIP database in America (Scarborough et al., 2015, Moghadamyeghaneh et al., 2015a, Morris et al., 2015b, Kiran et al., 2015) showing reduced rates of anastomotic leakage, intra-abdominal abscess formation and wound infection when patients were given MBP with intraluminal antibiotics pre-operatively. The NSQIP database was developed by the American College of Surgeons (ACS) and is a nationally validated database created with the aim of improving the quality of surgical care (Alluri et al., 2016), with data contributed by over 400 hospitals across the United States of America. One major advantage of the NSQIP database over other large databases such as the National Inpatient Sample (NIS) and Centres for Medicare and Medicaid Services (CMS) is that the data input process is completed by ‘nurse reviewers’ using well documented standard definitions and clear inclusion and exclusion criteria.

Studies have demonstrated high rates of inter-rater reliability associated with data extraction from the NSQIP database (Shiloach et al., 2010) and that application of the NSQIP data collection process is associated with improved clinical outcomes over time (Cohen et al., 2016). However, there are some well documented weaknesses associated with use of data from the NSQIP database including that follow up is only completed to 30 days post procedure and evidence has suggested that the reported incidence of SSI and urinary tract infection (UTI) are overestimated by the NSQIP database (O'Brien et al., 2014).

The expanding body of evidence concerning the role of MBP preparation has been assessed in this new comprehensive meta-analysis encompassing both RCTs and observational studies. This evidence synthesis sought to address deficiencies in previous studies by including all levels of evidence, separating those in which patients received a single rectal enema versus full or no preparation and including the recently published large database studies.

The aims for this meta-analysis were:

- to analyse the effect of MBP versus no preparation or rectal enema alone on postoperative infective complications in patients undergoing elective colorectal surgery,
- to examine the differences in results between evidence obtained from RCTs and observational studies, and
- to determine what effect, if any, bowel preparation had on postoperative complications in rectal surgery.

3.2 Materials and Methods

3.2.1 Specifics of Study Search Strategy

An electronic search was conducted to identify studies comparing outcomes in patients undergoing elective colorectal surgery treated with MBP versus either no preparation or a single rectal enema (last search on 1st May 2017). The search terms employed were "(bowel preparation OR bowel cleansing OR bowel cleaning) AND (surgery OR preoperative)". No language restrictions or time limitations were imposed upon the search.

3.2.2 Selection of Articles

The results of the literature search were dual screened as described previously. The inclusion criteria specified that studies must have a minimum of two comparator groups and were either designed as either RCTs or observational studies, which could be either prospective or retrospective in nature. Publications comparing preoperative MBP with no preparation or a single rectal enema were included and comparisons with other forms of bowel preparation (e.g. intraoperative colonic lavage) were excluded. Both laparoscopic and open surgical procedures were included but not endoscopic studies. The primary outcome measure included in this meta-analysis was the incidence of anastomotic leak, with secondary outcome measures of the incidence of SSI, intra-abdominal collection, hospital LOS, 30-day mortality and reoperation rates. These outcome measures were chosen as the most frequent and most important outcomes following colorectal surgery. Particular focus was placed upon infectious complications as an association has been drawn between MBP usage and reduced faecal bulk and bacterial colonisation.

Duplication of results was a particular hazard encountered when selecting which of the studies to include that extracted information from the NSQIP database (Scarborough et al., 2015, Moghadamyeghaneh et al., 2015a, Morris et al., 2015b, Kiran et al., 2015, Haskins et al., 2016, Rencuzogullari et al., 2017b, Dolejs et al., 2017, Connolly et al., 2016, Shwaartz et al., 2017b). The papers were scrutinised for their enrolment dates. There was overlap in these dates and after correspondence with the authors, it was apparent that there was considerable overlap in the data sets used. Hence, the largest study was selected for inclusion with the greatest number of clinically relevant outcome measures (Kiran et al., 2015). Two further studies (Zmora et al., 2003a, Zmora et al., 2006) had duplication of results and in this situation the larger of the two studies was included (Zmora et al., 2006). One study (Van't Sant et al., 2010) was a subgroup analysis of patients undergoing anastomosis below the peritoneal reflection taken from a study which was already included (Contant et al., 2007) in the meta-analysis so this was excluded from the main meta-analysis to prevent dual inclusion of patients. However, this subgroup was included in the separate analysis of rectal surgery. A further study (Scabini et al., 2010) reviewed as a full text article has been retracted (Scabini et al., 2012) since its inclusion in the 2011 Cochrane Review (Guenaga et al., 2011), due to large proportions of duplicated text from a previously published study. Hence, we chose to exclude this. One paper (Santos et al., 1994) analysed in the Cochrane Review included paediatric patients and so has been excluded from our meta-analysis.

3.2.3 Data Extraction

The data were extracted as described previously. Quantitative data relevant to the endpoints were selected and extracted. Several studies presented hospital LOS results in formats other than mean and standard deviation. Where this occurred, the authors were contacted for the raw data in order to ascertain the mean and standard deviation necessary for creation of

Forest plots as described previously. When the raw data were unavailable, mean and standard deviation were calculated using the technique described by Hozo *et al*. (Hozo et al., 2005).

3.2.4 Risk of bias and completeness of reporting of individual studies

The risk of bias was assessed using the Cochrane Collaboration tool in RevMan 5.3 (Cochrane Collaboration, 2014) as discussed in chapter 2.

3.2.5 Statistical Analysis

The analysis was performed using RevMan 5.3 software (Cochrane Collaboration, 2014). Continuous variables were calculated as a mean difference and 95% CI using an inverse variance random effects model. Dichotomous variables were analysed using the Mantel-Haenszel random effects model to quote the RR and 95% CI. These analyses were used to construct Forest plots, with statistical significance taken to be a p value of <0.05 on two tailed testing. Due to inclusion of studies conducted using two different methodologies, RCTs and observational studies, a decision was made to conduct separate pre-planned analyses of evidence arising from the two different study types as well as an overall analysis of all study data. A predetermined subgroup analysis was also performed to assess the impact of MBP in rectal surgery using the same methodology. Study inconsistency and heterogeneity were assessed using the I^2 statistic (Higgins and Thompson, 2002). The study protocol was prospectively registered with PROSPERO as detailed in chapter 2.

3.3 Results

From 1594 studies identified from the original search, 97 were reviewed as full text articles. Of these, 36 comprising 23 RCTs (Bertani et al., 2011, Bretagnol et al., 2010, Alcantara Moral et al., 2009, Pena-Soria et al., 2008, Contant et al., 2007, Jung et al., 2007b, B, 2006, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Zmora et al., 2003a, Young Tabusso et al., 2002, Miettinen et al., 2000, Burke et al., 1994, Brownson P, 1992, Leiro F, 2008, Fillmann EEP, 1995, Sasaki et al., 2012, Tahirkheli M.U.I., 2013, M, 2007, Hu et al., 2017, Bhattacharjee and Chakraborty, 2015) and 13 observational studies (Yamada et al., 2014, Otchy et al., 2014, Roig et al., 2011, Pitot et al., 2009, Miron et al., 2008, Bretagnol et al., 2007, Veenhof et al., 2007, Memon et al., 1997, Kiran et al., 2015, Allaix et al., 2015, Kim et al., 2014a, Ji et al., 2017, Chan et al., 2016) were eligible for inclusion (**Figure 3.3.1**). The risk of bias of the RCTs included in this meta-analysis was moderate (**Table 3.3.1).**

3.3.1 Patient demographics

Overall, 21,568 patients were included in the meta-analysis, of whom 6,166 had no bowel preparation of any sort, 2739 had a solitary rectal enema and 12,663 underwent full MBP as per local policy. Of these, 6277 patients were included in RCTs (of which 2523 had no bowel preparation, 599 had a solitary rectal enema and 3155 underwent full MBP) and 15,291 in observational studies (of which 3643 had no bowel preparation, 2140 had a solitary rectal enema and 9508 underwent full MBP). Demographic details are summarised in **Table 3.3.1.1** and of details of interventions (bowel preparation and perioperative antibiotics) in **Table 3.3.1.2**. Just two studies considered laparoscopic surgery alone (Chan et al., 2016, Allaix et al., 2015), five considered open surgery alone (Bhattacharjee and Chakraborty, 2015, Contant et al., 2007, Jung et al., 2007b, Fa-Si-Oen et al., 2005, Miettinen et al., 2000),

with the remaining studies including a mixture of open and laparoscopic cases. With these small study numbers, the decision was made not to conduct a separate meta-analysis to compare the outcomes for laparoscopic versus open surgery.

Figure 3.3.1 *– PRISMA Diagram for all studies identified by the literature search*

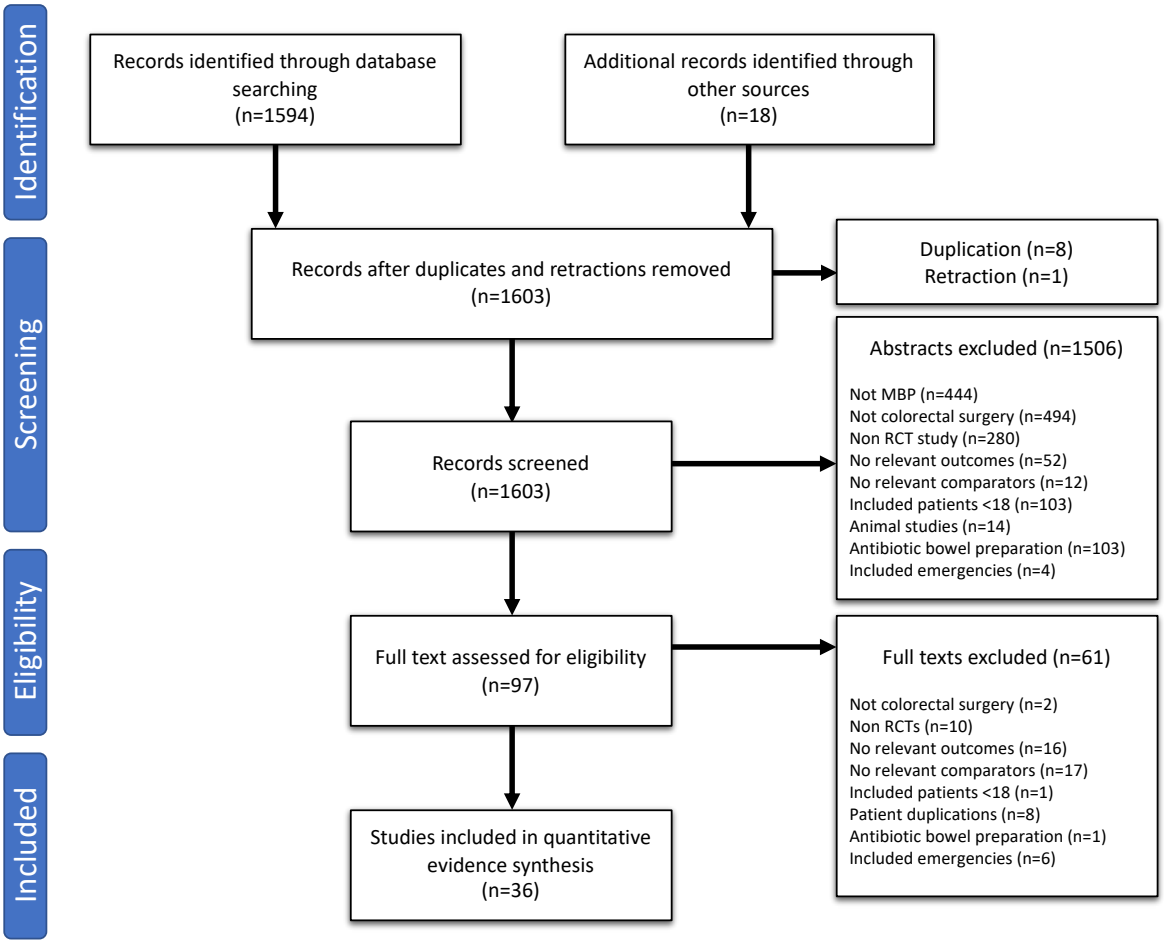


Table 3.3.1 *- Risk of bias of the RCTs included in this meta-analysis*

Reference	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Hu *et al.* 2017	?	?	?	?	?	?
Bhattacharjee *et al.* 2015	+	?	-	?	?	?
Tahirkheli *et al.* 2013	+	?	?	?	-	-
Sasaki *et al.* 2012	+	?	?	?	?	?
Bertani *et al.* 2011	+	+	?	?	+	+
Bretagnol *et al.* 2010	+	+	+	+	-	+
Alcantara Moral *et al.* 2009	+	+	?	?	?	+
Pena-Soria *et al.* 2008	+	+	+	+	-	+
Leiro *et al.* 2008	+	+	?	?	?	+
Contant *et al.* 2007	+	+	-	-	-	+
Jung *et al.* 2007	+	+	+	+	-	?
Ali *et al.* 2007	?	?	?	?	?	?

Jung *et al.* 2006	+	+	+	+	-	?
Platell *et al.* 2006	+	+	+	+	-	-
Fa-Si-Oen *et al.* 2005	+	+	?	?	+	+
Bucher *et al.* 2005	+	+	+	+	+	+
Ram *et al.* 2005	+	?	?	?	?	+
Zmora *et al.* 2003	+	+	?	?	-	+
Young Tabusso *et al.* 2002	?	?	?	?	?	?
Miettinen *et al.* 2000	+	+	?	?	+	+
Fillmann *et al.* 1995	+	+	+	+	+	+
Burke *et al.* 1994	?	?	+	+	-	-
Brownson *et al.* 1992	?	?	?	?	?	?

+ Low risk of bias; - High risk of bias; ?Unclear risk of bias

Table 3.3.1.1 *- Baseline patient demographics for all studies included.*

Reference	Year Published	Study Methodology	Study Numbers		Male: Female Gender		Indication for Surgery	Location	Primary Anastomosis	Laparoscopic Approach	
			MBP n=	No MBP n=	MBP	No MBP				MBP n=	No MBP n=
Ji *et al.*	2017	Observational	538	831	Unknown	Unknown	Cancer	Rectum	Y	Unknown	Unknown
Hu *et al.*	2017	RCT	76	72	Unknown	Unknown	Cancer	Colon and rectum	Y	Unknown	Unknown
Chan *et al.*	2016	Observational	159	97	85:74	55:42	Cancer	Colon and rectum	Y	159	97
Bhattacharjee *et al.*	2015	RCT	38	33	21:17	20:13	Cancer, IBD, volvulus, tuberculosis	Colon and rectum	Y	0	0
Allaix *et al.*	2015	Observational	706	829	361:345	432:397	Cancer, adenoma, diverticulitis, reversal of Hartmann's procedure, rectal prolapse	Colon and rectum	Y	706	829
Kiran *et al.*	2015	Observational	6146	2296	3030:3116	1111:1185	Unknown	Colon and rectum	N	4443	1389

Yamada *et al.*	2014	Observational	152	106	92:60	65:41	Cancer	Colon only	Y	97	64
Otchy *et al.*	2014	Observational	86	79	39:47	39:40	Cancer, diverticular disease, IBD, rectal prolapse, ischemic colitis, volvulus, colovaginal fistula	Colon and rectum	Y	37	48
Kim *et al.*	2014	Observational	1363	1112	502:694	669:610	Unknown	Colon and rectum	Y	709	472
Tahirkheli *et al.*	2013	RCT	48	48	28:20	24:24	Cancer, diverticular disease, IBD, ischemic colitis	Colon and rectum	Y	unknown	unknown
Sasaki *et al.*	2012	RCT	38	41	17:21	24:17	Cancer	Colon only	Y	29	19
Bertani *et al.*	2011	RCT	114	115	65:49	60:55	Cancer	Colon and rectum	Y	55	51
Roig *et al.*	2010	Observational	39	69	Unknown	Unknown	Cancer, diverticular disease, IBD, FAP	Colon and rectum	Y	12	20

Bretagnol *et al.*	2010	RCT	89	89	56:33	46:43	Rectal cancer	Rectum only	Y	73	74
Pitot *et al.*	2009	Observational	59	127	31:28	53:74	Cancer, diverticular disease, IBD	Colon only	Y	26	30
Alcantara Moral *et al.*	2009	RCT	70	69	41:28	48:22	Cancer	Left colon and rectum	Y	12	15
Miron *et al.*	2008	Observational	60	39	Unknown	Unknown	Unknown	Colon and rectum	Y	Unknown	Unknown
Pena-Soria *et al.*	2008	RCT	65	64	35:29	33:22	Cancer, IBD	Colon and rectum	Y	Unknown	Unknown
Leiro *et al.*	2008	RCT	64	65	39:25	38:27	Benign and malignant colorectal pathology	Colon and rectum	N	Unknown	Unknown
Contant *et al.*	2007	RCT	670	684	337:333	345:339	Cancer, IBD	Colon and rectum	Y	None	None
Bretagnol *et al.*	2007	Observational	61	52	42:19	32:20	Rectal cancer	Rectum only	Y	Unknown	27
Jung *et al.*	2007	RCT	686	657	306:380	317:340	Cancers, diverticular disease, adenoma	Colon only	Y	None	None

Veenhof *et al.*	2007	Observational	78	71	28:43	33:45	Not specified	Colon and rectum	Y	Unknown	Unknown
Ali *et al.*	2007	RCT	109	101	Unknown	Unknown	Unknown	Colon and rectum	Y	Unknown	Unknown
Jung *et al.*	2006	RCT	27	17	Unknown	Unknown	Cancer, adenoma and diverticular disease	Rectum only	Y	None	None
Platell *et al.*	2006	RCT	147	147	Unknown	Unknown	Cancer, IBD, diverticular disease, adenoma	Colon and rectum	N	Unknown	Unknown
Fa-Si-Oen *et al.*	2005	RCT	125	125	58:67	56:69	Cancer, diverticular disease	Colon only	Y	None	None
Bucher *et al.*	2005	RCT	78	75	47:31	34:41	Cancer, diverticular disease, reversal of Hartmann's procedure, adenoma, endometriosis	Left colon and rectum	Y	20	22

Ram *et al.*	2005	RCT	164	165	99:65	102:63	Cancer, diverticular disease, IBD	Colon and rectum	Y	Unknown	Unknown
Zmora *et al.*	2003	RCT	187	193	103:84	94:99	Cancer, diverticular disease, IBD	Colon and rectum	Y	Unknown	Unknown
Young Tabusso *et al.*	2002	RCT	24	23	12:12	9:14	Unknown	Colon and rectum	Y	Unknown	Unknown
Miettinen *et al.*	2000	RCT	138	129	68:70	62:67	Cancer, IBD, diverticular disease	Colon and rectum	91% primary anastomosis in both arms	None	None
Memon *et al.*	1997	Observational	61	75	32:29	44:31	Cancer, diverticular disease, IBD, adenoma, lipoma	Left colon and rectum	Y	Unknown	Unknown
Fillmann *et al.*	1995	RCT	30	30	Unknown	Unknown	Cancer, diverticular disease, IBD, ischemic colitis	Colon and rectum	N	Unknown	Unknown
Burke *et al.*	1994	RCT	82	87	52:30	43:44	Cancer, diverticular disease, IBD	Left colon and rectum	Y	Unknown	Unknown

Brownson *et al.*	1992	RCT	86	93	Unknown	Unknown	Cancer and other	Colon and rectum	Y	Unknown	Unknown

RCT – randomised controlled trial; IBD – inflammatory bowel disease; FAP – familial adenomatous polyposis

Table 3.3.1.2 *– Details of bowel preparation and antibiotics provided to the groups*

Reference	Details of MBP	Details of No MBP	Antibiotics Given
Ji *et al.* 2017	PEG and sodium phosphate	Single enema	Unknown
Chan *et al.* 2016	PEG	Single enema	Cefuroxime 1.5g and metronidazole 500mg
Hu *et al.* 2017	Sodium phosphate	No prep	Unknown
Bhattacharjee *et al.* 2015	PEG and sodium phosphate	No prep	Cefuroxime 1.5 g and metronidazole 500 mg
Allaix *et al.* 2015	PEG	Enema before left sided operations	As per local policy
Kiran *et al.* 2015	'As per local policy'	Unclear	As per local policy
Yamada *et al.* 2014	PEG	Glycerin Enema	Flomoxef at induction and 3 hourly intra op
Otchy *et al.* 2014	PEG	Colonic resections- no MBP Rectal resections- single enema	Ertapenem 1g or levofloxacin/ metronidazole 500mg 1hour post op then continued for 24 hours post op
Kim *et al.* 2014	'As per local policy'	Unclear	As per local policy
Tahirkheli *et al.* 2013	Saline	No prep	Oral ciprofloxacin plus unspecified intravenous antibiotics for 24 hours post op
Sasaki *et al.* 2012	PEG and sodium picosulphate	No prep	Antibiotic regime not specified
Bertani *et al.* 2011	PEG and a single enema	Single enema only	Cefotixin given at induction, 4, 12 and 24 hours. Ceftriaxone and metronidazole given for 5 days post op if heavy contamination
Roig *et al.* 2010	Mono and di sodium phosphate	No prep	Antibiotic regime not specified
Bretagnol *et al.* 2010	Senna plus povidone-iodine enema	No prep	Ceftriaxone and metronidazole at induction and every 2 hours intra op

Pitot *et al.* 2009	PEG	Rectal resections had single enema	Antibiotic regime not specified
Alcantara Moral *et al.* 2009	Sodium phosphate or PEG	Two preoperative enemas	Neomycin and metronidazole 1 day pre op, ceftriaxone and metronidazole at induction
Miron *et al.* 2008	PEG and sodium sulphate	No prep	Antibiotic regime not specified
Pena-Soria *et al.* 2008	PEG and standard enema	No prep	Gentamicin and metronidazole 30 mins pre op and 8 hourly post op
Leiro *et al.* 2008	Sodium di or monobasic phosphate or PEG	No prep	Ciprofloxacin and metronidazole 500mg pre op
Contant *et al.* 2007	PEG and bisocodyl/ sodium phosphate	No prep	Antibiotic regime not specified
Bretagnol *et al.* 2007	Senna plus povidone-iodine enema	No prep	Ceftriaxone and metronidazole at induction and every 2 hours intra op
Jung *et al.* 2007	As per local policy	No prep	Trimethoprim+ metronidazole or cefuroxime and metronidazole or dozy and met
Veenhof *et al.* 2007	PEG	Single enema	Antibiotic regime not specified
Ali *et al.* 2007	Saline	No prep	Antibiotic regime not specified
Jung *et al.* 2006	PEG or sodium phosphate	No prep	Oral sulphamethoxazole-trimethoprim and metronidazole, cephalsporin and metronidazole, doxycycline and metronidazole
Platell *et al.* 2006	PEG	Phosphate enema	Timentin or gentamycin and metronidazole at induction
Fa-Si-Oen *et al.* 2005	PEG	No prep	Ceftriaxone and metronidazole or gentamycin and metronidazole at induction

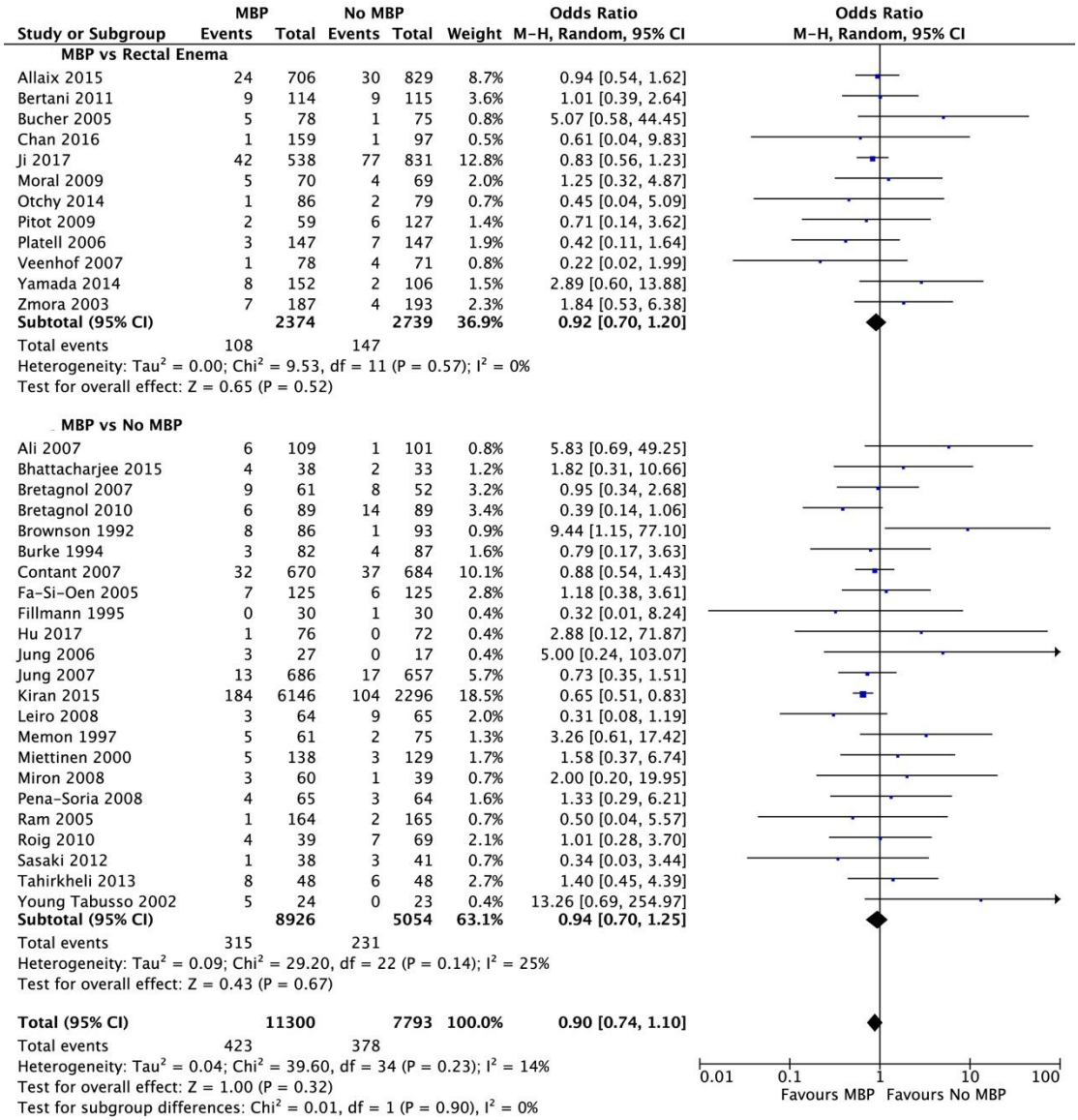
Bucher *et al.* 2005	PEG	Rectal resections had a single saline enema	Ceftriaxone and metronidazole at induction and 24 hours post op
Ram *et al.* 2005	Monobasic and dibasic sodium phosphate	No prep	Ceftriaxone and metronidazole 1 hour pre op and 48 post op
Zmora *et al.* 2003	PEG	Rectal resections had a single phosphate enema	Erythromycin and neomycin 3 doses and intravenous antibiotics for 24 hours
Young Tabusso *et al.* 2002	PEG or saline/mannitol	No prep	Antibiotic regime not specified
Miettinen *et al.* 2000	PEG	No prep	Ceftriaxone and metronidazole at induction
Memon *et al.* 1997	Phosphate enema, picolax, PEG, saline lavage	No prep	Antibiotic regime not specified
Fillmann *et al.* 1995	Mannitol	No prep	Metronidazole and gentamicin 1hr pre op then for 48 hours
Burke *et al.* 1994	Sodium picosulphate	No prep	Ceftriaxone 1g, metronidazole at induction and 8 and 16 hours
Brownson *et al.* 1992	PEG	No prep	Antibiotic regime not specified

MBP – mechanical bowel preparation; PEG – polyethylene glycol

3.3.2 Anastomotic leak

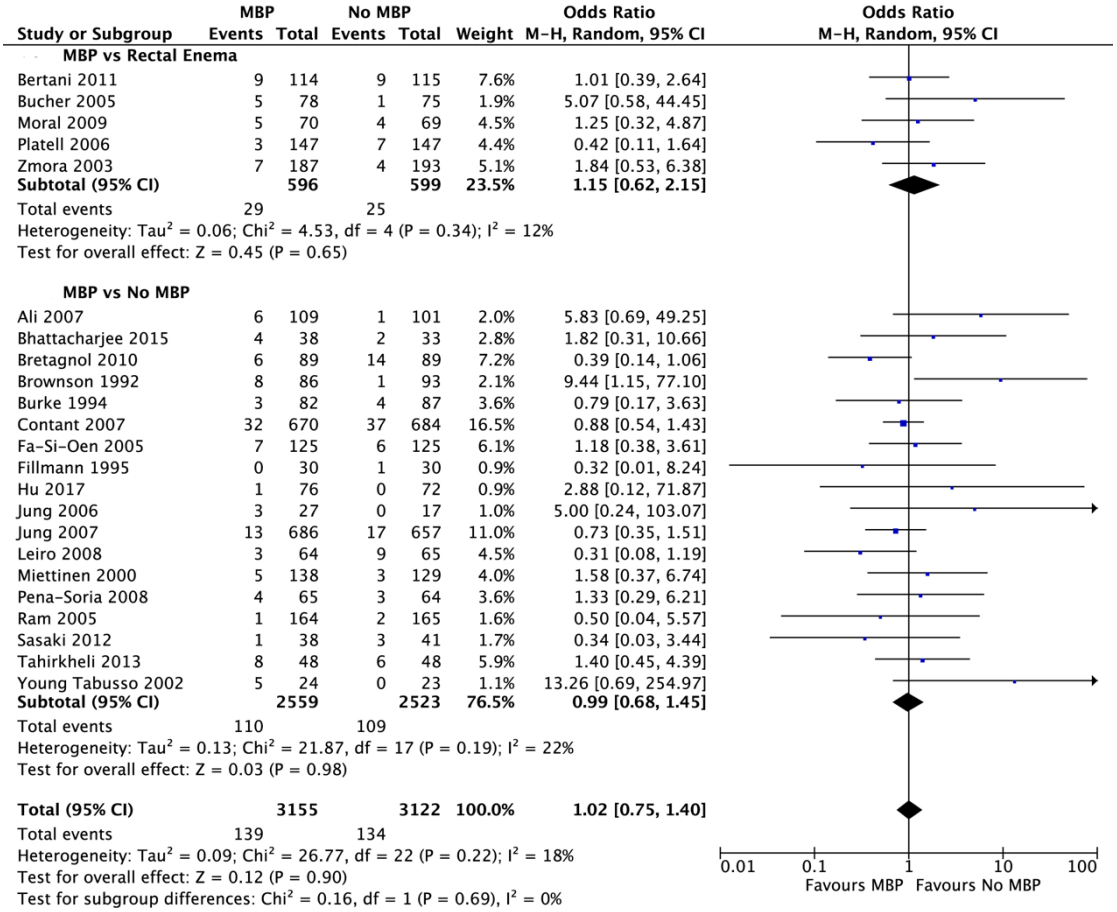
All studies except one (Kim et al., 2014a) included data on the primary outcome measure of this meta-analysis, the incidence of anastomotic leak (**Figure 3.3.2.1**). When MBP was compared with no MBP (including no preparation at all and those who underwent a single rectal enema), there was no difference in the incidence of anastomotic leak (OR 0.90, 95% CI 0.74 to 1.10, p=0.32). When MBP versus absolutely no MBP was analysed (M, 2007, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2007, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, Jung et al., 2007b, B, 2006, Kiran et al., 2015, Leiro F, 2008, Memon et al., 1997, Miettinen et al., 2000, Miron et al., 2008, Pena-Soria et al., 2008, Ram et al., 2005, Roig et al., 2011, Sasaki et al., 2012, Tahirkheli M.U.I., 2013, Young Tabusso et al., 2002), this made no difference to anastomotic leak rates (OR 0.94, 95% CI 0.70 to 1.25, p=0.67), nor when MBP was compared with a single rectal enema (Allaix et al., 2015, Bertani et al., 2011, Bucher et al., 2005, Chan et al., 2016, Ji et al., 2017, Alcantara Moral et al., 2009, Otchy et al., 2014, Pitot et al., 2009, Platell et al., 2006, Veenhof et al., 2007, Yamada et al., 2014, Zmora et al., 2003a) (OR 0.92, 95% CI 0.70 to 1.20, p=0.52).

Figure 3.3.2.1 *- Forest plot comparing overall anastomotic leak rate for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom)*



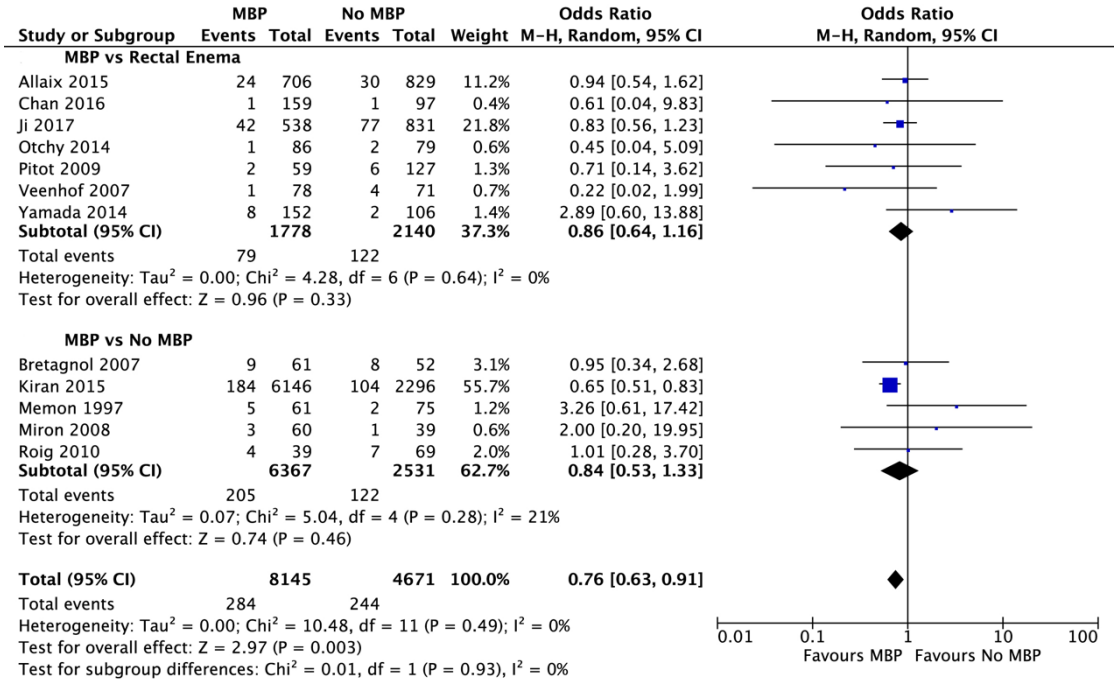
When RCTs alone were included in the analysis (Bertani et al., 2011, Bretagnol et al., 2010, Alcantara Moral et al., 2009, Pena-Soria et al., 2008, Contant et al., 2007, B, 2006, Jung et al., 2007b, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Zmora et al., 2003a, Young Tabusso et al., 2002, Miettinen et al., 2000, Burke et al., 1994, Brownson P, 1992, Leiro F, 2008, Fillmann EEP, 1995, Sasaki et al., 2012, Tahirkheli M.U.I., 2013, M, 2007, Hu et al., 2017, Bhattacharjee and Chakraborty, 2015) (**Figure 3.3.2.2**), the use of MBP versus no MBP did not affect the incidence of anastomotic leak (OR 1.02, 95% CI 0.75 to 1.40, p=0.90), nor when MBP versus absolutely no MBP (M, 2007, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, B, 2006, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Pena-Soria et al., 2008, Ram et al., 2005, Sasaki et al., 2012, Tahirkheli M.U.I., 2013, Young Tabusso et al., 2002) or MBP versus single rectal enema (Bertani et al., 2011, Bucher et al., 2005, Alcantara Moral et al., 2009, Platell et al., 2006, Zmora et al., 2003a) were considered.

Figure 3.3.2.2 *- Forest plot comparing anastomotic leak rate for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



When observational studies alone were analysed (Yamada et al., 2014, Otchy et al., 2014, Roig et al., 2011, Pitot et al., 2009, Miron et al., 2008, Bretagnol et al., 2007, Veenhof et al., 2007, Memon et al., 1997, Ji et al., 2017, Chan et al., 2016) (**Figure 3.3.2.3**), the use of MBP versus no MBP did significantly affect the incidence of anastomotic leak (OR 0.76, 95% CI 0.63 to 0.91, p=0.003), although this was not significant when MBP versus single rectal enema (Allaix et al., 2015, Chan et al., 2016, Ji et al., 2017, Otchy et al., 2014, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014) and MBP versus absolutely no MBP (Bretagnol et al., 2007, Kiran et al., 2015, Memon et al., 1997, Miron et al., 2008, Roig et al., 2011) were considered separately.

Figure 3.3.2.3 *- Forest plot comparing anastomotic leak rate for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*

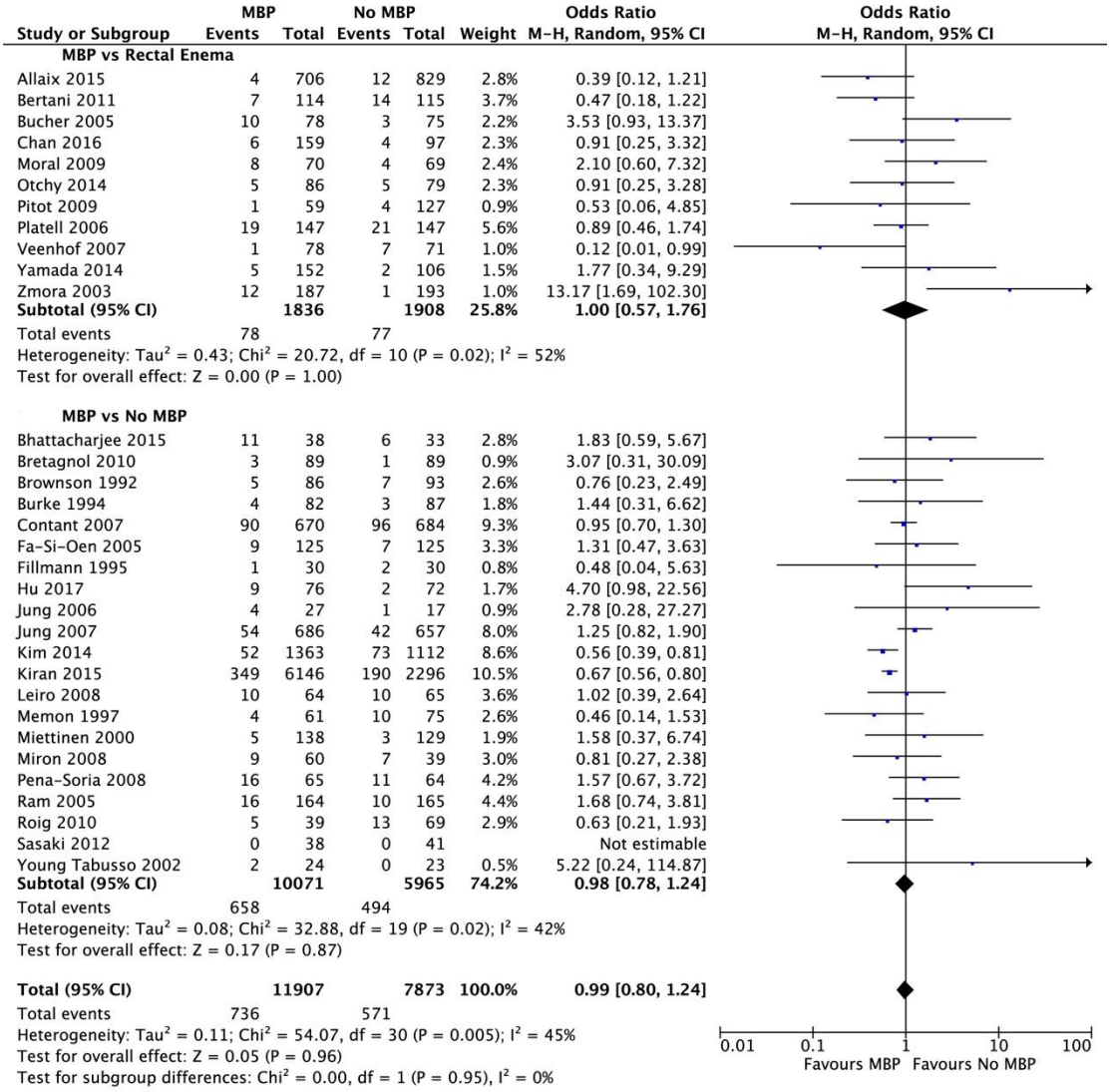


3.3.3 Surgical Site Infection

Data on the incidence of SSI were presented in a total of 19,780 patients in 32 studies (Allaix et al., 2015, Kiran et al., 2015, Yamada et al., 2014, Otchy et al., 2014, Kim et al., 2014a, Sasaki et al., 2012, Bertani et al., 2011, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Alcantara Moral et al., 2009, Miron et al., 2008, Pena-Soria et al., 2008, Leiro F, 2008, Contant et al., 2007, Jung et al., 2007b, B, 2006, Veenhof et al., 2007, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Zmora et al., 2003a, Young Tabusso et al., 2002, Miettinen et al., 2000, Memon et al., 1997, Fillmann EEP, 1995, Burke et al., 1994, Brownson P, 1992, Chan et al., 2016, Hu et al., 2017, Bhattacharjee and Chakraborty, 2015) (**Figure 3.3.3.1**). There was no difference in the incidence of SSI in those who did versus those who did not undergo MBP (OR 0.99, 95% CI 0.80 to 1.24,

p=0.96), nor in those who had MBP versus those with a single rectal enema (Alcantara Moral et al., 2009, Allaix et al., 2015, Bertani et al., 2011, Bucher et al., 2005, Chan et al., 2016, Otchy et al., 2014, Pitot et al., 2009, Platell et al., 2006, Veenhof et al., 2007, Yamada et al., 2014, Zmora et al., 2003a) (OR 1.00, 95% CI 0.57 to 1.76, p=1.00) or those who had MBP versus those with absolutely no preparation (Bhattacharjee and Chakraborty, 2015, B, 2006, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, Jung et al., 2007b, Kim et al., 2014a, Kiran et al., 2015, Leiro F, 2008, Memon et al., 1997, Miettinen et al., 2000, Miron et al., 2008, Pena-Soria et al., 2008, Ram et al., 2005, Roig et al., 2011, Sasaki et al., 2012, Young Tabusso et al., 2002) (OR 0.98, 95% CI 0.78 to 1.24, p=0.87).

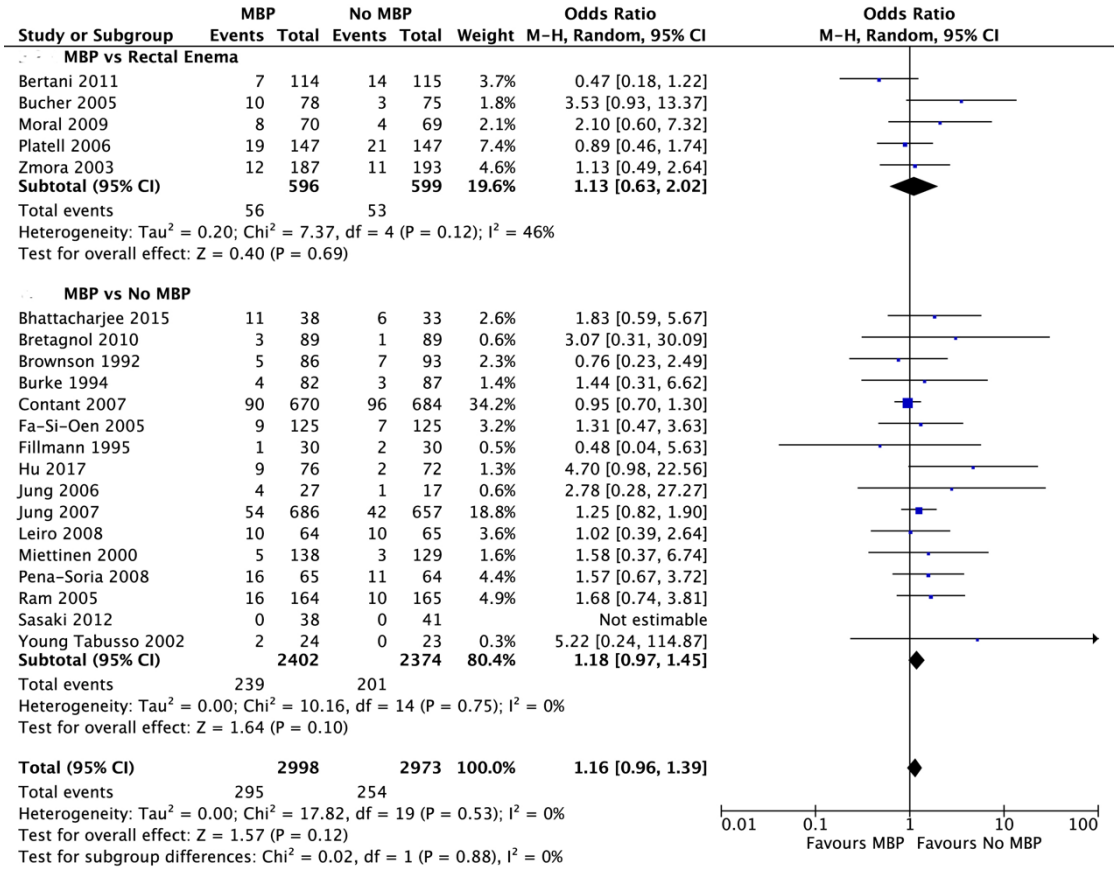
Figure 3.3.3.1 *- Forest plot comparing overall SSI rates for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom).*



When data obtained from 21 RCTs (Alcantara Moral et al., 2009, Bertani et al., 2011, Bucher et al., 2005, Platell et al., 2006, Zmora et al., 2003a, Cochrane Collaboration, 2014, B, 2006, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Pena-Soria et al., 2008, Ram et al., 2005, Sasaki et al., 2012, Young Tabusso et al., 2002) alone with a total of 5971 patients were included (**Figure 3.3.3.2**), the use of MBP versus no MBP did not impact upon the

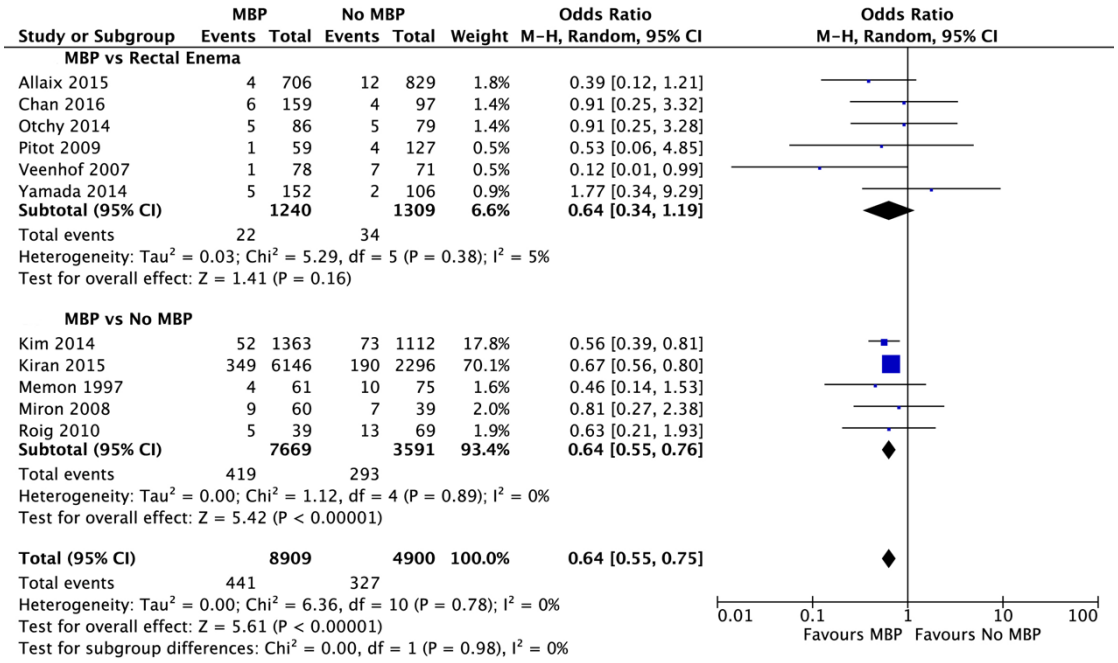
incidence of SSI (OR 1.16, 95% CI 0.96 to 1.39, p=0.12), nor when MBP versus single rectal enema (Alcantara Moral et al., 2009, Bertani et al., 2011, Bucher et al., 2005, Platell et al., 2006, Zmora et al., 2003a) or MBP versus absolutely no preparation (B, 2006, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Pena-Soria et al., 2008, Ram et al., 2005, Sasaki et al., 2012, Young Tabusso et al., 2002) were considered.

Figure 3.3.3.2 *- Forest plot comparing SSI rate for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



When just observational studies were included (Allaix et al., 2015, Chan et al., 2016, Otchy et al., 2014, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014, Kim et al., 2014a, Kiran et al., 2015, Memon et al., 1997, Miron et al., 2008, Roig et al., 2011) (11 studies, 13,809 patients; **Figure 3.3.3.3**), patients who received MBP had a significantly reduced incidence of SSI than those who did not receive MBP (OR 0.64, 95% CI 0.55 to 0.75, p<0.0001), with similar results seen in those who received MBP versus absolutely no MBP (Kim et al., 2014a, Kiran et al., 2015, Memon et al., 1997, Miron et al., 2008, Roig et al., 2011), although no difference was seen between those who received full MBP versus a single rectal enema (Allaix et al., 2015, Chan et al., 2016, Otchy et al., 2014, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014).

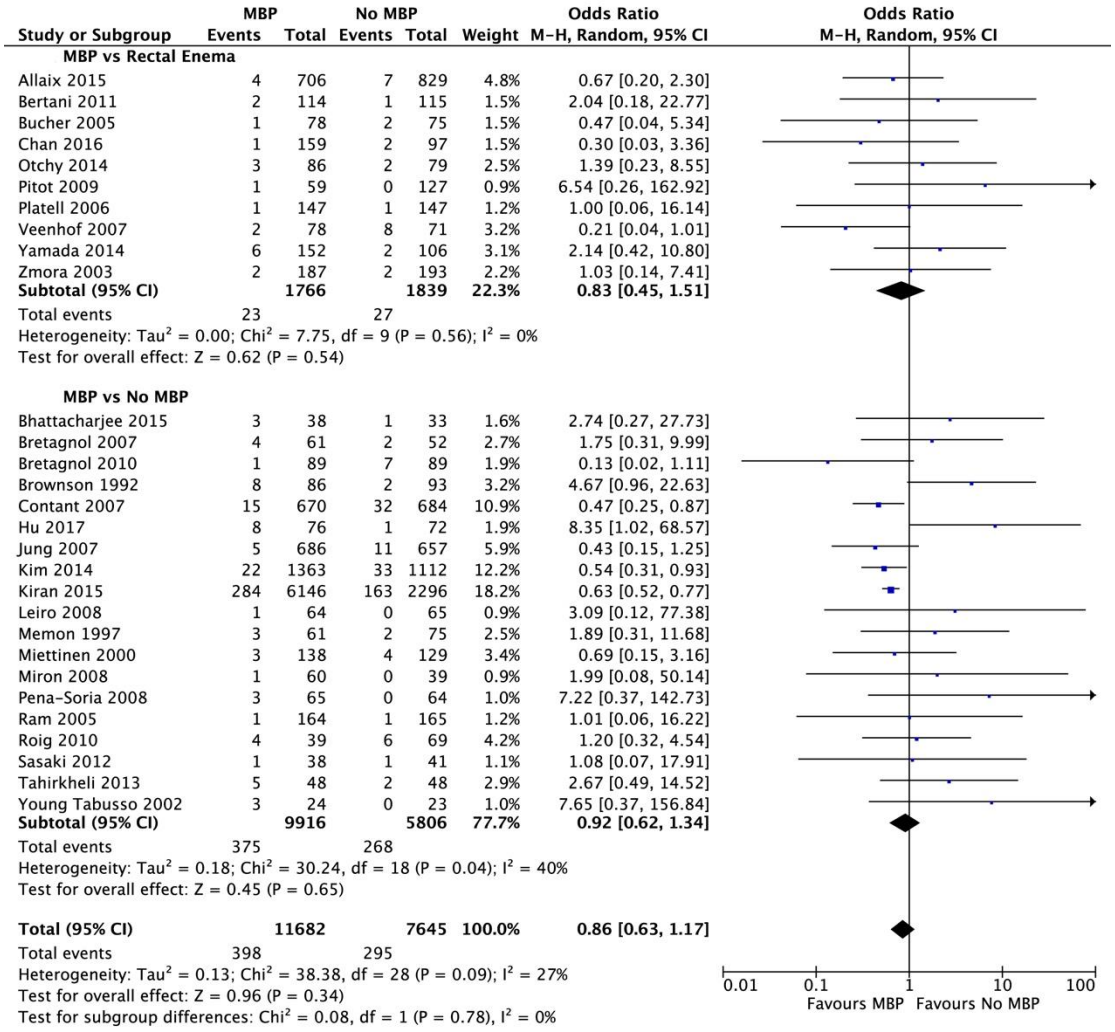
Figure 3.3.3.3 *- Forest plot comparing SSI rate for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



3.3.4 Intra-abdominal collection

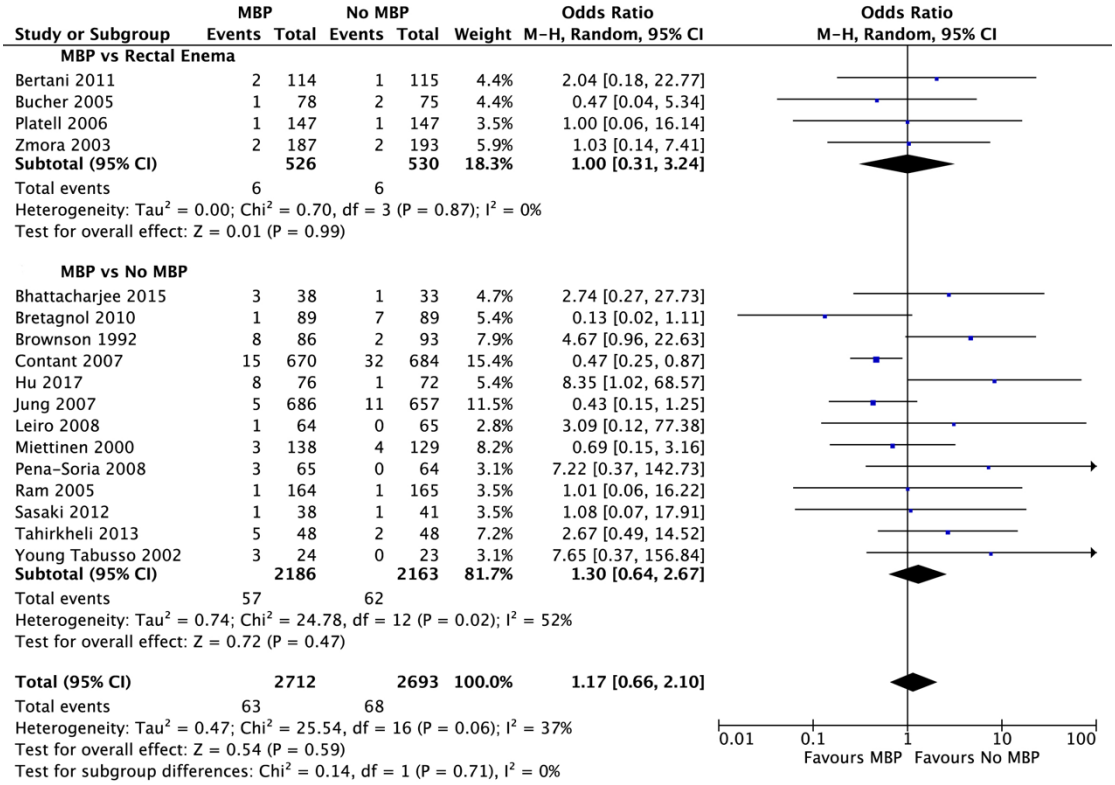
A total of 29 studies (Allaix et al., 2015, Kiran et al., 2015, Yamada et al., 2014, Otchy et al., 2014, Kim et al., 2014a, Tahirkheli M.U.I., 2013, Sasaki et al., 2012, Bertani et al., 2011, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Miron et al., 2008, Pena-Soria et al., 2008, Leiro F, 2008, Contant et al., 2007, Bretagnol et al., 2007, Jung et al., 2007b, Veenhof et al., 2007, Platell et al., 2006, Bucher et al., 2005, Ram et al., 2005, Zmora et al., 2003a, Young Tabusso et al., 2002, Miettinen et al., 2000, Memon et al., 1997, Brownson P, 1992, Chan et al., 2016, Hu et al., 2017, Bhattacharjee and Chakraborty, 2015) on 19,327 patients included data on postoperative intra-abdominal collections (**Figure 3.3.4.1**). The administration of MBP versus no MBP did not impact upon the incidence of intra-abdominal collection (OR 0.86, 95% CI 0.63 to 1.17, p=0.34), nor when full MBP versus single rectal enema (Alcantara Moral et al., 2009, Allaix et al., 2015, Bertani et al., 2011, Bucher et al., 2005, Chan et al., 2016, Otchy et al., 2014, Pitot et al., 2009, Platell et al., 2006, Veenhof et al., 2007, Yamada et al., 2014, Zmora et al., 2003a) (OR 0.83, 95% CI 0.45 to 1.51, p=0.54) or MBP versus absolutely no preparation at all were considered (B, 2006, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Brownson P, 1992, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Hu et al., 2017, Jung et al., 2007b, Kim et al., 2014a, Kiran et al., 2015, Leiro F, 2008, Memon et al., 1997, Miettinen et al., 2000, Miron et al., 2008, Pena-Soria et al., 2008, Ram et al., 2005, Roig et al., 2011, Sasaki et al., 2012, Young Tabusso et al., 2002) (OR 0.92, 95% CI 0.62 to 1.34, p=0.65).

Figure 3.3.4.1 *- Forest plot comparing overall intra-abdominal collection rates for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom).*



When RCTs alone were considered (Bertani et al., 2011, Bucher et al., 2005, Platell et al., 2006, Zmora et al., 2003a, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Brownson P, 1992, Contant et al., 2007, Hu et al., 2017, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Pena-Soria et al., 2008, Ram et al., 2005, Sasaki et al., 2012, Tahirkheli M.U.I., 2013, Young Tabusso et al., 2002) (**Figure 3.3.4.2**), no differences were seen in the incidence of intra-abdominal collection between any of the groups (OR 1.17, 95% CI 0.66 to 2.10, p=0.59).

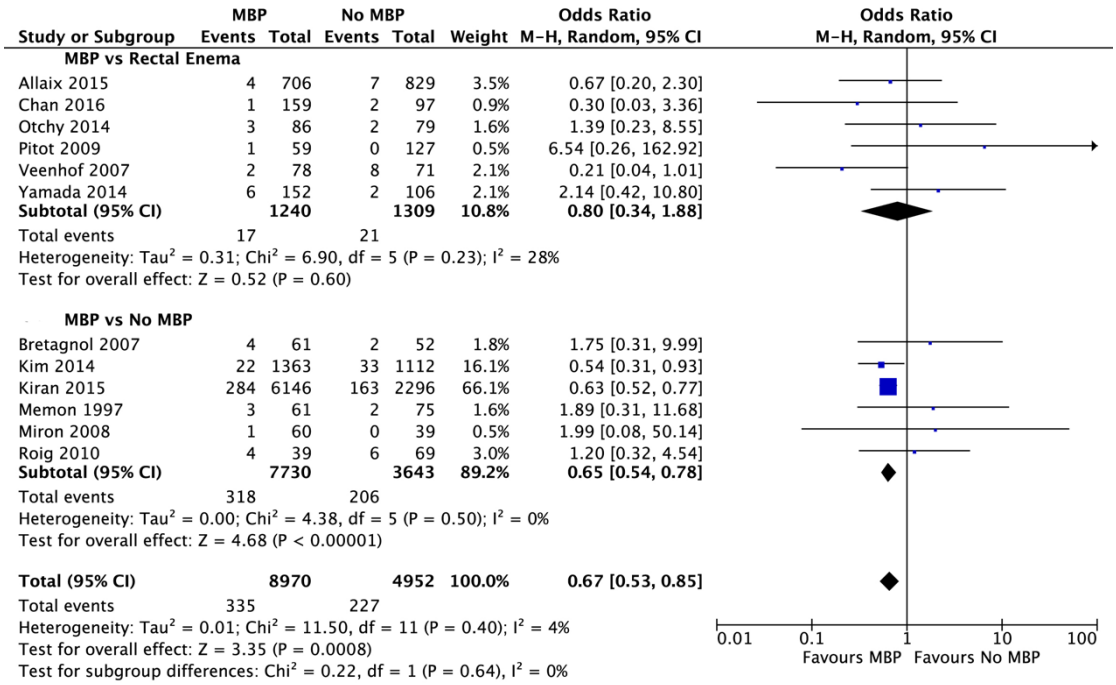
Figure 3.3.4.2 *- Forest plot comparing intra-abdominal collection rate for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



However, when observational studies were analysed (Allaix et al., 2015, Bretagnol et al., 2007, Chan et al., 2016, Kim et al., 2014a, Kiran et al., 2015, Memon et al., 1997, Miron et al., 2008, Otchy et al., 2014, Pitot et al., 2009, Roig et al., 2011, Veenhof et al., 2007, Yamada et al., 2014) (**Figure 3.3.4.3**), the incidence of intra-abdominal collection was significantly reduced in those who had MBP versus those who did not (OR 0.67, 95% CI 0.53 to 0.85, p=0.0008). A significant reduction in the incidence of intra-abdominal collection was seen in the subgroup of patients who underwent MBP versus absolutely no preparation (Bretagnol et al., 2007, Kim et al., 2014a, Kiran et al., 2015, Memon et al., 1997, Miron et al., 2008, Roig et al., 2011) (OR 0.65, 95% CI 0.54 to 0.78, p<0.0001), however no difference was seen in those undergoing MBP versus a single rectal enema (Allaix et al.,

2015, Chan et al., 2016, Otchy et al., 2014, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014) (OR 0.80, 95% CI 0.34 to 1.88, p=0.60).

Figure 3.3.4.3 *- Forest plot comparing intra-abdominal collection rate for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*

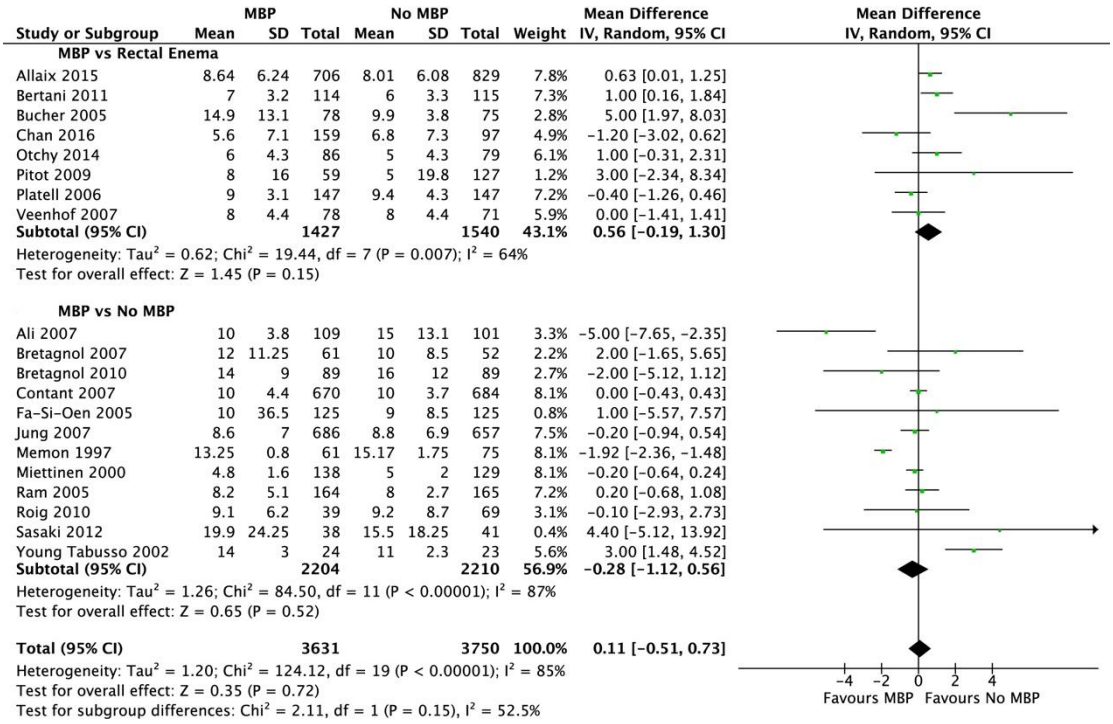


3.3.5 Hospital LOS

Hospital LOS was reported in 20 studies (Allaix et al., 2015, Otchy et al., 2014, Sasaki et al., 2012, Bertani et al., 2011, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Contant et al., 2007, Bretagnol et al., 2007, Jung et al., 2007b, Veenhof et al., 2007, M, 2007, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Young Tabusso et al., 2002, Miettinen et al., 2000, Memon et al., 1997, Chan et al., 2016) including 7381 patients (**Figure 3.3.5.1**), with the use of MBP versus not (including those who

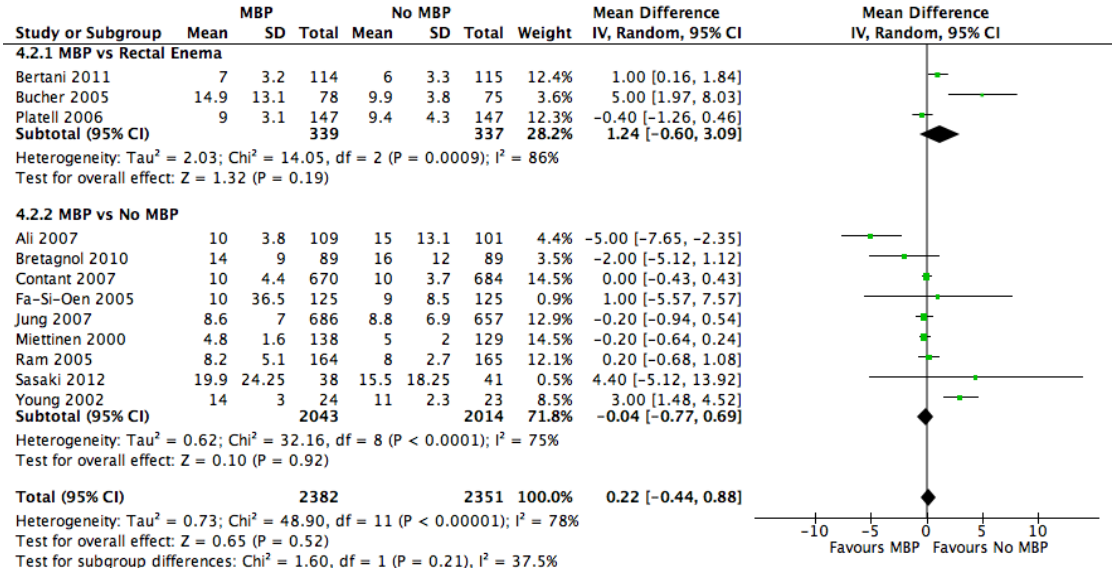
received a single rectal enema) resulting in no significant difference in hospital LOS (overall mean difference 0.11 days, 95% CI -0.51 to 0.73, p=0.72).

Figure 3.3.5.1 *- Forest plot comparing overall hospital LOS for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom).*



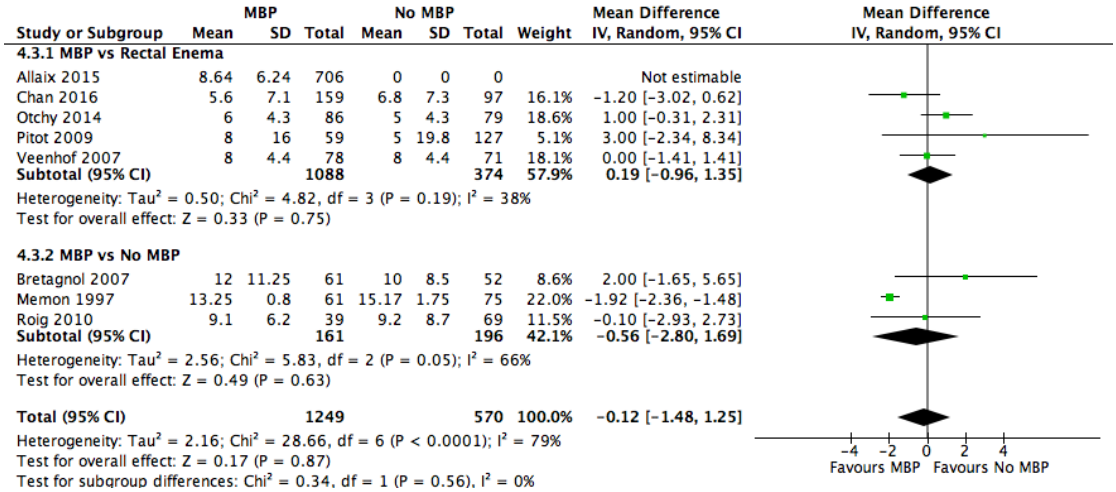
This was mirrored when just RCTs were examined (Bretagnol et al., 2010, Contant et al., 2007, Fa-Si-Oen et al., 2005, Jung et al., 2007b, M, 2007, Miettinen et al., 2000, Ram et al., 2005, Sasaki et al., 2012, Young Tabusso et al., 2002, Bertani et al., 2011, Bucher et al., 2005, Platell et al., 2006) (**Figure 3.3.5.2**; mean difference 0.22 days, 95% CI -0.44 to 0.88, p=0.52).

Figure 3.3.5.2 *- Forest plot comparing hospital LOS for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



A similar outcome was found when just observational studies were included (Allaix et al., 2015, Bretagnol et al., 2007, Chan et al., 2016, Memon et al., 1997, Otchy et al., 2014, Pitot et al., 2009, Roig et al., 2011, Veenhof et al., 2007) (**Figure 3.3.5.3**; mean difference -0.12 days, 95% CI -1.48 to 1.25, p=0.87).

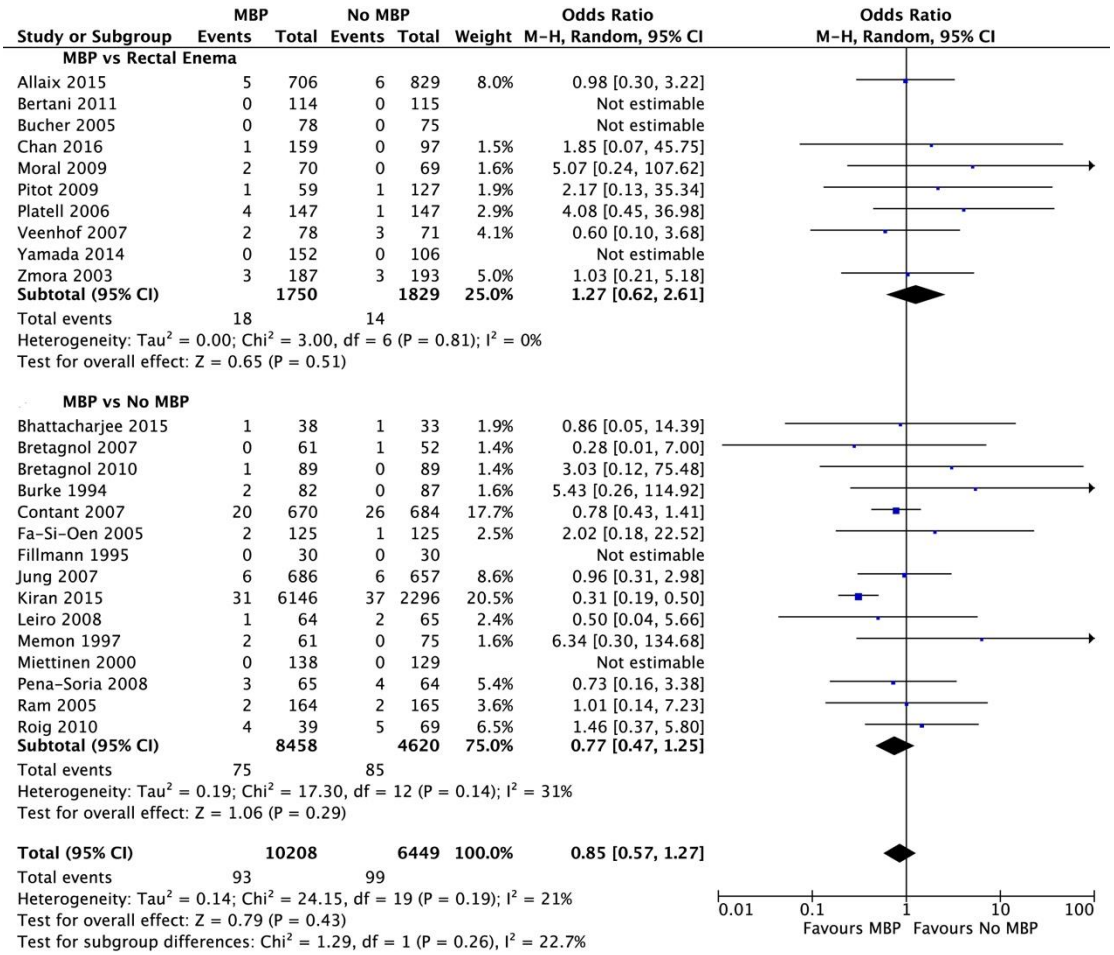
Figure 3.3.5.3: *Forest plot comparing hospital LOS for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



3.3.6 Mortality

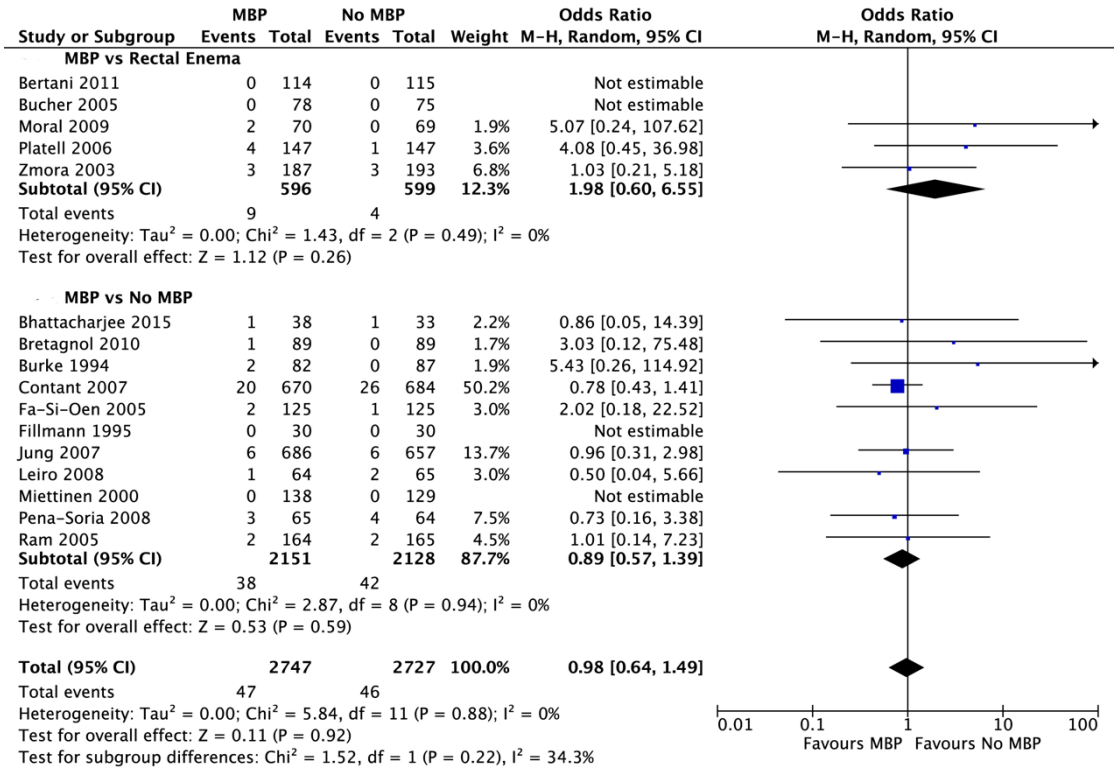
Mortality was reported in 25 studies (Allaix et al., 2015, Kiran et al., 2015, Yamada et al., 2014, Bertani et al., 2011, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Alcantara Moral et al., 2009, Pena-Soria et al., 2008, Leiro F, 2008, Contant et al., 2007, Bretagnol et al., 2007, Jung et al., 2007b, Veenhof et al., 2007, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Zmora et al., 2003a, Miettinen et al., 2000, Memon et al., 1997, Fillmann EEP, 1995, Burke et al., 1994, Chan et al., 2016, Bhattacharjee and Chakraborty, 2015) that included 16,657 patients (**Figure 3.3.6.1**). The time point this outcome measure was measured was variable between studies, with the majority taken at 30 days (Kiran et al., 2015, Bertani et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Alcantara Moral et al., 2009, Pena-Soria et al., 2008, Bretagnol et al., 2007, Jung et al., 2007b, Platell et al., 2006, Bucher et al., 2005, Zmora et al., 2003a, Memon et al., 1997, Fillmann EEP, 1995, Chan et al., 2016, Bhattacharjee and Chakraborty, 2015), two taken at first outpatient clinic quoted to be approximately two weeks following hospital discharge (Contant et al., 2007) or four weeks following surgery (Yamada et al., 2014), one at two months (Miettinen et al., 2000) and one at three months (Fa-Si-Oen et al., 2005), with six papers not stating when mortality was taken from (Allaix et al., 2015, Roig et al., 2011, Leiro F, 2008, Veenhof et al., 2007, Ram et al., 2005, Burke et al., 1994). No difference was seen with the use of full MBP, single rectal enema or no preparation at all.

Figure 3.3.6.1 *- Forest plot comparing overall mortality rates for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom).*



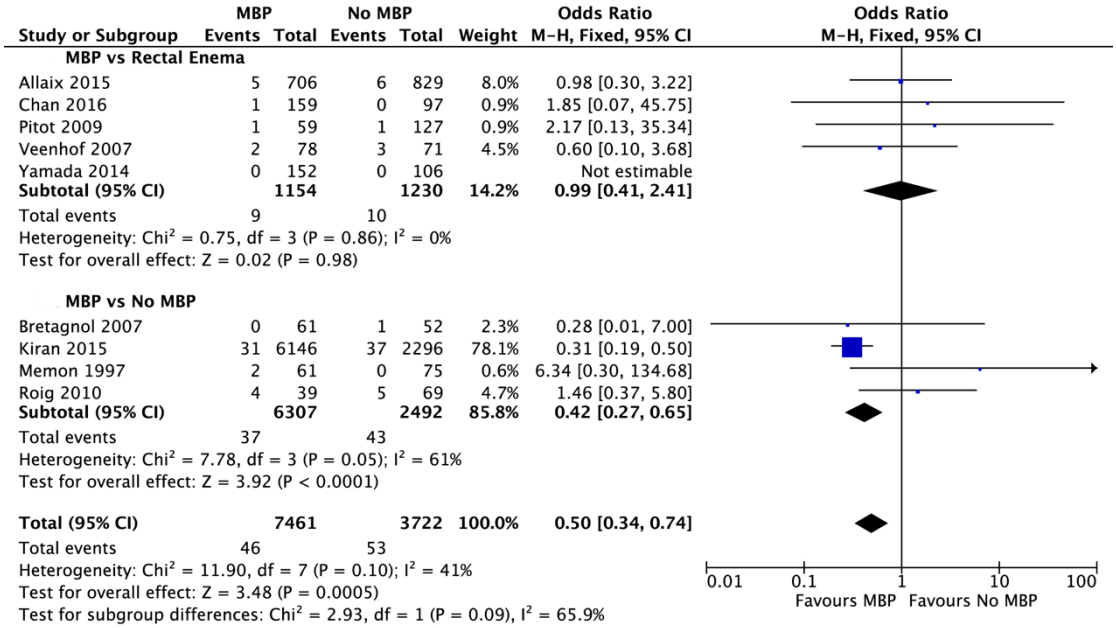
A similar result was seen, with no significant differences, when this comparison was made using only RCTs (Alcantara Moral et al., 2009, Bertani et al., 2011, Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Bucher et al., 2005, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Fillmann EEP, 1995, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Pena-Soria et al., 2008, Platell et al., 2006, Ram et al., 2005, Zmora et al., 2003a) (**Figure 3.3.6.2**).

Figure 3.3.6.2 *- Forest plot comparing mortality rate for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



However, in observational studies (Allaix et al., 2015, Chan et al., 2016, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014, Bretagnol et al., 2007, Kiran et al., 2015, Memon et al., 1997, Roig et al., 2011), MBP was associated with a significant reduction in mortality (OR 0.50, 95% CI 0.34 to 0.74, p=0.0005) (**Figure 3.3.6.3**). A significant reduction in the incidence of mortality was seen in the subgroup of patients in observational studies who underwent MBP versus absolutely no preparation (Bretagnol et al., 2007, Kiran et al., 2015, Memon et al., 1997, Roig et al., 2011) (OR 0.42, 95% CI 0.27 to 0.65, p<0.0001). However, no difference was seen in those undergoing MBP versus a single rectal enema (Allaix et al., 2015, Chan et al., 2016, Pitot et al., 2009, Veenhof et al., 2007, Yamada et al., 2014) (OR 0.99, 95% CI 0.41 to 2.41, p=0.98).

***Figure 3.3.6.3**: Forest plot comparing mortality rate for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*

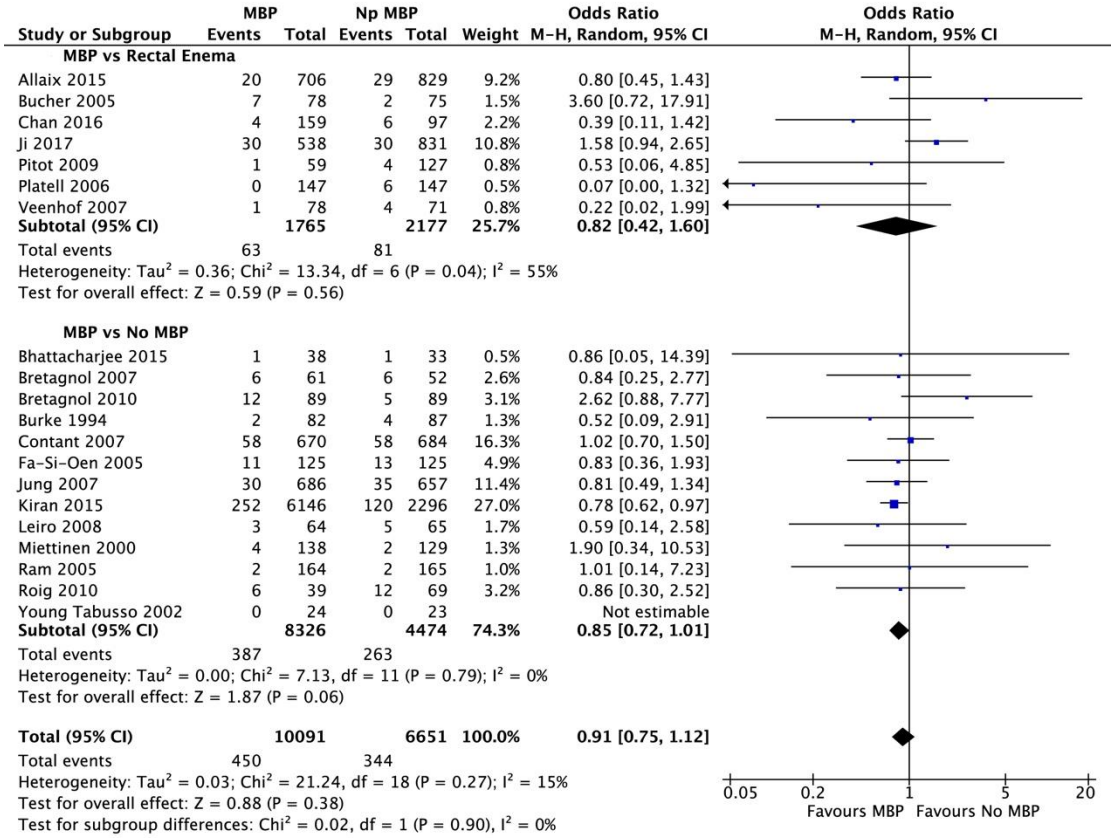


3.3.7 Reoperation

A total of 20 studies on 16,742 patients (Allaix et al., 2015, Kiran et al., 2015, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Leiro F, 2008, Contant et al., 2007, Bretagnol et al., 2007, Jung et al., 2007b, Veenhof et al., 2007, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Young Tabusso et al., 2002, Miettinen et al., 2000, Burke et al., 1994, Ji et al., 2017, Chan et al., 2016, Bhattacharjee and Chakraborty, 2015) examined the impact of MBP upon reoperation rates (**Figure 3.3.7.1**). Overall the use of MBP versus no MBP did not impact upon requirement for reoperation (Allaix et al., 2015, Kiran et al., 2015, Roig et al., 2011, Bretagnol et al., 2010, Pitot et al., 2009, Leiro F, 2008, Contant et al., 2007, Bretagnol et al., 2007, Jung et al., 2007b, Veenhof et al., 2007, Platell et al., 2006, Fa-Si-Oen et al., 2005, Bucher et al., 2005, Ram et al., 2005, Young Tabusso et al., 2002, Miettinen et al., 2000, Burke et al., 1994, Ji et al., 2017, Chan et al., 2016,

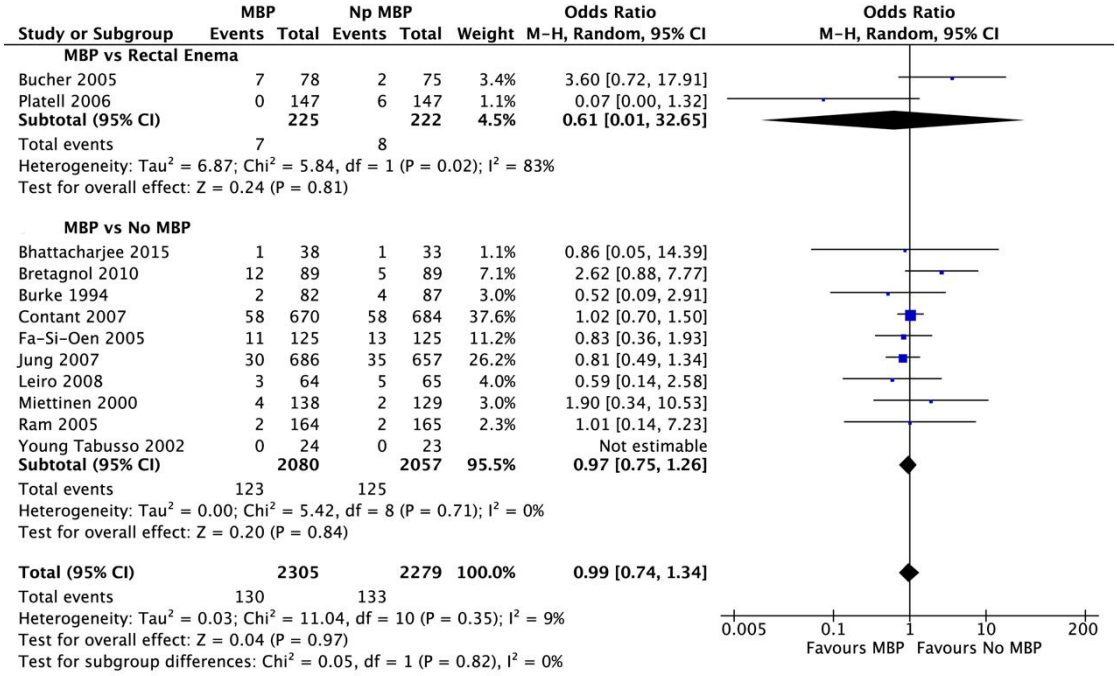
Bhattacharjee and Chakraborty, 2015) (OR 0.91, 95% CI 0.75 to 1.12, p=0.38), nor when MBP versus a single rectal enema (Allaix et al., 2015, Bucher et al., 2005, Chan et al., 2016, Ji et al., 2017, Pitot et al., 2009, Platell et al., 2006, Veenhof et al., 2007) (OR 0.82, 95% CI 0.42 to 1.60, p=0.56) or MBP versus absolutely no preparation (Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2007, Bretagnol et al., 2010, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Jung et al., 2007b, Kiran et al., 2015, Leiro F, 2008, Miettinen et al., 2000, Ram et al., 2005, Roig et al., 2011, Young Tabusso et al., 2002) (OR 0.85, 95% CI 0.72 to 1.01, p=0.06) were compared.

Figure 3.3.7.1 *- Forest plot comparing overall reoperation rates for patients receiving MBP versus either a single rectal enema (top) or absolutely no preparation (bottom).*



When only RCTs were examined (Bhattacharjee and Chakraborty, 2015, Bretagnol et al., 2010, Bucher et al., 2005, Burke et al., 1994, Contant et al., 2007, Fa-Si-Oen et al., 2005, Jung et al., 2007b, Leiro F, 2008, Miettinen et al., 2000, Platell et al., 2006, Ram et al., 2005, Young Tabusso et al., 2002) (**Figure 3.3.7.2**), again no difference was seen by the use of MBP, a single rectal enema or absolutely no preparation.

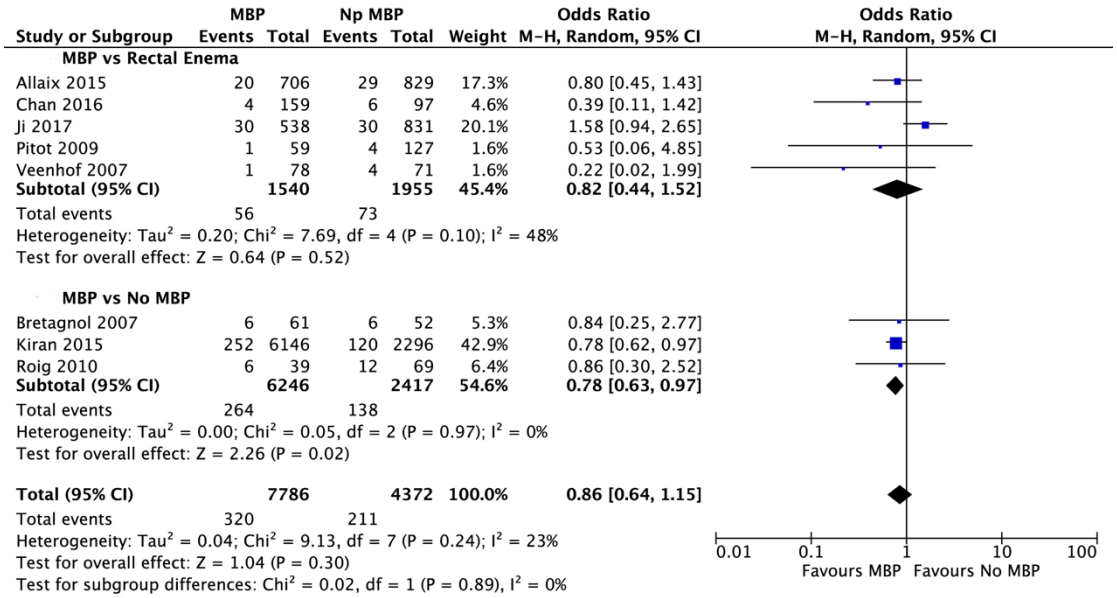
Figure 3.3.7.2 *- Forest plot comparing reoperation rate for patients enrolled in a RCT receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation.*



When observational studies were examined (Allaix et al., 2015, Bretagnol et al., 2007, Chan et al., 2016, Ji et al., 2017, Kiran et al., 2015, Pitot et al., 2009, Roig et al., 2011, Veenhof et al., 2007) (**Figure 3.3.7.3**) overall MPB resulted in no significant reduction in the reoperation rate versus those who did not have bowel preparation but may have had a rectal enema (OR 0.86, 95% CI 0.64 to 1.15, p=0.30), as well as when those who has a single rectal enema (OR 0.82, 95% CI 0.44 to 1.52, p=0.52), however a significant difference was seen

when MBP was compared with patients who received absolutely no preparation (OR 0.78, 95% CI 0.63 to 0.97, p=0.02).

Figure 3.3.7.3 *- Forest plot comparing reoperation rate for patients enrolled in an observational study receiving MBP versus not, divided by those receiving a single rectal enema or absolutely no preparation*.



3.3.8 Rectal Surgery

A total of 11 studies (Kim et al., 2014a, Bertani et al., 2011, Van't Sant et al., 2010, Bretagnol et al., 2007, Bretagnol et al., 2010, Leiro F, 2008, B, 2006, Miettinen et al., 2000, Burke et al., 1994, Ji et al., 2017, Chan et al., 2016) included either only patients who were undergoing rectal or surgery, or outcome measures for the subgroup of patients who had undergone rectal surgery. Ten studies compared MBP with no MBP, with just one study comparing MBP with a single rectal enema (Bertani et al., 2011). All studies except one (Chan et al., 2016) included data on anastomotic leak rates, finding MBP not to be associated with any difference in incidence (OR 0.86, 95% CI 0.64 to 1.15, p=0.30). Only seven studies (Kim et

al., 2014a, Bertani et al., 2011, Van't Sant et al., 2010, Bretagnol et al., 2007, Bretagnol et al., 2010, B, 2006, Chan et al., 2016) included data on SSI, which also demonstrated no significant difference (OR 1.22, 95% CI 0.82 to 1.81, p=0.33). Intra-abdominal collection and mortality data were similarly only available for five (Bertani et al., 2011, Bretagnol et al., 2007, Bretagnol et al., 2010, Chan et al., 2016, Van't Sant et al., 2010) and four studies (Van't Sant et al., 2010, Bretagnol et al., 2007, Bretagnol et al., 2010, Bertani et al., 2011) respectively, neither of which were associated with the use of MBP (OR 0.54, 95% CI 0.21 to 1.38, p=0.20; and OR 0.73, 95% CI 0.29 to 1.82, p=0.50, respectively). The results in patients undergoing rectal surgery are summarised in **Table 3.3.8**.

Table 3.3.8 *- Effect of MBP versus no MBP on outcome in patients undergoing rectal surgery.*

	Number of Participants (MBP vs. No MBP)	Odds Ratio (95% CI) MBP vs. No MBP	P value
Anastomotic Leak	2351 (1042 vs. 1309)	0.86 (0.64 to 1.15)	0.30
SSI	965 (513 vs. 452)	1.22 (0.82 to 1.81)	0.33
Intra-abdominal Collection	921 (486 vs 435)	0.54 (0.21 to 1.38)	0.20
Mortality	813 (419 vs 394)	0.73 (0.29 to 1.82)	0.50
Re-operation	1660 (688 vs 392)	1.57 (1.02 to 2.43)	**0.04**

Data from (Kim et al., 2014a, Bertani et al., 2011, Van't Sant et al., 2010, Bretagnol et al., 2007, Bretagnol et al., 2010, Leiro F, 2008, B, 2006, Miettinen et al., 2000, Burke et al., 1994, Ji et al., 2017, Chan et al., 2016).

3.4 Discussion

3.4.1 Summary of Results

This meta-analysis of 23 RCTs and 13 observational studies has demonstrated that, overall, the use of MBP versus either no bowel preparation or a single rectal enema was not associated with a statistically significant difference in the incidence of anastomotic leak, SSI, intra-abdominal collection, mortality, reoperation or total hospital LOS (**Table 3.4.1.1**). When just RCT evidence was analysed, there was again no significant difference by preparation method in any clinical outcome measure. Finally, when observational studies were analysed, the use of full bowel preparation was associated overall with a reduced incidence of anastomotic leak, SSI, intra-abdominal collection and mortality rates, with these results mirrored in patients receiving MBP versus absolutely no preparation, but no significant differences in those receiving MBP versus a single rectal enema. When a separate subgroup of just rectal surgery was considered, MBP was not associated with a statistically significant difference in anastomotic leak rates, SSI, intra-abdominal collection or mortality, irrespective of whether patients not receiving MBP were given a single rectal enema.

3.4.2 Strengths of Meta-Analysis

This meta-analysis represents the most comprehensive examination of the role of MBP prior to elective colorectal surgery to date. As part of the methodology for the meta-analysis, the decision was made to include observational studies as well as RCTs. However, in order to ensure that inclusion of studies of less rigorous methodology did not result in an undue bias, a predetermined analysis of studies of both methodologies was conducted. This revealed that the overall results and those from analysing just evidence from RCTs were much the same. However, when analysing evidence from observational studies, this resulted in a significant

Table 3.4.1.1 *– Overall summary of results comparing MBP with no MBP*

Outcome Measure	All Studies	RCT only	Cohort study only
Anastomotic leak	No difference (RR 0.90, 95% CI 0.74 to 1.10, p=0.32, I^2=14%)	No difference (RR 1.02, 95% CI 0.75 to 1.40, p=0.90, I^2=18%)	Significant ↓ (RR 0.76, 95% CI 0.63 to 0.91, p=0.003, I^2=0%)
SSI	No difference (RR 0.99, 95% CI 0.80 to 1.24, p=0.96, I^2=45%)	No difference (RR 1.16, 95% CI 0.96 to 1.39, p=0.12, I^2=0%)	Significant ↓ (RR 0.64, 95% CI 0.55 to 0.75, p<0.00001, I^2=0%)
Intra-abdominal collection	No difference (RR 0.86, 95% CI 0.63 to 1.17, p=0.34, I^2=27%)	No difference (RR 1.17, 95% CI 0.66 to 2.10, p=0.59, I^2=37%)	Significant ↓ (RR 0.67, 95% CI 0.53 to 0.85, p=0.0008, I^2=4%)
Hospital LOS	No difference (mean difference 0.11 days, 95% CI -0.51 to 0.73, p=0.72, I^2=85%)	No difference (mean difference 0.22 days, 95% CI -0.44 to 0.88, p=0.52, I^2=78%)	No difference (mean difference -0.12 days, 95% CI -1.48 to 1.25, p=0.87, I^2=79%)
Mortality	No difference (RR 0.85, 95% CI 0.57 to 1.27, p=0.43, I^2=21%)	No difference (RR 0.98, 95% CI 0.64 to 1.49, p=0.92, I^2=0%)	Significant ↓ (RR 0.50, 95% CI 0.34 to 0.74, p=0.0005, I^2=41%)
Reoperation	No difference (RR 0.91, 95% CI 0.75 to 1.12, p=0.38, I^2=15%)	No difference (RR 0.99, 95% CI 0.74 to 1.34, p=0.97, I^2=9%)	No difference (RR 0.86, 95% CI 0.64 to 1.15, p=0.30, I^2=23%)

CI- confidence interval; LOS – length of stay; RR – risk ratio; SSI – surgical site infection

reduction in anastomotic leak, SSI, intra-abdominal collection and mortality rates. The reasons for this difference in results is not clear from this meta-analysis, but it is possible that selection bias may exert a confounding effect upon the results, and as such the use of MBP in selected patients as determined by the physician in charge may be appropriate.

With the exception of hospital LOS (I^2=85%), overall study heterogeneity was low to moderate (0-34%) for all clinical outcome measures, suggesting the studies to be relatively homogeneous. The risk of bias for the RCTs included in the meta-analysis (**Table 3.3.1**) was relatively low.

3.4.3 Limitations of Meta-Analysis

As the raw mean and standard deviation data was not available on the hospital LOS for all studies, despite several attempts at obtaining this directly from the authors, it was necessary to infer this from what was available (either median and range or interquartile range) using statistical techniques previously described (Hozo et al., 2005). This is a valid technique which has been well described previously, but this may exert some degree of bias upon the results of the meta-analysis. Other techniques for handling missing data necessary for meta-analysis are described, however a systematic review (Wiebe et al., 2006) of these techniques revealed a lack of consistency in their application, and no clear optimal methodology.

There was poor documentation within the studies included regarding the side effects of MBP including the incidence of electrolyte disturbance, fluid depletion and requirement of resuscitation, and renal disturbance or failure, hence this could not be included as an outcome within the meta-analysis. However, these issues continue to form one of the major clinical

concerns regarding the routine application of MBP and as such this meta-analysis is unable to address these issues and provide definitive evidence in the debate for and against MBP.

Emerging evidence, much of which has been derived from the studies based upon NSQIP datasets have focused upon the combination between intraluminal antibiotics and MBP and have demonstrated a reduction in SSI rates. However, the data contained within the studies included within this meta-analysis has been scanty regarding the use of intraluminal antibiotics and as such it has not been possible to include this data within the meta-analysis. This may act as a potential confounder when considering the effect of MBP and clinical outcomes.

The studies contained predominantly mixed populations of colonic and rectal procedures, with inadequate documentation to differentiate results between the two, which may be particularly important in addressing the question regarding the use of a single rectal enema as bowel preparation. The majority of studies included a predominance of colonic procedures, with some focusing entirely on colonic rather than rectal surgery. Only a small number of studies were available to perform the planned sub-group analysis on the impact of MBP in rectal surgery, from which it is therefore very difficult to draw strong conclusions. Further studies are required to discern the importance of a pre-operative enema in this setting. Similarly, the level of documentation in studies regarding laparoscopic versus open surgery was not sufficient to be able to discern the importance of MBP in this setting. Only one recent observational study has focused entirely on laparoscopic procedures (Allaix et al., 2015) which demonstrated no significant difference in the rates of intra-abdominal septic complications by the use of MBP, and prior to this evidence was purely based on several small studies (Pirro et al., 2006, Zmora et al., 2006).

The nature of the MBP used was inconsistent between studies, with evidence suggesting that the side effect profile and surgical complication rates are different according to the MBP agent used (Tajima et al., 2015, Johanson et al., 2007, Shapira et al., 2010). This therefore represents a potential source of bias which may alter the risk benefit profile associated with MBP administration. There was also poor documentation regarding antibiotic usage, particularly in the early studies. Much of the recent literature regarding preparation of the bowel has focused upon the use of oral luminal antibiotics in combination with MBP, with these studies suggesting a potential role for this therapy (Scarborough et al., 2015, Moghadamyeghaneh et al., 2015a). A recent meta-analysis on this topic has demonstrated a significant reduction in the risk of SSI in patients undergoing elective colorectal surgery given oral systemic antibiotics with MBP versus systemic antibiotics and MBP (Chen et al., 2016), thus representing a further weakness in the studies included in this meta-analysis.

3.4.4 Comparison with Other Studies

A recently published meta-analysis (Dahabreh et al., 2015) of 18 RCTs, 7 non-randomised comparative studies, and 6 single-group cohorts compared the use of oral MBP with or without an enema versus no oral MBP with or without an enema. This meta-analysis found that MBP versus no MBP was associated with no difference in the rates of all-cause mortality (OR 1.17, 95% CI 0.67 to 2.67), anastomotic leakage (OR 1.08, 95% CI 0.79 to 1.63), SSI (OR 1.19, 95% CI 0.56 to 2.63) as well as wound infections, peritonitis or intra-abdominal abscess or reoperation. There was, however, considerable variance in the estimation of treatment effects, possibly due to the large range of study methodology included, which may mask a treatment effect seen.

This topic has previously been reviewed by the Cochrane Collaboration (Guenaga et al., 2009, Guenaga et al., 2003, Guenaga et al., 2005), with the most recent review conducted in 2011 (Guenaga et al., 2011). This included a total of 18 RCTs in elective colorectal surgery (5805 patients) and demonstrated no statistically significant evidence to support the use of MBP in either low anterior resection, rectal or colonic surgery in terms of anastomotic leakage or wound infection.

A previous meta-analysis has examined the role of MBP prior to proctectomy (Courtney et al., 2015) from eleven publications (1258 patients), although extractable data were only available in a limited number of studies for outcome measures other than anastomotic leakage rates. This study (Courtney et al., 2015) found no beneficial effect from MBP prior to proctectomy with regards to anastomotic leakage (OR 1.14, 95% CI 0.77 to 1.71, p=0.51), SSI (OR 0.95, 95% CI 0.60 to 1.50, p=0.81), intra-abdominal collection (OR 1.72, 95% CI 0.53 to 5.62, p=0.37) or postoperative mortality.

3.4.5 Health Policy Implications

Worldwide, elective colorectal surgery is performed frequently. Current opinion regarding the use of MBP prior to this surgery is inconsistent (Zmora et al., 2003b, Drummond et al., 2011), despite several previous meta-analyses which have suggested this is not useful in reducing postoperative complications (Cao et al., 2012, Guenaga et al., 2011). The use of MBP is not without cost implications, including the preparation itself and in elderly and frail patients, MBP may also necessitate an additional stay in hospital prior to surgery due to the risk of dehydration and electrolyte disturbance which is associated with considerable additional healthcare costs. This meta-analysis further reinforces that MBP is not associated

with any difference in postoperative complication rates, mortality of hospital LOS, particularly in elective colonic surgery, and as such should not be administered routinely.

3.4.6 Conclusion

This work represents the most comprehensive meta-analysis to date on MBP in elective colorectal surgery. It has demonstrated that MBP versus a single rectal enema or no bowel preparation at all is associated with no difference in any of the clinical outcome measures studied. Given the risks of electrolyte disturbance and patient dissatisfaction as well as potentially significant levels of dehydration and requirement for pre-admission prior to surgery, MBP should no longer be considered a standard of care prior to elective colorectal surgery.

Chapter 4 – The Role of Oral Antibiotic Preparation in Elective Colorectal Surgery

4.1 Introduction

4.1.1 Background

The use of oral antibiotic (OAB) prophylaxis, in the form of non-absorbable luminal antibiotics, was first proposed in 1971 by Rosenberg *et al.* (Rosenberg et al., 1971) in a RCT of 150 patients undergoing large bowel surgery receiving MBP alone, or MBP in combination with phthalylsulphathiazole or phthalylsulphathiazole and neomycin. The combination of MBP+OAB was associated with a significant reduction in SSI (23% *versus* 40%), anastomotic leak rates (24% *versus* 52%) and sepsis rates (37.3% *versus* 64.4%). Although several studies provided evidence for the role of oral antibiotics in elective colorectal surgery, the regimens included large volume preparations (Washington et al., 1974, Clarke et al., 1977, Nichols et al., 1977), prolonged preoperative hospital admission, and in the setting of prolonged preoperative starvation protocols, dehydration and electrolyte disturbances were commonplace (Holte et al., 2004, Shapira et al., 2010). Decreased compliance and inconsistent bowel cleansing resulted in a reduced intervention effect, and this combined with reduced preoperative admission times, resulted in the practice of combined MBP+OAB dwindling in favour of more restrictive MBP regimens alone.

The role of MBP with PEG or sodium phosphate has subsequently been studied in multiple RCTs, with perceived benefits including ease of manipulation of the bowel, reduced spillage and resultant contamination, reduced luminal pressure and bacterial load as discussed in chapter 3. However, the meta-analysis presented in the previous chapter (Rollins et al.,

2018b) demonstrated that that the administration of MBP does not impact upon postoperative morbidity or mortality. This, in combination with high rates of patient dissatisfaction and fluid and electrolyte disturbance, has led to the conclusion that MBP should not be prescribed routinely. This is reflected in Guidelines from the ERAS Society (Gustafsson et al., 2012a, Nygren et al., 2012), the National Institute of Health and Care Excellence (NICE, 2008) and the American Society for Enhanced Recovery (ASER) (Holubar et al., 2017), all of which suggest that MBP should not be administered routinely. However, although the ASER guidelines suggest that MBP should not be given in isolation, they recommend routine use of an isosmotic bowel preparation and combined oral antibiotic prior to elective colorectal surgery (Holubar et al., 2017) for the prevention of infectious complications.

This recommendation for the use of OAB preparation has been associated with a significant resurgence of interest in the use of OAB in colorectal surgery (Cirocco, 2016, Zelhart et al., 2014), particularly in light of a large number of retrospective cohort and database studies, many of which originated from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) targeted colectomy database (Scarborough et al., 2015, Klinger et al., 2017, Haskins et al., 2016, Garfinkle et al., 2017, Dolejs et al., 2017, Kiran et al., 2015). Evidence for the role of OAB has been recently summarised in several narrative reviews (Yost et al., 2018, Badia and Arroyo-Garcia, 2018) as well as meta-analyses (Bellows et al., 2011, Miller et al., 2014b, Koullouros et al., 2017), which have supported a reduction in SSI associated with the combination of MBP, OAB and parenteral antibiotics over MBP and parenteral antibiotics alone. However, the most recent of these studies have been flawed in their inclusion of multiple studies based on the NSQIP database which have large degrees of cross-over of the same study population and have mostly

focused upon SSI alone rather than other postoperative outcomes. In addition, recent studies (Garfinkle et al., 2017, Parthasarathy et al., 2017) have suggested that OAB alone may provide equivalent prophylaxis in terms of SSI and anastomotic leak rates when compared with a combined regimen of MBP+OAB, which has not been significantly explored in any recent evidence synthesis. This meta-analysis will aim, in part, to address this gap within the literature surrounding the role of OAB preparation alone and compare clinical outcomes with those following combined MBP and OAB preparation.

4.1.2 Aims

The aims of this meta-analysis of RCTs and observational cohort studies in patients undergoing elective colorectal surgery were to:

- Compare the impact of OAB with or without MBP in elective colorectal surgery in terms of SSI, anastomotic leak, 30-day mortality, overall morbidity, development of ileus, reoperations and *Clostridium difficile* infection.
- Compare evidence derived from RCTs and cohort studies.
- Compare the role of administration of OAB with and without MBP in the setting of laparoscopic *versus* open surgery.

4.2 Methods

4.2.1 Search Strategy

The PubMed, Google™ Scholar, MEDLINE and the Cochrane Library databases were searched to identify studies evaluating the effect of OAB in adults undergoing elective colorectal surgery published between 1 January 1981 and 30 May 2018. This date restriction was imposed as recommendations that parenteral antibiotics should be administered routinely for prophylaxis against SSI in colorectal surgery were made in 1981 (Baum et al., 1981) and it was felt that all studies considering the role of oral antibiotic prophylaxis should include parenteral antibiotic prophylaxis, to represent current perioperative care. The search terms used were: (oral antibiotic OR oral antibacterial) AND (colon OR rectal OR colorectal) AND surgery. The bibliographies of all studies which met the inclusion criteria, and previous systematic reviews and meta-analyses on the subject were reviewed to ensure study inclusion was as complete as possible. Non-English language papers were translated for inclusion.

4.2.2 Selection of Articles

Articles were screened for suitability on the basis of title and abstract by two independent researchers, with studies being eligible if they examined the role of OAB preparation with or without MBP, compared with either MBP alone, OAB alone, or no preparation in adult patients due to undergo elective colorectal surgery, with at least one relevant clinical outcome reported. The type of colorectal surgery performed in terms of location of type of resection, details of whether approached via laparoscopic or open technique, the presence or absence of rectal enema administration, or the indication for surgery were not discriminants such that this meta-analysis was representative of general elective colorectal surgery. Studies were excluded if they did not consider any relevant clinical outcomes, included emergency

procedures, or duplicated study populations from other included studies. From the large number of ACS NSQIP studies published (Althumairi et al., 2016, Connolly et al., 2016, Dolejs et al., 2017, Garfinkle et al., 2017, Haskins et al., 2016, Kiran et al., 2015, Klinger et al., 2017, Midura et al., 2018, Moghadamyeghaneh et al., 2015a, Moghadamyeghaneh et al., 2016, Morris et al., 2015a, Ohman et al., 2017, Parthasarathy et al., 2018, Parthasarathy et al., 2017, Rencuzogullari et al., 2017a, Rencuzogullari et al., 2017b, Scarborough et al., 2015, Shwaartz et al., 2017a, Tevis et al., 2016) (**Table 4.2.2**), the decision was made to include only the largest study by Midura *et al.* (Midura et al., 2018) in order to avoid the risk of duplication of patient populations within the analysis. Similarly, three publications (Kim et al., 2014a, Hendren et al., 2013, Englesbe et al., 2010) have been authored from the Michigan Surgical Quality Collaborative (MSQC) Colectomy Best Practices Project. When these were reviewed, two studies (Hendren et al., 2013, Kim et al., 2014a) considered the same comparison of preparations (MBP+OAB *versus* no preparation), and as such only the more comprehensive study including a larger number of clinical outcomes was included (Kim et al., 2014a). The third study from the MSQC database (Englesbe et al., 2010) examined a different preparation combination, thus this was included in the meta-analysis. Finally, the national Veterans Affairs Surgical Quality Improvement Program was the basis for several studies (Toneva et al., 2013, Cannon et al., 2012) on the same regimen comparison, thus only the largest study was included within the meta-analysis (Cannon et al., 2012). One study (Mik et al., 2016) included a small proportion of patients undergoing emergency colorectal resection within the cohort (311 of a total population of 2240), so any outcomes which included this study were analysed both with and without it included to discern any difference in results.

Table 4.2.2 *- Summary of literature published based upon data obtained from the ACS NSQIP database*

Author	**Years of study**	**Study population**	**Outcomes**
Althumairi *et al*. 2016	2012-13	19,686 patients Elective colectomy	Combined MBP+OAB ↓ SSI, anastomotic leak, ileus, sepsis and readmission vs. no prep.
Connolly *et al*. 2016	2006-14	1018 patients Colorectal resection	SSI reduction strategy (including OAB) resulted in 41% decrease in SSI rates
Dolejs *et al*. 2017	2012-14	4829 patients aged ≥75 years Elective colectomy	Combined MBP+OAB ↓ anastomotic leak, ileus, SSI and hospital LOS vs. no prep. MBP alone or OAB alone no different to no prep.
Garfinkle *et al*. 2017	2012-14	40,446 patients Elective colectomy	Combined MBP+OAB significantly ↓ SSI, anastomotic leak, ileus, major morbidity and mortality vs. no prep. No superiority of MBP/OAB vs. OAB alone. OAB alone protective against SSI, anastomotic leak, ileus, overall morbidity but not mortality rates.
Haskins *et al*. 2016	2012-13	6297 patients Elective colectomy with primary anastomosis for colon cancer	No difference in severity of anastomotic leak or 30-day mortality by type of preparation used or no prep.
Kiran *et al*. 2015	2012	8442 patients Elective colorectal resection	Combined MBP+OAB significantly ↓ ileus, anastomotic leak and SSI
Klinger *et al*. 2017	2012-15	27,804 patients Elective colorectal resection	Combined MBP+OAB significantly ↓ SSI, wound dehiscence and anastomotic leak vs. no prep and lower rate than with OAB alone

Midura *et al*. 2018	2012-15	45,724 patients Elective colectomy with anastomosis	Combined MBP+OAB associated with significantly ↓ SSI and anastomotic leak. OAB alone associated with significantly ↓ SSI
Moghadamyeghaneh *et al*. 2015	2012–13	5021 patients Elective colon resection	Combined MBP+OAB in left sided resection significantly ↓ morbidity, SSI, anastomotic leak and intra-abdominal collection vs. no prep. MBP or OAB alone no difference vs. no prep.
Moghadamyeghaneh *et al*. 2016	2012-13	27,560 patients Elective colon resection	OAB administration associated with significant ↓ in incidence of prolonged ileus
Morris *et al*. 2015	2011-12	8415 patients Colorectal resection	OAB significantly ↓ SSI, hospital LOS and readmission vs. no prep or MBP alone
Ohman *et al*. 2017	2011-15	307 patients Elective colectomy	Combined MBP+OAB strongest predictor of ↓ SSI *versus* MBP or OAB alone in infection prevention bundle
Parthasarathy *et al*. 2017	2013	Overall 17,518 patients undergoing elective colorectal resection with anastomosis, of whom 687 patients developed an anastomotic leak	Preoperative OAB preparation alone associated with reduced risk of anastomotic leak. Preoperative MBP was not associated with anastomotic leak.
Parthasarathy *et al*. 2018	2015	13,959 patients Colectomy	Preoperative OAB associated with a significantly lower rate of Clostridium difficile infection on univariate analysis, however this significance was lost on multivariate testing.
Rencuzogullari *et al*. 2017	2012-13	Overall 10,392 patients aged ≥65 years undergoing elective segmental colectomy with an anastomosis at different levels, of whom 332 patients developed an anastomotic leak	Omitting MBP and/or preoperative oral antibiotic use were associated with an increased risk of anastomotic leak.

Rencuzogullari *et al*. 2017	2012-13	Overall 29,201 patients undergoing elective colectomy, of whom 3834 patients developed postoperative ileus	Omission of OAB pre-operatively associated with significantly increased risk of postoperative ileus
Scarborough *et al*. 2015	2012	4999 patients Elective colorectal resection	Combined MBP+OAB significantly ↓ SSI, anastomotic leak and procedure-related readmission vs. no prep. MBP or OAB alone no different to no preparation.
Schwaartz *et al*. 2017	2012-14	3679 patients with IBD Colorectal resection	Combined MBP+OAB significantly ↓ anastomotic leak, ileus, SSI, organ space infection and wound dehiscence
Tevis *et al*. 2016	2012-13	30,101 patients Non-emergent colectomy	Preoperative bowel preparation protective against anastomotic leak

IBD – inflammatory bowel disease; LOS – length of stay; MBP – mechanical bowel preparation; OAB – oral antibiotic; SSI – surgical site infection

4.2.3 Data Extraction

Data were extracted by two independent researchers and any discrepancies resolved by an independent reviewer. The primary outcome measure was the overall incidence of SSI, with secondary outcome measures of anastomotic leak, 30-day mortality, overall morbidity, development of ileus, reoperation and *Clostridium difficile* infection. In terms of SSI, where quoted the incidence of overall SSI was used for the meta-analysis, however a number of included studies separated SSI into superficial incisional, deep incisional and organ/space surgical site infection as per the Center for Disease Control (CDC) definition of SSI (Horan et al., 1992). Where these data were quoted separately, the data provided on superficial incisional SSI were used for the meta-analysis, as the combination of different SSI locations may result in dual reporting of SSI for individual patients. Data were also collected on patient demographics (age, gender), surgical variables (type of resection, open *versus* laparoscopic, underlying cause necessitating resection), and details of the preparation used, in terms of parenteral and oral antibiotics as well as MBP. Several studies stated that MBP was not used in patients with obstructing masses, which is mirrored in standard clinical practice, thus these papers were included in the meta-analysis. The risk of bias was assessed for the RCTs included using the Cochrane Collaboration tool within the RevMan software (Cochrane Collaboration, 2014) as discussed previously

4.2.4 Statistical Analysis

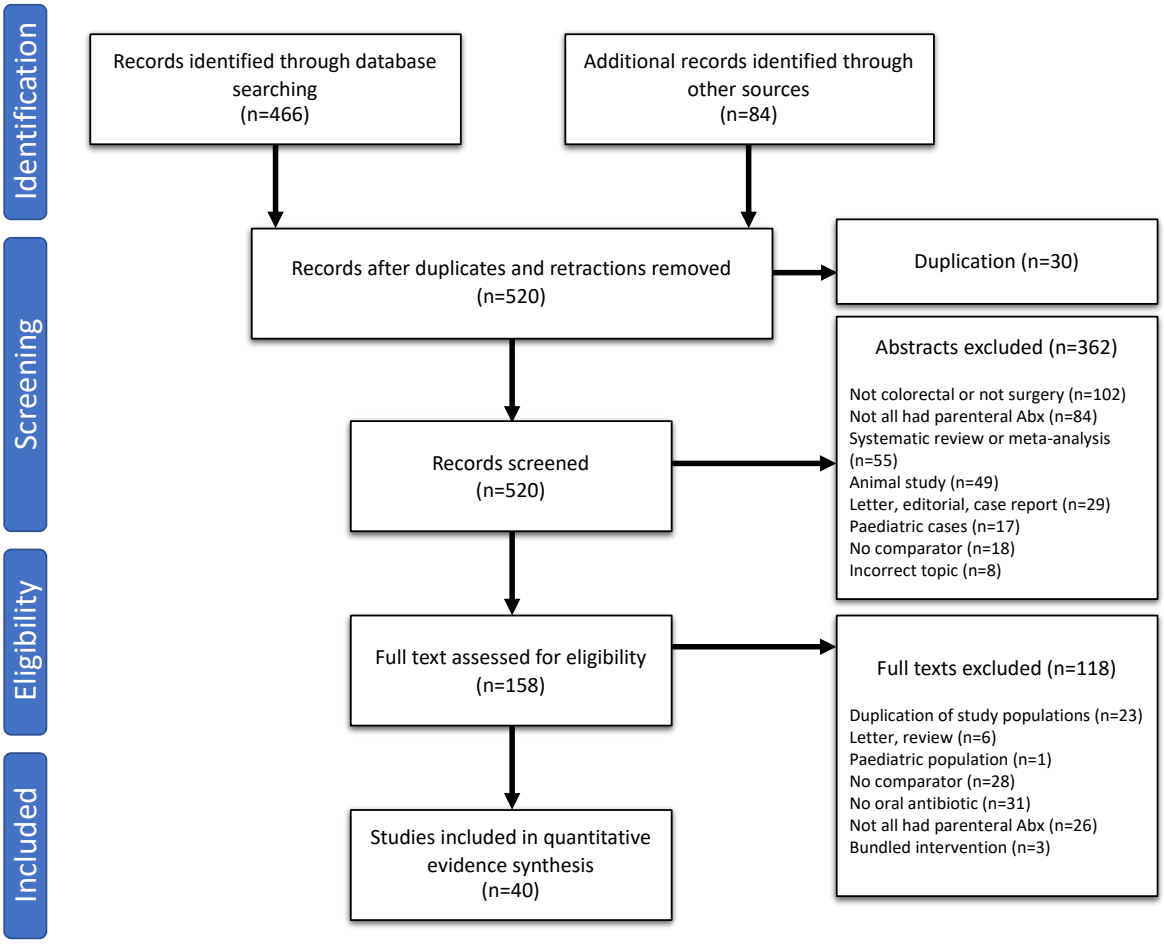
Data were inputted into RevMan 5.3 (Cochrane Collaboration, 2014). Dichotomous variables were calculated as RR with a 95% CI using the Mantel-Haenszel random effects model. From this, forest plots were derived, with a p value of less than 0.05 on two tailed testing taken to represent a statistically significant difference. Data from RCTs and cohort

studies were included separately within each forest plot, with a summative analysis of all the evidence performed in addition. Inconsistency and heterogeneity between studies was estimated using the I^2 statistic (Higgins and Thompson, 2002); ≤25% represented low heterogeneity, 25-50% represented moderate and >50% high heterogeneity.

4.3 Results

From the 520 studies identified in the initial search, 40 studies (Anjum et al., 2017, Cannon et al., 2012, Coppa and Eng, 1988, Englesbe et al., 2010, Espin-Basany et al., 2005, Hanel et al., 1980, Hata et al., 2016, Ichimanda et al., 2017, Ikeda et al., 2016, Ishida et al., 2001, Kaiser et al., 1983, Khubchandani et al., 1989, Kim et al., 2014a, Kobayashi et al., 2007, Konishi et al., 2006, Lau et al., 1988, Lazorthes et al., 1982, Lewis, 2002, McArdle et al., 1995, Midura et al., 2018, Mik et al., 2016, Monrozies et al., 1983, Nohr et al., 1990, Oshima et al., 2013, Ozdemir et al., 2016, Peruzzo et al., 1987, Playforth et al., 1988, Ram et al., 2005, Reddy et al., 2007, Reynolds et al., 1989, Rohwedder et al., 1993, Sadahiro et al., 2014, Stellato et al., 1990, Sun et al., 2018, Takesue et al., 2000, Taylor and Lindsay, 1994, Uchino et al., 2017, Vo et al., 2018, Wren et al., 2005, Zmora et al., 2003a) on 69,517 participants were included (**Figure 4.3.1**). Of these, 28 were RCTs (6437 participants) (Anjum et al., 2017, Coppa and Eng, 1988, Espin-Basany et al., 2005, Hanel et al., 1980, Hata et al., 2016, Ikeda et al., 2016, Ishida et al., 2001, Kaiser et al., 1983, Khubchandani et al., 1989, Kobayashi et al., 2007, Lau et al., 1988, Lazorthes et al., 1982, Lewis, 2002, McArdle et al., 1995, Monrozies et al., 1983, Nohr et al., 1990, Oshima et al., 2013, Peruzzo et al., 1987, Playforth et al., 1988, Ram et al., 2005, Reddy et al., 2007, Reynolds et al., 1989, Sadahiro et al., 2014, Stellato et al., 1990, Takesue et al., 2000, Taylor and Lindsay, 1994, Uchino et al., 2017, Zmora et al., 2003a) and 12 were cohort (case control) studies (63,080 participants) (Cannon et al., 2012, Englesbe et al., 2010, Ichimanda et al., 2017, Kim et al., 2014a, Konishi et al., 2006, Midura et al., 2018, Mik et al., 2016, Ozdemir et al., 2016, Rohwedder et al., 1993, Sun et al., 2018, Vo et al., 2018, Wren et al., 2005). The risk of bias in the included RCTs was variable, with poor levels of documentation particularly surrounding randomisation methods, allocation concealment and blinding in the earliest studies (**Table 4.3.1**).

Figure 4.3.1 *– PRISMA diagram demonstrating identification of studies from the initial literature search.*



Six studies (Kaiser et al., 1983, Khubchandani et al., 1989, Lazorthes et al., 1982, McArdle et al., 1995, Monrozies et al., 1983, Nohr et al., 1990) administered different parenteral antibiotic regimens depending upon whether the patient was receiving MBP+OAB or MBP alone, which may provide significant source of bias. In addition, one study (Reynolds et al., 1989) included two different parenteral antibiotic regimens, both combined with MBP, *versus* OAB, MBP and parenteral antibiotics. As both of the parenteral antibiotic regimens were eligible for inclusion, these were grouped together to form the MBP alone group. In terms of oral antibiotics, two studies administered OAB preparation only on the day of surgery; one (McArdle et al., 1995) gave ciprofloxacin 1 g one hour preoperatively and the other (Rohwedder et al., 1993) ciprofloxacin 750 mg 1-3 h preoperatively.

Table 4.3.1– *Risk of bias within RCTs included within the meta-analysis*

Reference	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other Bias
Anjum *et al.* 2017	+	+	?	+	+	+	
Coppa *et al.* 1988	?	?	-	+	-	-	
Espin-Basany *et al.* 2005	?	?	?	+	+	+	
Hanel *et al.* 1980	-	?	?	+	-	+	
Hata *et al.* 2016	+	+	-	-	+	+	36 patients in the MBP+OAB group received reduced doses of kanamycin due to prescription error
Ikeda *et al.* 2016	+	+	-	+	+	+	
Ishida *et al.* 2001	+	-	-	-	+	?	
Kaiser *et al.* 1983	?	+	+	+	+	-	Different IV antibiotic regimens given to the two groups
Khubchandani *et al.* 1989	?	?	+	+	-	-	Different IV antibiotic regimens given to the two groups

Kobayashi *et al.* 2007	+	?	-	-	-	-	
Lau *et al.* 1988	+	?	?	?	+	+	
Lazorthes *et al.* 1982	?	?	?	?	?	-	Different IV antibiotic regimens given to the two groups
Lewis 2002	-	-	+	+	+	+	
McArdle *et al.* 1995	?	?	?	?	+	?	Different IV antibiotic regimens given to the two groups
Monrozies *et al.* 1983	?	?	?	?	+	+	Different IV antibiotic regimens given to the two groups
Nohr *et al.* 1990	?	?	+	+	-	+	Different IV antibiotic regimens given to the two groups
Oshima *et al.* 2013	?	?	-	-	+	+	
Peruzzo *et al.* 1987	?	?	?	?	+	+	
Playforth *et al.* 1988	?	?	?	?	+	+	
Ram *et al.* 2005	-	?	?	?	+	+	
Reddy *et al.* 2007	+	+	-	-	+	+	Group also randomised to

							probiotics – not included within meta-analysis
Reynolds *et al.* 1989	+	-	?	?	-	-	Two different IV antibiotic regimens in the MBP group
Sadahiro *et al.* 2014	+	-	+	+	?	?	Group also randomized to probiotics – not included within meta-analysis
Stellato *et al.* 1990	+	?	+	+	-	+	
Takesue *et al.* 2000	?	?	?	?	-	?	
Taylor *et al.* 1994	?	?	-	-	-	+	
Uchino *et al.* 2017	+	+	-	+	-	?	*C. difficile* toxin and faecal cultures only pre-op
Zmora *et al.* 2003	+	+	?	?	-	+	

+ Low risk of bias; - High risk of bias; ? Unclear risk of bias

A subgroup of another study (Espin-Basany et al., 2005) received only one dose of OAB the day before surgery, with the remainder receiving three doses. These three studies may, therefore, have an attenuated the intervention effect from the OAB administered.

4.3.1 Patient Demographics

Two studies (Hata et al., 2016, Ikeda et al., 2016) focused on laparoscopic surgery, 21 on open surgery (Coppa and Eng, 1988, Hanel et al., 1980, Kaiser et al., 1983, Khubchandani et al., 1989, Lau et al., 1988, Lazorthes et al., 1982, McArdle et al., 1995, Mik et al., 2016, Monrozies et al., 1983, Nohr et al., 1990, Oshima et al., 2013, Ozdemir et al., 2016, Peruzzo et al., 1987, Playforth et al., 1988, Ram et al., 2005, Reddy et al., 2007, Reynolds et al., 1989, Rohwedder et al., 1993, Stellato et al., 1990, Takesue et al., 2000, Uchino et al., 2017), with 9 studies (Kim et al., 2014a, Englesbe et al., 2010, Anjum et al., 2017, Ichimanda et al., 2017, Konishi et al., 2006, Sadahiro et al., 2014, Sun et al., 2018, Vo et al., 2018, Wren et al., 2005) mixing both open and laparoscopic. The remaining eight studies did not provide this information (Midura et al., 2018, Cannon et al., 2012, Espin-Basany et al., 2005, Ishida et al., 2001, Kobayashi et al., 2007, Lewis, 2002, Taylor and Lindsay, 1994, Zmora et al., 2003a). The most recent publication (Midura et al., 2018) included patients undergoing robotic surgery. The indication for surgery was colorectal cancer in eight studies (Ikeda et al., 2016, Kobayashi et al., 2007, Lau et al., 1988, Mik et al., 2016, Sadahiro et al., 2014, Takesue et al., 2000, Vo et al., 2018), IBD in two (Oshima et al., 2013, Uchino et al., 2017), with the remaining including a mixture of benign and malignant pathologies. Patient demographics and surgical variables as well as the details of MBP, OAB and parenteral antibiotics administered are detailed in **Table 4.3.2**.

Table 4.3.2 *– Baseline patient demographics in studies included*

Reference	Study methodology	Number of patients	Indication for surgery	Location of resection	Laparoscopic or open	OAB agent	MBP agent	Parenteral agent	Comparison included
Anjum *et al.* 2017	RCT	190	Gastrointestinal tract fistula IBD Trauma Malignancy	Partial small bowel resection – 39 Right colectomy – 67 Left colectomy – 50 LAR - 34	Laparoscopic – 40 Open - 150	Metronidazole 400 mg and levofloxacin 200 mg TDS on the day before surgery.	Sodium phosphate 133 ml twice a day on the day before surgery.	Second generation cephalosporin+ metronidazole 30-60 min pre-incision, every 3 h intra-op then 24 h post-op.	MBP+OAB vs. MBP
Cannon *et al.* 2012	Retrospective database study – Veterans Affairs Surgical Quality Improvement Program	9940	Neoplasm – 7871 IBD – 176 Diverticulitis – 644 Other - 1248	Ileocolic resection – 984 Partial colectomy – 6847 Rectal resection – 1771 Total colectomy - 338	Not stated	Erythromycin, neomycin or metronidazole.	Polyethylene glycol, phospho-soda or magnesium citrate.	Not stated	MBP+OAB vs. MBP MBP+OAB vs. OAB MBP+OAB vs. no prep OAB vs. no prep OAB vs. MBP

Coppa *et al.* 1988	RCT	350	Cancer – 255 Inflammatory – 46 Other - 9	Not stated	All open	Neomycin 8 g/day and erythromycin 4 g/day in divided doses for 24 h pre-op.	Fleet phospho-soda between 1 and 3 days pre-op, and saline enemas for the last two days.	Cefoxitin 1-2 g according to patient body weight given preoperatively, intraoperatively and every 6 h for the first post-op day.	MBP+OAB vs. MBP
Englesbe *et al.* 2010	Retrospective propensity-matched database study – Michigan Surgical Quality Collaborative – Colectomy Best Practices Project	740	Not stated	Segmental colectomy Ileocolic resection	Open and laparoscopic	Neomycin and erythromycin 76.3% Neomycin alone 7.9% Erythromycin alone 2.6% Metronidazole alone 2.6% Clindamycin alone 2.6%	Polyethylene glycol 20.9% Phospho-soda 5.9% Fleet enema 38.5% Magnesium citrate 5% Other 29.7%	Not stated	MBP+OAB vs. MBP

Espin-Basany *et al.* 2005	RCT	300	Cancer - 269 IBD - 4 Diverticular disease - 21 Other - 6	Segmental resection – 120 Sigmoidectomy - 69 Anterior resection - 27 TME-coloanal - 66 APR - 18	Not stated	Neomycin 1 g and metronidazole 1 g EITHER TDS the day before surgery OR OD the day before surgery.	Sodium phosphate 45 ml diluted in 90 ml water BD the day before surgery	Cefoxitin 1 g pre-incision and two doses at 8 and 16 h post-op.	MBP+OAB vs. MBP
Hanel *et al.* 1980	RCT	77	Adenoma - 2 Carcinoma - 48 IBD - 4 Diverticular disease - 7 Hodgkin's disease - 1 Villous papilloma -1 Caecal volvulus - 2	Right colectomy - 15 Left colectomy - 6 Transverse colectomy - 2 Sigmoid colectomy - 10 Colonic bypass - 1 Caecostomy – 1 Colostomy – 1 Colostomy closure - 5 Colotomy and polypectomy - 2	All open	Metronidazole 1 g QDS for four days and neomycin 1 g TDS for two days prior to surgery.	Four day standard mechanical preparation including a low residue diet, and alternating enemas or washouts.	Clindamyin 7 mg/kg and cephazolin sodium 1 g given at the start of the anaesthetic.	MBP+OAB vs. MBP

			Sigmoid volvulus - 2	Anterior resection - 14 APR - 7 Proctocolectomy - 2					
Hata *et al.* 2016	RCT	579	Colorectal malignancy Adenoma	Colectomy – 376 Anterior resection - 183 APR - 20	All laparoscopic	Kanamycin 1g and metronidazole 750 mg BD at 13 h and 9 h pre-op.	Sodium picosulfate 75 mg and magnesium citrate 34 g with 180 ml water the day before surgery.	Cefmetazole 1 g 30 min pre-incision then every 3 h intra-op.	MBP+OAB vs. MBP
Ichimanda *et al.* 2017	Retrospective case controlled series	344	All colorectal cancer	Not stated. Primary site: Colon – 181 Rectum - 163	Laparoscopic – 293 Open - 51	Kanamycin 1 g TDS and metronidazole 1 g TDS for 24 h prior to surgery.	Polyethylene glycol 2 L and nasoside (Pulsenide) 24 mg.	Second generation cephem on the day of surgery until the second post-op day.	MBP+OAB vs. MBP
Ikeda *et al.* 2016	RCT	511	Colorectal malignancy	Colonic surgery – 309 Anterior resection – 177 APR - 25	All laparoscopic	Kanamycin 1 g and metronidazole 750 mg BD the day before surgery.	Magnesium citrate and sodium picosulfate the day before surgery.	Cefmetazole 1 g at least 30 min pre-incision, every 3 h intra-op and for 24 h post-op.	MBP+OAB vs. MBP

Ishida *et al.* 2001	RCT	143	Cancer – 135 IBD – 4 Diverticular disease – 1 Other – 3	Colectomy – 76 Anterior resection – 47 APR – 9 Total proctectomy with J pouch – 3 Total pelvic exenteration – 4 Other – 4	Not stated	Kanamycin 2 g/day and erythromycin 1.6 g/day in 4 divided doses from 2 days prior to surgery.	Polyethylene glycol 2 L given the day before surgery.	Cefotiam 1 g after induction, 1 g at one hour after completion of surgery and 4 additional doses given BD for 2 consecutive days.	MBP+OAB vs. MBP
Kaiser *et al.* 1983	RCT	119	Local malignancy – 50 Metastatic malignancy – 30 Diverticulitis - 17 Polyps – 9 IBD – 9 Other - 4	Right colectomy – 34 Left colectomy – 25 Sigmoid resection – 25 APR – 11 Anterior resection – 7 Subtotal colectomy – 6 Operative colotomy – 6 Total colectomy – 3 Colostomy closure - 2	All open	Neomycin 1 g TDS and erythromycin 1 g TDS the day prior to surgery.	Magnesium citrate and cleansing enemas for 2 days prior to surgery.	Cefoxitin 2 g with the 'on call' medications, 1 g intra-operatively and 1 g every 6 h following surgery for four doses in the MBP alone group. Cefazolin 1 g with the 'on call' medications, 500 mg intra-operatively and 1 g every 6 h following surgery for four doses	MBP+OAB vs. MBP

								in the MBP+OAB group.	
Khubchandani *et al.* 1989	RCT	155	'Colonic surgery'	Not stated	All open	Neomycin 1 g and erythromycin 1 g at 1 pm, 2 pm and 10 pm the day before surgery.	Castor oil 60 ml the afternoon of admission and saline enemas the night of admission and the following morning until the effluent was clear.	Metronidazole 1 g given 1 h before surgery, then 500 mg at 6 and 12 h post-op in MBP alone group. Cefazolin 1 g given 1 h before surgery, then 1 g at 6 and 12 h post-op in the MBP+OAB group.	MBP+OAB vs. MBP
Kim *et al.* 2014	Retrospective propensity-matched database study – Michigan Surgical Quality Collaborative –	1914	Not stated	Ileocolic resection with anastomosis Segmental colectomy with anastomosis	Open – 1294 Laparoscopic - 1181	Not stated	Not stated	Not stated	MBP+OAB vs. no prep

	Colectomy Best Practices Project								
Kobayashi *et al.* 2007	RCT	484	Colorectal malignancy	Surgical procedure: Colon – 241 Rectum - 243	Not stated	Kanamycin 1 g and erythromycin 400 mg TDS the day before surgery.	Polyethylene glycol 2 L the morning of the day before surgery.	Cefmetazole 1 g at induction, an additional dose if operation exceeded 3 h, then BD for 3 days post-op.	MBP+OAB vs. MBP
Konishi *et al.* 2006	Retrospective case controlled series – National Nosocomial Infection Surveillance program	556	Not stated.	Right colectomy – 94 Left colectomy – 155 Other colectomy – 90 LAR – 126 APR – 51 Total colectomy or panproctocolectomy – 34 Hartmann's procedure – 6	Open - 515 Laparoscopic - 41	Kanamycin and metronidazole.	Oral laxative and glycerine enema.	Second generation cephalosporin given 30 min prior to incision, repeated every 3 h intra-op and stopped within 24 h after the operation.	MBP+OAB vs. MBP

				Ostomy closure – 47 Ostomy formation – 106 Multiple organ resection - 93					
Lau *et al.* 1988	RCT	194	All cancer	Right colectomy – 39 Left colectomy - 7 Transverse colectomy - 9 Sigmoid colectomy - 22 Subtotal colectomy - 10 Pelvic exenteration - 2 Palliative bypass - 4 Anterior resection - 39 LAR - 17 APR - 45	All open	Neomycin 1 g and erythromycin 1 g at 1 pm, 2 pm and 11 pm the day prior to surgery.	3 days of oral bisacodyl, magnesium sulphate and saline enemas prior to surgery.	Metronidazole 500 mg and gentamycin 2mg/kg body weight given 30 min prior to surgery, then repeated at 8 h intervals for two further doses.	MBP+OAB vs. MBP

Lazorthes *et al.* 1982	RCT	90	Cancer – 51 Colostomy closure – 23 Benign disease - 16	Colectomy - 30 APR - 9 Sphincter-saving resection - 23 Miscellaneous - 28	All open	Kanamycin 1 g QDS and metronidazole 250 mg QDS for 3 days prior to surgery.	Three days of low residue diet, enemas and magnesium sulfate purges.	Cephradine 2 g at induction with metronidazole 500 mg infusion over 4 h in MBP alone group. Cephradine 2 g and gentamycin 2 mg/kg as IM injection at time of premedication in the MBP+OAB group.	MBP+OAB vs. MBP
Lewis 2002	RCT	208	Cancer – 150 IBD – 51 Rectal prolapse – 10 Other - 2	Anterior resection – 119 APR – 19 Right colectomy – 55 Left colectomy – 13 Transverse colectomy - 4	Not stated	Neomycin 2 g and metronidazole 2 g BD the day before surgery.	Sodium phosphate the day before surgery, with saline enemas if this did not result in a clear effluent.	Amikacin 1 g and metronidazole 1 g on the day of surgery.	MBP+OAB vs. MBP
McArdle *et al.* 1995	RCT	169	Cancer – 76 IBD – 13	Right colectomy – 35 Left colectomy – 26	All open	Ciprofloxacin 1 g 1 h prior to surgery – one group received		MBP alone: Gentamycin 120 mg + metronidazole 500 mg at induction then	MBP+OAB vs. MBP

			Diverticular disease – 5	Anterior resection - 24 APR – 17 Total colectomy – 5 Hartmann's procedure/reversal – 15 Bypass – 7 Small bowel resection – 14 Formation or revision of stoma – 18 Other - 8		no further doses and one group received ciprofloxacin 750 mg BD for 3 days.		one group received gentamycin 80 mg + metronidazole 500 mg at 8 and 16 h post-op and one group received gentamycin 80 mg + metronidazole 500 mg TDS for 3 days. MBP+OAB: metronidazole 500 mg at induction then in one group at 8 and 16 h post-op and in the other metronidazole 500 mg TDS for 3 days.	
Midura *et al.* 2018	Database study – ACS NSQIP	45,724	IBD Cancer Diverticulitis Other	Left colectomy Right colectomy Segmental colectomy	Open Laparoscopic Robotic	Not stated	Not stated	Not stated	MBP+OAB vs. MBP MBP+OAB vs. OAB MBP+OAB vs. no prep

									MBP vs. OAB OAB vs. no prep
Mik *et al.* 2016	Retrospective cohort study	2240	Colorectal malignancy	Right colectomy - 470 Left colectomy - 200 Sigmoidectomy - 328 Hartmann's - 194 Anterior resection - 358 LAR - 452 APR - 206	All open	Erythromycin 500 mg and neomycin 500 mg TDS the day before surgery.	Oral macrogol the day before surgery.	Cefazolin 1 g and metronidazole 500 mg directly before incision, and broadened to 3 doses if surgery lasted longer than 3 h.	MBP+OAB vs. no prep
Monrozies *et al.* 1983	RCT	60	Cancer – 34 Closure of colostomy – 8 Benign - 18	Colectomy – 35 Proctectomy - 2 Other - 10	All open	Kanamycin 1 g QDS and metronidazole 1 g QDS for 3 days pre-op.	Magnesium suphate and enemas.	MBP+OAB: Cephradine 2 g at induction and IM gentamycin 2 mg/kg at premedication according to patient body weight. MBP alone: cephradine 2 g at induction and 500mg	

								metronidazole infusion then two further infusions within 24 h of metronidazole.	
Nohr *et al.* 1990	RCT	149	Cancer – 116 Complicated diverticulitis - 9 Crohn's disease - 8 UC - 1 Other - 15	Right colectomy – 29 Rectal resection – 44 Sigmoid resection – 30 APR - 19	All open	Bacitracin 250 mg and neomycin 250 mg TDS for 2 days pre-op. Metronidazole 500 mg TDS the day before surgery.	Frangula bark 2 tablets 2 days pre-op and magnesium sulphate (7.5 g) daily for 2 days pre-op.	Ampicillin 1 g within 1 h pre-op in MBP+OAB group. Fosfomycin 8 g and metronidazole 1 g within 1 h pre-op in MBP alone group.	MBP+OAB vs MBP
Oshima *et al.* 2013	RCT	200	Ulcerative colitis	Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA)	All open	Kanamycin 500 mg and metronidazole 500 mg TDS the day before surgery.	Magnesium citrate 1.8 L the day before surgery.	Flomoxef 30 min before surgery, repeated every 3 h intra-op and then 24 h post-op.	MBP+OAB vs. MBP

Ozdemir *et al.* 2016	Retrospective cohort study	90	Colonic malignancy Ulcerative colitis	Right colectomy – 17 Left colectomy – 10 Transverse colectomy – 9 LAR – 45 Total colectomy - 8	All open	Gentamycin 240 ml and metronidazole 2 g at 11 and 9 h pre-op.	Sodium dibasic phosphate 45 ml BD at 12 and 10 h pre-op, fleet enema 8 and 3-4 h pre-op.	Cefazolin 1 g and metronidazole 500 mg during anesthetic induction, continued BD for 5 days post-op.	MBP+OAB vs. MBP
Peruzzo *et al.* 1987	RCT	80	Cancer – 61 Diverticular disease – 6 Colostomy - 12	Right colectomy – 17 Left colectomy – 27 Sigmoid colectomy – 9 Anterior resection – 13 APR – 2 Colostomy closure - 12	All open	Neomycin 1 g at 19, 18 and 9 h pre-op and 2 g oral tinidazole.	'According to standard practice'.	Cefoxitin 30 min pre-op then at 6 and 12 h post-op.	MBP+OAB vs. MBP
Playforth *et al.* 1988	RCT	119 + 83 non randomised cohort	Cancer (curative) - 115 Cancer (palliative) - 25	Not stated Right colon – 55 Left colon and rectum - 135	All open	Neomycin 1 g every 6 h and metronidazole 200 mg every 8 h for 24 h prior to surgery.	Mannitol 100 g in 1 L water the day before surgery.	Metronidazole 500 mg at the time of premedication.	MBP+OAB vs. MBP

			Inflammatory - 50						
Ram *et al.* 2005	RCT	329	Cancer – 268 Benign - 61	Right colectomy - 42 Left colectomy - 74 Sigmoidectomy - 76 Subtotal colectomy - 11 APR - 34 Transverse colectomy – 3 Anterior resection – 50 LAR - 29	All open	Not stated	Monobasic sodium phosphate 2.4 g and dibasic sodium phosphate 0.9 g given the day before surgery.	Metronidazole 500 mg and ceftriaxone 1 g given 1 h pre-induction and continued for 48 h post-op.	MBP+OAB vs. OAB
Reddy *et al.* 2007	RCT	92 (46 pertinent to this meta-analysis)	Cancer and benign	Right colectomy- 16 Left colectomy - 6 Anterior resection - 18 APR - 3 Subtotal colectomy - 2	All open	3 g neomycin in three divided doses the day before surgery.	Sodium picosulfate and magnesium citrate given the day before surgery.	Not stated	MBP+OAB vs. MBP

				Panproctocolectomy - 1					
Reynolds *et al.* 1989	RCT	330	Cancer – 247 Benign – 5 Inflammatory lesion – 19 Other - 59	Right colectomy – 65 Left colectomy - 9 Sigmoid colectomy - 48 APR - 50 Anterior resection - 97 Panproctocolectomy - 2 Subtotal colectomy – 9 Hartmann's procedure – 10 Colostomy surgery - 35 Other - 4	All open	Metronidazole 400 mg eight hourly and neomycin 1 g six hourly for 48 h prior to surgery. Last dose of antibiotics given 8 and 12 h prior to surgery, respectively.	Magnesium sulphate up to 8×4 g doses for 48 h starting 72 h pre-op. Followed by two doses of sodium picosulphate the day before surgery.	Either piperacillin 2 g IV at induction and 3 further doses 8 hourly or metronidazole 500 mg and cefuroxime 1.5 g at induction followed by 3 further doses of metronidazole and 2 further doses of cefuroxime.	MBP+OAB vs. MBP
Rohwedder *et al.* 1993	Retrospective historical case	818	Of those with MBP/OAB: Right colectomy – 14	Of those with MBP/OAB:	All open	Ciprofloxacin 750 mg taken between 1 and 3 h pre-op.	Polyethylene glycol the day before surgery.	Gentamycin 80 mg and metronidazole 500 mg at the beginning of induction, then	MBP+OAB vs. MBP

	controlled series		Colorectal cancer – 89 Anal cancer – 1 Pelvic recurrence – 1 Villous tumour – 1 Diverticular disease – 6 UC – 1 Crohn's colitis - 1	Left colectomy – 25 LAR – 37 Miles APR – 12 Total colectomy – 6 Subtotal colectomy – 1 Double colectomy – 2 Other - 3				gentamycin 80 mg every 8 h for 3 days.	
Sadahiro *et al.* 2014	RCT	294	Colorectal malignancy	Not stated – tumour location: Right colon - 99 Transverse colon – 38 Left colon - 157	Open – 214 Laparoscopic - 80	Kanamycin sulfate 500 mg + metronidazole 500 mg TDS the day before surgery.	Sodium picosulfate 10 ml 2 days pre-op and 2 L polyethylene glycol the day before surgery.	Flomoxef 1 g 1 h pre-incision and further dose given if operative duration exceeded 3 h.	MBP+OAB vs. MBP

Stellato *et al.* 1990	RCT	146	Cancer – 123 Polyp – 11 Diverticular disease – 6 IBD – 6	Right colectomy - 44 Left colectomy – 17 Transverse colectomy - 4 Sigmoid colectomy - 30 LAR - 31 APR - 15 Subtotal colectomy - 5	All open	Neomycin 1g and erythromycin 1g TDS on the day before surgery.	Magnesium citrate 1.745 g in 296 ml in the morning and an enema (19 g sodium biphosphate and 7 g sodium phosphate in 118 ml) in the evening 2 days prior to surgery. Magnesium citrate 1.745 g in 296 ml in the morning and saline enemas until clear in the evening of the day before surgery.	Cefoxitin 2 g at induction then at 6 and 12 h following the first dose.	MBP+OAB vs. MBP
Sun *et al.* 2018	Retrospective case controlled series	321	Malignancy - 306 Benign - 12 IBD - 3	Right colectomy – 86 Left colectomy – 24 Sigmoid colectomy – 65 LAR – 90	Laparoscopic - 35 Open - 269	Neomycin 1 g and erythromycin 1 g at 20, 19 and 10 h prior to surgery.	Fleet phospho-soda 45 ml at 24 and 15 h before surgery then tap water enema at 2 h pre-op.	Cefazolin 1 g at induction.	MBP+OAB vs. MBP

				APR - 16 Laparoscopic anterior resection – 12 Laparoscopic sigmoidectomy – 15 Subtotal colectomy – 4 Laparoscopic right hemicolectomy - 8					
Takesue *et al.* 2000	RCT	83	Dukes A – 16 Dukes B – 43 Dukes C - 24	Ileocecal resection – 5 Right colectomy – 14 Left colectomy – 3 Transverse colectomy – 6 Sigmoidectomy – 24 LAR – 24 Miles' operation - 7	All open	Kanamycin 500 mg and metronidazole 500 mg at 2 pm, 3 pm and 11 pm the day before surgery.	Polyethylene glycol commence at 10 am the day before surgery.	Cefmetazole 1 g given at induction, then TDS for 3 days following surgery.	MBP+OAB vs. MBP
Taylor *et al.* 1994	RCT	327	Benign – 53 Cancer – 259	Anastomosis right colon - 93	Not stated	Ciprofloxacin 500 mg BD the	Sodium picosulfate one	Piperacillin 4 g at induction of anesthesia.	MBP+OAB vs. MBP

			IBD – 15	Anastomosis left colon/rectum - 168 Hartmann's resection - 6 APR - 43 Other - 17		day before surgery.	sachet BD the day before surgery.		
Uchino *et al.* 2017	RCT	325	Crohn's disease	Small bowel resection Colonic resection Rectal resection	All open	Kanamycin 500 mg and metronidazole 500 mg TDS the day before surgery.	Sodium picosulfate hydrate (20 ml of 0.75%) pre-operatively.	Flomoxef sodium 30 min before surgery, every 3 h intra-op then 24 h post-op.	MBP+OAB vs. MBP
Vo *et al.* 2018	Retrospective case control series	89	Colorectal cancer	Left colectomy - 14 Sigmoid colectomy – 16 LAR – 35 APR – 14 Subtotal colectomy or other - 10	Open - 21 Minimally invasive - 68	Neomycin sulfate 1 g and metronidazole hydrochloride 1 g TDS. Commenced one day prior to surgery.	Magnesium citrate 296 ml twice daily. Commenced one day prior to surgery.	Ertapenem – 82 Non-ertapenem - 7	MBP+OAB vs. MBP

Wren *et al*. 2005	Retrospective case controlled study	304	Not stated	Colon and/or rectal resection – 258 Colostomy creation or take down - 46	Open and laparoscopic	Neomycin 1 g and erythromycin 1 g	GoLYTELY, magnesium citrate or Fleet phospho-soda	Cephalosporin and metronidazole 59.2% Second generation cephalosporin 21.0% Fluoroquinolone and metronidazoleorclindamycin9.5% First-generation cephalosporin alone 3.9% Extended-spectrum penicillin 3.6%	MBP+OAB vs. MBP
Zmora *et al.* 2003	RCT	380	Cancer – 296 Diverticular disease – 16 Hartmann's procedure (for closure) – 29 Benign polyp – 14	Right colectomy - 113 Left colectomy - 33 Sigmoidectomy - 89 Anterior resection - 83 Closure of Hartmann's - 29	Not stated	Neomycin and erythromycin	Polyethylene glycol 1 gallon 12 to 16 h pre-op. Rectal surgery – given Fleet enema.	'Broad spectrum antibiotics' continued for 24 h post-op.	MBP+OAB vs. OAB

			IBD – 13 Other - 12	Subtotal/total abdominal colectomy – 24 Total proctectomy and ileal pouch - 9					

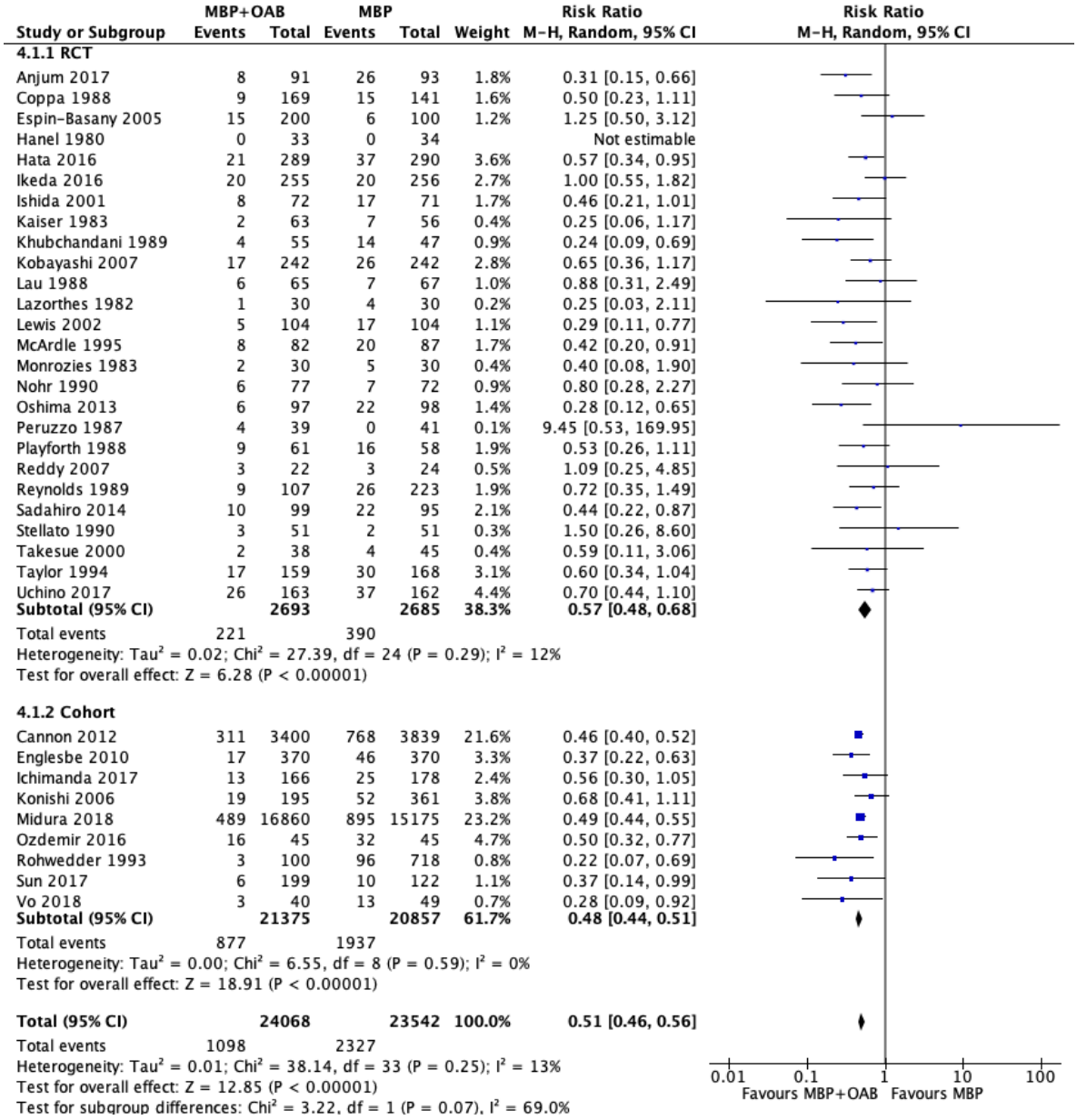
APR – abdominoperineal resection; IBD – inflammatory bowel disease; LAR – low anterior resection; RCT – randomised controlled trial

4.3.2 SSI

MBP+OAB *versus* MBP

The comparison between MBP+OAB *versus* MBP alone was performed in 35 studies; 26 RCTs (Anjum et al., 2017, Coppa and Eng, 1988, Espin-Basany et al., 2005, Hanel et al., 1980, Hata et al., 2016, Ikeda et al., 2016, Ishida et al., 2001, Kaiser et al., 1983, Khubchandani et al., 1989, Kobayashi et al., 2007, Lau et al., 1988, Lazorthes et al., 1982, Lewis, 2002, McArdle et al., 1995, Monrozies et al., 1983, Nohr et al., 1990, Oshima et al., 2013, Peruzzo et al., 1987, Playforth et al., 1988, Reddy et al., 2007, Reynolds et al., 1989, Sadahiro et al., 2014, Stellato et al., 1990, Takesue et al., 2000, Taylor and Lindsay, 1994, Uchino et al., 2017) and 9 cohort studies (Cannon et al., 2012, Englesbe et al., 2010, Ichimanda et al., 2017, Konishi et al., 2006, Midura et al., 2018, Ozdemir et al., 2016, Rohwedder et al., 1993, Sun et al., 2018, Vo et al., 2018) with 47,610 patients. When all studies were considered (**Figure 4.3.2.1**), the combination of MBP+OAB was associated with a significant reduction in SSI *versus* MBP alone (RR 0.51, 95% CI 0.46 to 0.56, $p<0.00001$, $I^2=13\%$). The results remained consistent when just RCT studies were examined (5378 patients; RR 0.57, 95% CI 0.48 to 0.68, $p<0.00001$, $I^2=12\%$), as well as cohort studies (42,232 patients; RR 0.48, 95% CI 0.44 to 0.51, $p<0.00001$, $I^2=0\%$).

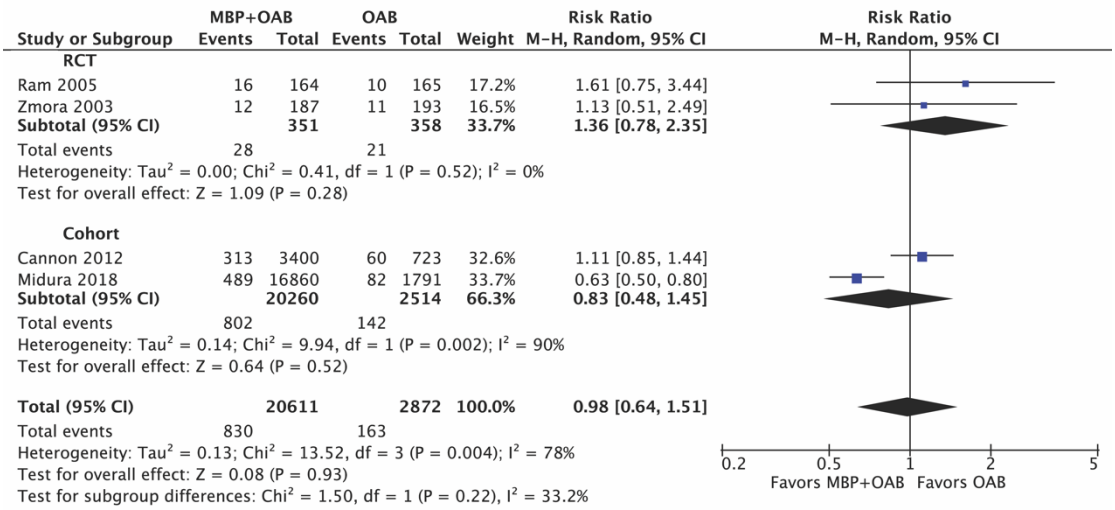
Figure 4.3.2.1 *- Forest plot comparing SSI rate for patients receiving MBP+OAB versus MBP alone, divided by evidence from RCTs and cohort studies.*



MBP+OAB *versus* OAB

The analysis of MBP+OAB *versus* OAB alone was considered by 4 studies; 2 RCTs (Ram et al., 2005, Zmora et al., 2003a) and 2 cohort studies (Cannon et al., 2012, Midura et al., 2018) including 23,483 patients (**Figure 4.3.2.2**). Overall, the combination of MBP+OAB was not associated with any difference in the incidence of SSI *versus* OAB alone (RR 0.98, 95% CI 0.64 to 1.50, p=0.92), with high heterogeneity (I^2=77%). When just RCTs were considered, again no difference was seen (RR 1.36, 95% CI 0.78 to 2.35, p=0.28, I^2=0%), as with cohort studies (RR 0.83, 95% CI 0.48 to 1.43, p=0.51, I^2=90%).

Figure 4.3.2.2 *- Forest plot comparing SSI rate for patients receiving MBP+OAB versus OAB alone, divided by evidence from RCTs and cohort studies*.

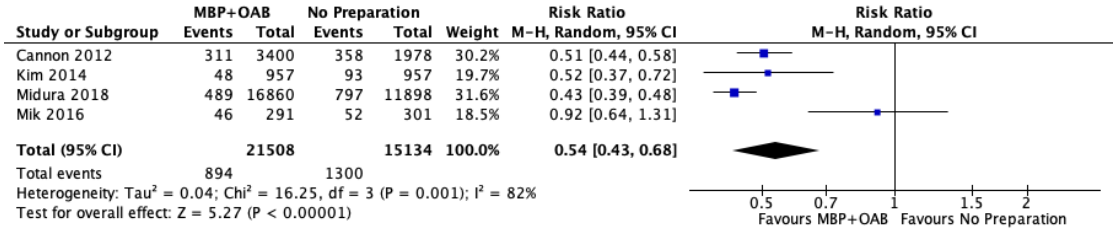


MBP+OAB *versus* No Preparation

No RCTs considered the comparison between combined MBP+OAB and no preparation, with evidence arising from just 4 cohort studies (36,642 patients; **Figure 4.3.2.3**) (Cannon et al., 2012, Kim et al., 2014a, Mik et al., 2016, Midura et al., 2018). The combination of

MBP+OAB was associated with a significant reduction in SSI (RR 0.54, 95% CI 0.43 to 0.68, p<0.00001, I^2=82%) when compared with no preparation.

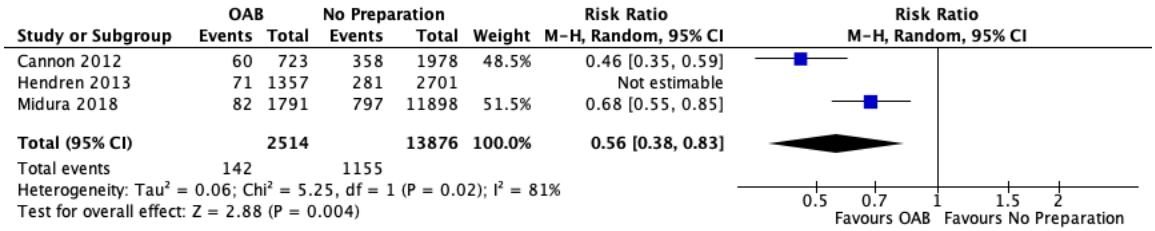
Figure 4.3.2.3 *- Forest plot comparing SSI rate for patients receiving MBP+OAB versus no preparation. All evidence from cohort studies.*



OAB alone *versus* No Preparation

No RCTs focused upon the comparison between OAB alone *versus* no preparation, with evidence arising from 16,390 patients included in two cohort studies (Cannon et al., 2012, Midura et al., 2018). OAB alone reduced the incidence of SSI *versus* no preparation (RR 0.56, 95% CI 0.38 to 0.83, p=0.004, I^2=81%).

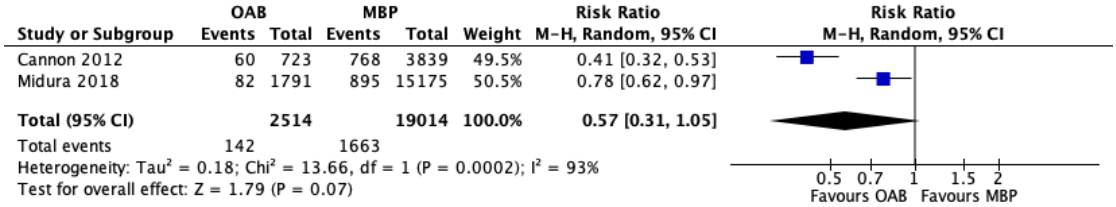
Figure 4.3.2.4 *– Forest plot comparing SSI rate for patients receiving OAB alone versus no preparation. All evidence from cohort studies.*



OAB *versus* MBP

Two studies (Cannon et al., 2012, Midura et al., 2018) considered the incidence of SSI with OAB alone *versus* MBP alone, with OAB associated with a reduction in SSI rates. However, this did not reach statistical significance (RR 0.57, 95% CI 0.31 to 1.05, p=0.07, I^2=93%).

Figure 4.3.2.5 *– Forest plot comparing SSI rate for patients receiving OAB alone versus MBP alone. All evidence from cohort studies.*



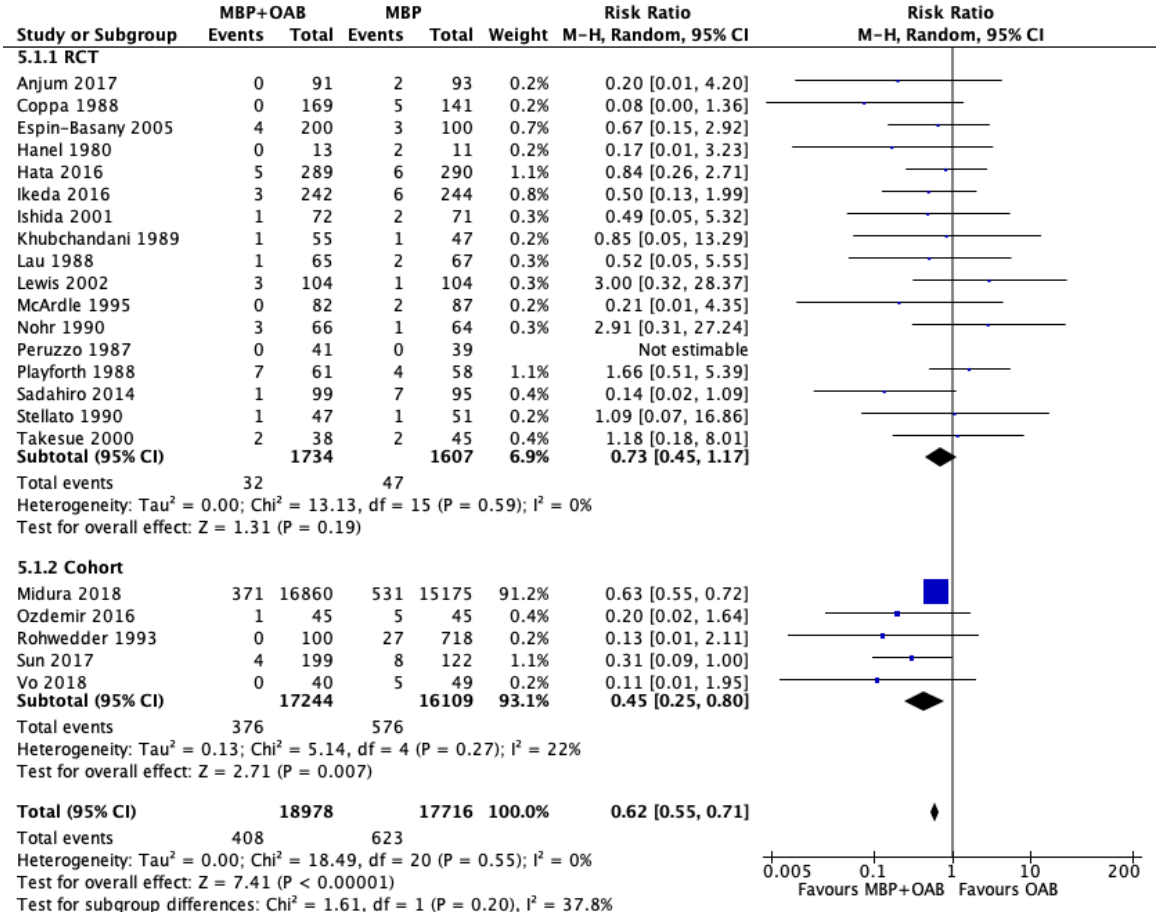
4.3.3 Anastomotic Leak

MBP+OAB *versus* MBP

Rates of anastomotic leak in those receiving combined MBP+OAB *versus* MBP alone were compared in 22 studies (**Figure 4.3.3.1**); 17 RCTs (Anjum et al., 2017, Coppa and Eng, 1988, Espin-Basany et al., 2005, Hanel et al., 1980, Hata et al., 2016, Ikeda et al., 2016, Ishida et al., 2001, Khubchandani et al., 1989, Lau et al., 1988, McArdle et al., 1995, Nohr et al., 1990, Peruzzo et al., 1987, Playforth et al., 1988, Sadahiro et al., 2014, Stellato et al., 1990, Takesue et al., 2000, Lewis, 2002) and 5 cohort studies (Midura et al., 2018, Ozdemir et al., 2016, Sun et al., 2018, Vo et al., 2018, Rohwedder et al., 1993). Only two RCTs (Anjum et al., 2017, Hanel et al., 1980) included data regarding the management of the anastomotic leak, with no patients receiving combined MBP+OAB requiring return to theatre for anastomotic leakage of 124 patients included, and 2 of 127 patients receiving MBP alone. Overall, the combination of MBP+OAB was associated with a significant

reduction in anastomotic leak rates (RR 0.62, 95% CI 0.55 to 0.70, p<0.00001, I^2=0%), and when evidence from cohort studies alone was considered (RR 0.45, 95% CI 0.25 to 0.80, p=0.007, I^2=22%), but no significant difference was seen when RCTs were analysed (RR 0.69, 95% CI 0.43 to 1.11, p=0.13, I^2=0%). Six studies (Espin-Basany et al., 2005, Hata et al., 2016, Ikeda et al., 2016, Ozdemir et al., 2016, Sun et al., 2018, Vo et al., 2018) included data on the use of a diverting stoma, with 133 patients of 1028 in the combined MBP+OAB group and 99 patients of 862 in the MBP alone group undergoing a protective stoma formation.

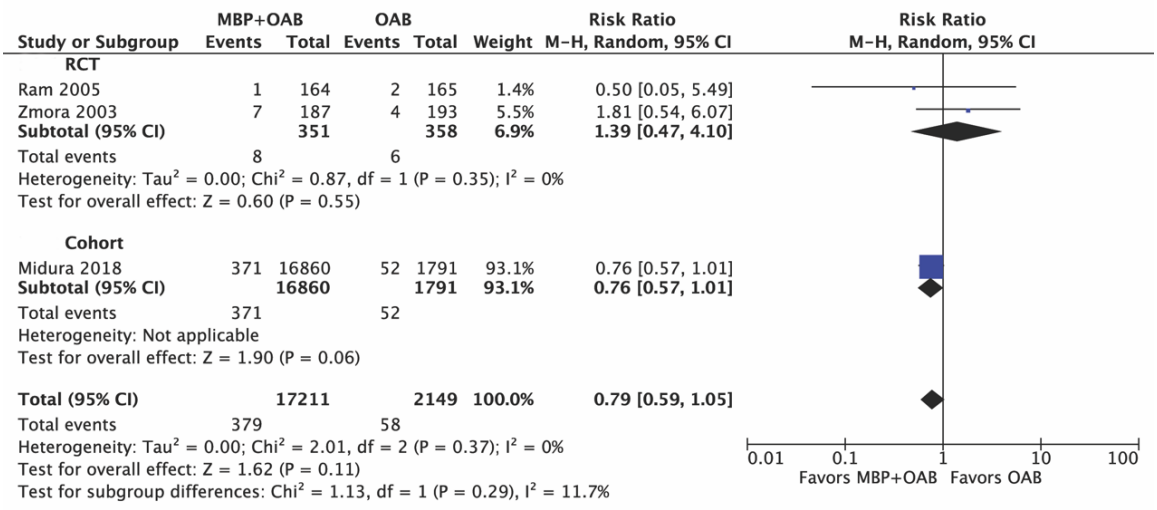
Figure 4.3.3.1 *- Forest plot comparing anastomotic leak rate for patients receiving MBP+OAB versus MBP alone, divided by evidence from RCTs and cohort studies.*



MBP+OAB *versus* OAB

The combination of MBP+OAB *versus* OAB alone was considered by three studies; two RCTs (Ram et al., 2005, Zmora et al., 2003a) and one cohort study (Midura et al., 2018), with no difference observed in anastomotic leak rates when all studies (RR 0.79, 95% CI 0.59 to 1.05, p=0.11, I^2=0%), or just RCTs (RR 1.39, 95% CI 0.47 to 4.10, p=0.55, I^2=0%) were considered (**Figure 4.3.3.2**). No data were available on return to theatre rates related to anastomotic leaks.

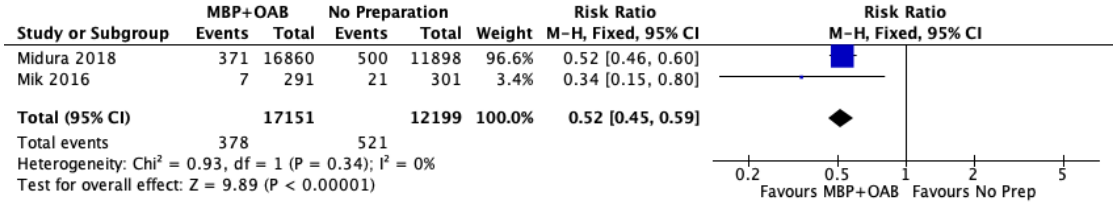
Figure 4.3.3.2 *- Forest plot comparing anastomotic leak rate for patients receiving MBP+OAB versus OAB alone, divided by evidence from RCTs and cohort studies.*



MBP+OAB *versus* No Preparation

The comparison between MBP+OAB *versus* no preparation in terms of anastomotic leak was considered by just two cohort studies (Midura et al., 2018, Mik et al., 2016), with combined MBP+OAB being associated with a significant reduction in anastomotic leak rates (RR 0.52, 95% CI 0.45 to 0.59, p<0.00001, I^2=0%; **Figure 4.3.3.2**). No data were available on return to theatre rates secondary to anastomotic leaks or diverting stoma rates.

Figure 4.3.3.2 *- Forest plot comparing anastomotic leak rate for patients receiving MBP+OAB versus no preparation. All evidence from cohort studies.*



Other Comparisons

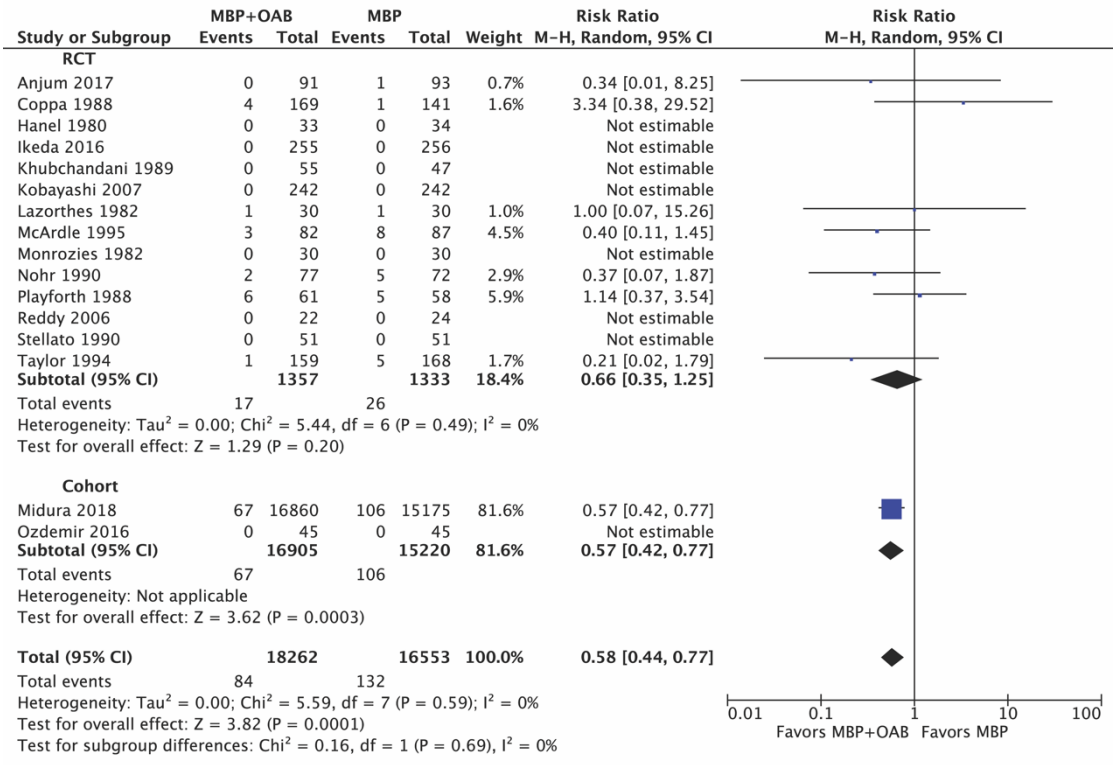
The comparison of anastomotic leak rates between OAB alone *versus* no preparation and OAB *versus* MBP were each only considered by one cohort study (Midura et al., 2018), and as such meta-analysis was not feasible.

4.3.4 30-Day Mortality

MBP+OAB *versus* MBP

Seventeen studies (35,633 patients) examined 30-day mortality rates between those receiving MBP+OAB *versus* MBP alone; 14 RCTs (Anjum et al., 2017, Coppa and Eng, 1988, Hanel et al., 1980, Ikeda et al., 2016, Khubchandani et al., 1989, Kobayashi et al., 2007, Lazorthes et al., 1982, McArdle et al., 1995, Monrozies et al., 1983, Nohr et al., 1990, Playforth et al., 1988, Reddy et al., 2007, Stellato et al., 1990, Taylor and Lindsay, 1994) and 3 cohort studies (Midura et al., 2018, Ozdemir et al., 2016, Rohwedder et al., 1993) (**Figure 4.3.4.1**). Overall, the combination of MBP+OAB was associated with a significant reduction in 30-day mortality *versus* MBP alone (RR 0.58, 95% CI 0.44 to 0.77, p=0.0001, I^2=0%). This was also the case when evidence arising from cohort studies alone was considered (RR 0.56, 95% CI 0.42 to 0.76, p=0.0002, I^2 not estimable), but not when RCTs alone were examined (RR 0.66, 95% CI 0.35 to 1.25, p=0.20, I^2=0%).

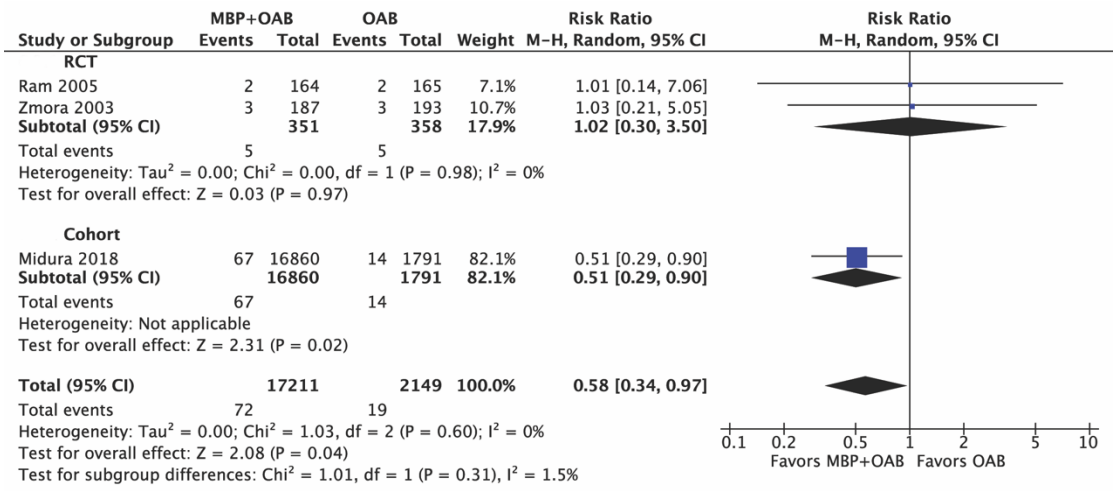
Figure 4.3.4.1 *- Forest plot comparing 30-day mortality rates for patients receiving MBP+OAB versus MBP alone, divided by evidence from RCTs and cohort studies.*



MBP+OAB *versus* OAB

Three studies consisting of two RCTs (Ram et al., 2005, Zmora et al., 2003a) and one cohort study (Midura et al., 2018)) including 19,360 patients considered 30-day mortality in those receiving MBP+OAB *versus* OAB alone (**Figure 4.3.4.2**), with the combination being associated with a significant reduction in 30-day mortality in all studies (RR 0.58, 95% CI 0.34 to 0.97, p=0.04, I^2=0%). However, no difference was observed in evidence taken from RCTs (RR 1.02, 95% CI 0.30 to 3.50, p=0.97, I^2=0%).

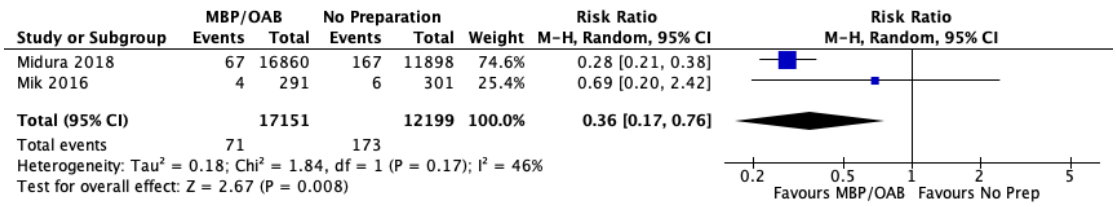
Figure 4.3.4.2 *- Forest plot comparing 30-day mortality rates for patients receiving MBP+OAB versus OAB alone, divided by evidence from RCTs and cohort studies.*



MBP+OAB *versus* No Preparation

Just two cohort studies (Midura et al., 2018, Mik et al., 2016) including 29,350 patients considered the impact of MBP+OAB *versus* no preparation on 30-day mortality. The combination of MBP+OAB was associated with a significant reduction in 30-day mortality (RR 0.36, 95% CI 0.17 to 0.76, p=0.008, I^2=46%).

Figure 4.3.4.3 *- Forest plot comparing 30-day mortality rates for patients receiving MBP+OAB versus no preparation, divided by evidence from RCTs and cohort studies.*



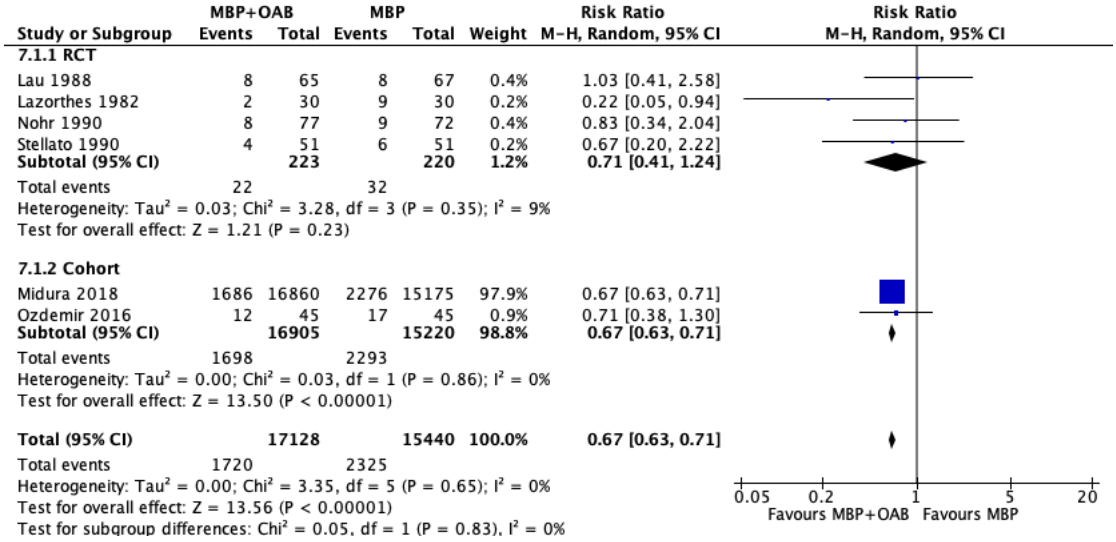
Other Comparisons

Comparison of 30-day mortality between those receiving OAB *versus* no preparation and OAB *versus* MBP included just a single cohort study (Midura et al., 2018), thus meta-analysis was not conducted.

4.3.5 Overall Morbidity

Only studies comparing MBP+OAB *versus* MBP alone were considered in terms of overall morbidity rates due to a paucity of data available for all other comparisons. When all 6 studies (Lau et al., 1988, Lazorthes et al., 1982, Midura et al., 2018, Nohr et al., 1990, Ozdemir et al., 2016, Stellato et al., 1990) (32,568 patients) were compared, the combination of MBP+OAB was associated a significant reduction in overall morbidity (RR 0.67, 95% CI 0.63 to 0.71, $p<0.00001$, $I^2=0\%$), as well as when evidence from cohort studies alone (Midura et al., 2018, Ozdemir et al., 2016) was considered (RR 0.67, 95% CI 0.63 to 0.71, $p<0.00001$, $I^2=0\%$). However, with RCTs alone (Lau et al., 1988, Lazorthes et al., 1982, Nohr et al., 1990, Stellato et al., 1990), there was no difference in overall morbidity between preparation methods (RR 0.71, 95% CI 0.41 to 1.24, $p=0.23$, $I^2=9\%$) (**Figure 4.3.5.1**).

Figure 4.3.5.1 *- Forest plot comparing overall morbidity rates for patients receiving MBP+OAB versus OAB alone, divided by evidence from RCTs and cohort studies.*

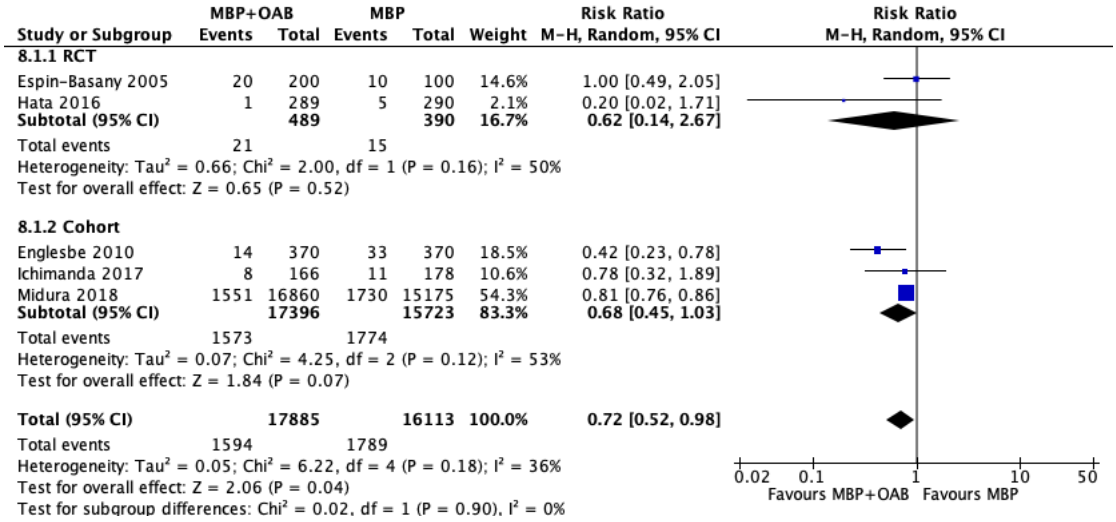


4.3.6 Development of Ileus

MBP+OAB *versus* MBP

Five studies (Englesbe et al., 2010, Espin-Basany et al., 2005, Hata et al., 2016, Ichimanda et al., 2017, Midura et al., 2018) were included in the comparison of MBP+OAB *versus* MBP; two RCTs (Espin-Basany et al., 2005, Hata et al., 2016) (879 patients) and three cohort studies (33,119 patients) (Englesbe et al., 2010, Ichimanda et al., 2017, Midura et al., 2018) (**Figure 4.3.6.1**). Only one study (Englesbe et al., 2010) provided a definition of ileus, with the other four studies (Englesbe et al., 2010, Hata et al., 2016, Ichimanda et al., 2017, Midura et al., 2018) not providing a definition. Overall, the combination of MBP+OAB was associated a significant reduction in the incidence of postoperative ileus (RR 0.72, 95% CI 0.52 to 0.98, p=0.04, I^2=36%). However, no difference was seen when just RCTs were considered (RR 0.62, 95% CI 0.14 to 2.67, p=0.52, I^2=50%) or cohort studies alone (RR 0.68, 95% CI 0.45 to 1.03, p=0.07, I^2=53%).

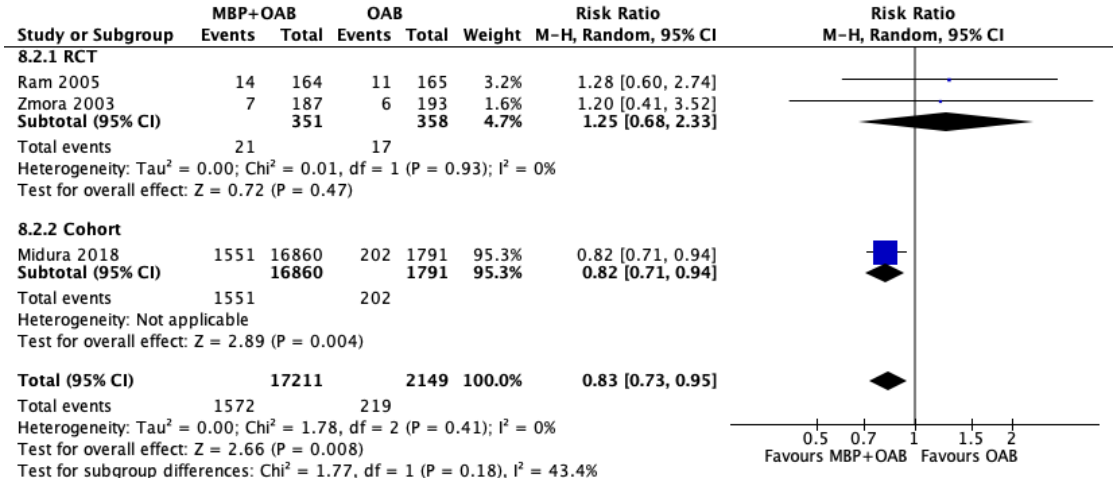
Figure 4.3.6.1 *- Forest plot comparing incidence of postoperative ileus for patients receiving MBP+OAB versus MBP, divided by evidence from RCTs and cohort studies*



MBP+OAB *versus* OAB

Three studies (Midura et al., 2018, Ram et al., 2005, Zmora et al., 2003a) were included in the comparison between MBP+OAB *versus* OAB; two RCTs (Ram et al., 2005, Zmora et al., 2003a) and one cohort study (Midura et al., 2018). None of these studies provided a definition for ileus. Overall, the combination of MBP+OAB was associated with a significant reduction in the incidence of postoperative ileus (RR 0.83, 95% CI 0.73 to 0.95, p=0.008, I^2=0%; **Figure 4.3.6.2**), mostly determined by the large single cohort study (Midura et al., 2018). However, no difference was seen when RCTs were considered (RR 1.25, 95% CI 0.68 to 2.33, p=0.47, I^2=0%).

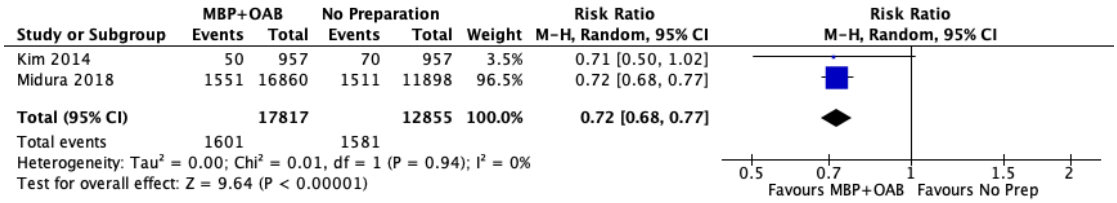
Figure 4.3.6.2 *- Forest plot comparing incidence of postoperative ileus for patients receiving MBP+OAB versus OAB, divided by evidence from RCTs and cohort studies*



MBP+OAB *versus* No Preparation

No RCTs considered the comparison between MBP+OAB *versus* no preparation, with evidence arising from two cohort studies only (Kim et al., 2014a, Midura et al., 2018). Only one study (Kim et al., 2014a) provided a definition of ileus. This demonstrated that the combination of MBP+OAB was associated with a significant reduction in ileus (RR 0.72, 95% CI 0.68 to 0.77, p<0.00001, I^2=0%; **Figure 4.3.6.3**).

Figure 4.3.6.3 *- Forest plot comparing incidence of postoperative ileus for patients receiving MBP+OAB versus MBP. All evidence taken from cohort studies.*



Other Comparisons

The comparison in reoperation rates between OAB alone *versus* no preparation and OAB *versus* MBP were each only considered by one cohort study (Midura et al., 2018), thus meta-analysis was not performed.

4.3.7 Reoperation

Insufficient data was available for any of the planned analyses on reoperation rates, with two studies including data comparing MBP+OAB *versus* MBP, one RCT (Anjum et al., 2017) and one cohort study (Midura et al., 2018), and just two studies again comparing MBP+OAB *versus* OAB alone, again one RCT (Ram et al., 2005) and one cohort study (Midura et al., 2018). Thus, no meta-analysis was performed. The comparison in reoperation rates between MBP+OAB *versus* no preparation, OAB alone *versus* no preparation and OAB *versus* MBP were each only considered by one cohort study (Midura et al., 2018), and as such meta-analysis was not performed. However, the largest cohort study (Midura et al., 2018) showed a significant reduction ($p<0.0001$) in reoperation rates with combined MBP+OAB (3.2%) compared with OAB alone (4.7%), MBP alone (4.2%) and no preparation (4.5%).

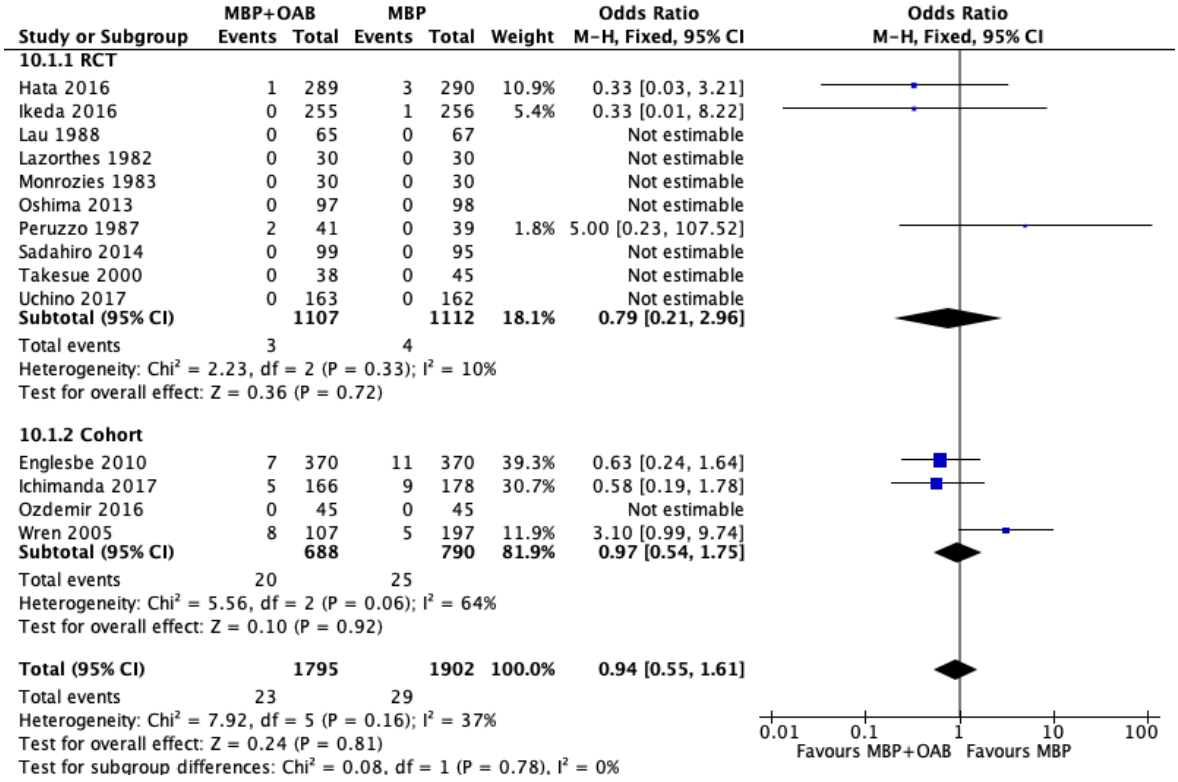
4.3.8 *Clostridium difficile* Infection

MBP+OAB vs. MBP

Data on *Clostridium difficile* infection were sufficient only for the comparison between MBP+OAB *versus* MBP alone, with data from 14 studies, including 10 RCTs (Hata et al., 2016, Ikeda et al., 2016, Lau et al., 1988, Monrozies et al., 1983, Peruzzo et al., 1987, Takesue et al., 2000, Uchino et al., 2017, Lazorthes et al., 1982, Oshima et al., 2013, Sadahiro et al., 2014) and four cohort studies (Wren et al., 2005, Englesbe et al., 2010, Ozdemir et al., 2016). No difference in *C. difficile* infection rates were seen when all

evidence was considered (RR 0.94, 95% CI 0.55 to 1.61, p=0.81, I^2=37%), nor when just RCT studies or cohort studies alone were analysed (RR 0.79, 95% CI 0.21 to 2.96, p=0.72, I^2=10% and RR 0.97, 95% CI 0.54 to 1.75, p=0.92, I^2=64%, respectively)(**Figure 4.3.8.1**).

Figure 4.3.8.1 - *Forest plot comparing Clostridium difficile infection rates for patients receiving MBP+OAB versus MBP, divided by evidence from RCTs and cohort studies*

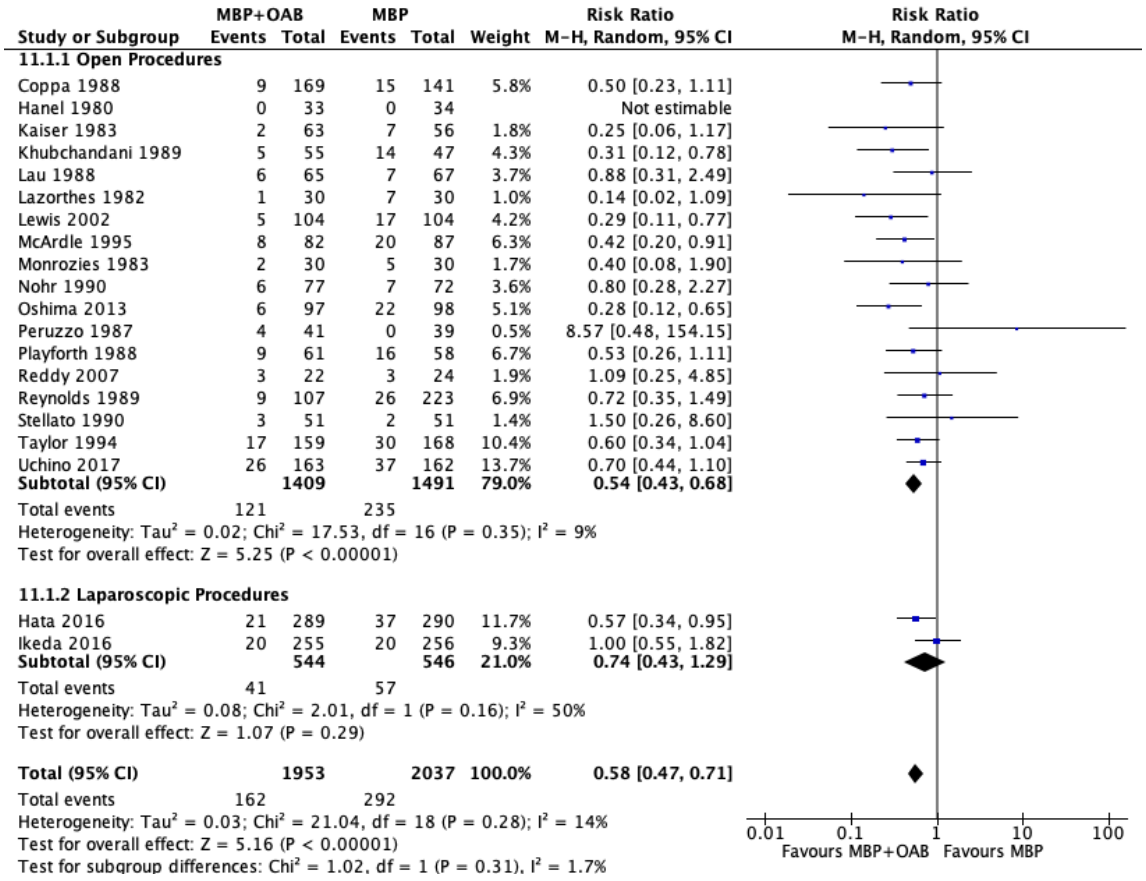


4.3.9 Laparoscopic versus Open Procedures

Nineteen RCTs (Coppa and Eng, 1988, Hanel et al., 1980, Kaiser et al., 1983, Khubchandani et al., 1989, Lau et al., 1988, Lazorthes et al., 1982, Lewis, 2002, McArdle et al., 1995, Monrozies et al., 1983, Nohr et al., 1990, Oshima et al., 2013, Peruzzo et al., 1987, Playforth et al., 1988, Reddy et al., 2007, Reynolds et al., 1989, Rohwedder et al., 1993, Stellato et al., 1990, Taylor and Lindsay, 1994, Uchino et al., 2017) provided data on SSI rates in patients undergoing open elective colorectal procedures between patients receiving combined

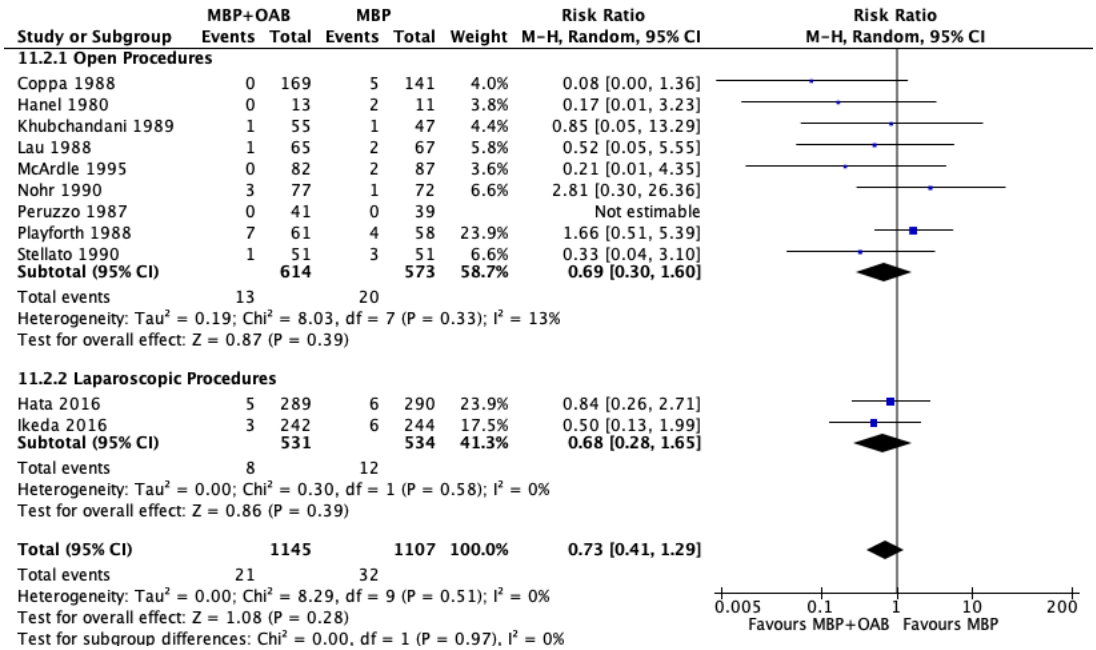
MBP+OAB *versus* MBP alone, and two RCTs (Hata et al., 2016, Ikeda et al., 2016) provided data on laparoscopic procedures alone. The remaining studies included either both open and laparoscopic procedures which could not be separated for analysis or did not state the surgical approach. No other comparison between preparations was considered due to a paucity of data. The combination of MBP+OAB *versus* MBP alone was associated with a significant reduction in SSI rates in patients undergoing an open resection (RR 0.55, 95% CI 0.44 to 0.69, p<0.00001, I^2=5%; **Figure 4.3.9.1**), however no significant difference was seen in patients undergoing a laparoscopic procedure (RR 0.74, 95% CI 0.43 to 1.29, p=0.29, I^2=50%), although it should be borne in mind that this evidence was based upon two studies (1090 patients).

Figure 4.3.9.1 - *Forest plot comparing SSI rates for patients receiving MBP+OAB versus MBP, divided by patients undergoing laparoscopic versus open procedures*



When anastomotic leak rates were compared between MBP+OAB *versus* MBP alone, divided by open and laparoscopic procedures, data could be analysed from 9 RCTs (Coppa and Eng, 1988, Hanel et al., 1980, Khubchandani et al., 1989, Lau et al., 1988, McArdle et al., 1995, Nohr et al., 1990, Peruzzo et al., 1987, Playforth et al., 1988, Stellato et al., 1990) in the open group and two RCTs (Hata et al., 2016, Ikeda et al., 2016) in the laparoscopic group. There was no significant difference in anastomotic leak rates in either the open or laparoscopic groups (RR 0.69, 95% CI 0.30 to 1.60, p=0.39, I^2=13% and RR 0.68, 95% CI 0.28 to 1.65, p=0.39, I^2=0%, respectively).

Figure 4.3.9.2 *- Forest plot comparing anastomotic leak rates for patients receiving MBP+OAB versus MBP, divided by patients undergoing laparoscopic versus open procedures*



4.4 Discussion

4.4.1 Main findings

This meta-analysis has provided evidence to suggest that MBP+OAB should be given serious consideration in patients undergoing elective colorectal surgery in order to reduce the risk of SSI versus MBP alone or no preparation. In addition, it has shown that the combination of MBP+OAB is associated with significant reductions in anastomotic leak rates, 30-day mortality, overall morbidity and the incidence of post-operative ileus, without increasing the risk of developing *Clostridium difficile* infection (**Table 4.4.1**). Its findings are in contradiction with previous meta-analyses (Slim et al., 2009) that did not account for the role of luminal antibiotics and showed that MBP on its own was of no benefit when compared with no bowel preparation or rectal enemas alone. However, as only 9.3% (6437 patients) of the 69,517 patients included were studied in the context of RCTs, the results must be interpreted with some caution. Hence, when evidence arising from RCTs alone was considered, the combination of MBP+OAB was associated with a significant reduction in SSI alone. The evidence for the combination of MBP+OAB to reduce SSI rates is, thus, strong. European data reporting the results of colorectal surgery in the context of ERAS protocols where MBP is not used routinely, have shown SSI rates of >10% (ERAS Compliance Group, 2015, Hendry et al., 2009), whereas, the ACS NSQIP studies have shown that SSI rates are approximately 6% with a combination of MBP+OAB (Midura et al., 2018).

When the combination of MBP+OAB was compared with OAB alone, a significant reduction in 30-day mortality and incidence of postoperative ileus was seen, but no difference was seen between the two preparations in RCTs alone. There are no RCTs focusing on the combinations of MBP+OAB *versus* no preparation, OAB alone *versus* no

preparation or OAB alone *versus* MBP alone. However, evidence from cohort studies suggests that the combination of MBP+OAB *versus* no preparation is associated with a significant reduction in SSI, anastomotic leak, 30-day mortality and post-operative ileus. For OAB *versus* no preparation, the only significant reduction was in SSI rates, and for OAB *versus* MBP there was no significant difference in any of the clinical outcome measures. When a planned subgroup analysis of patients undergoing open *versus* laparoscopic surgery was undertaken, the combination of MBP+OAB *versus* MBP alone was associated with a significant reduction in SSI rates in patients undergoing open procedures, but not in those undergoing laparoscopic procedures.

4.4.2 Strengths and Weaknesses of Meta-Analysis

The main weakness of this meta-analysis is the inclusion of both RCTs and cohort studies. Whilst this lowers the overall level of evidence, the decision to include cohort studies and large database studies was made as a large proportion of the recent evidence supporting the potential role of OAB or combined MBP+OAB has arisen from such studies. However, every analysis was conducted separately using evidence from RCT and cohort studies alone, as well as a summative analysis, to provide a more robust interpretation of the data.

The role of parenteral antibiotic prophylaxis is considered a standard of care in current practice, with evidence published in 1981 (Baum et al., 1981) providing evidence for its benefit in terms of infection prevention and overall mortality and dictating that no further placebo or no intervention trials should be conducted. Definitive support was provided in a Cochrane Review (Nelson et al., 2014) demonstrating a significant reduction in SSI in patients receiving parenteral antibiotic prophylaxis *versus* those receiving no antibiotics or placebo (RR 0.34, 95% CI 0.28 to 0.41, $p<0.0001$).

Table 4.4.1 *- Overall summary of results comparing MBP +OAB versus OAB versus no preparation*

Preparation considered	Outcome measure	All Studies	RCT only	Cohort studies only
MBP+OAB vs. MBP	SSI	Significant ↓ (RR 0.51, 95% CI 0.46-0.56, p<0.00001, I^2=13%)	Significant ↓ (RR 0.57, 95% CI 0.48-0.68, p<0.00001, I^2=12%)	Significant ↓ (RR 0.48, 95% CI 0.44-0.51, p<0.00001, I^2=0%)
	Anastomotic Leak	Significant ↓ (RR 0.62, 95% CI 0.55-0.70, p<0.00001, I^2=0%)	No difference (RR 0.69, 95% CI 0.43-1.11, p=0.13, I^2=0%)	Significant ↓ (RR 0.45, 95% CI 0.25-0.80, p=0.007, I^2=22%)
	30-day mortality	Significant ↓ (RR 0.58, 95% CI 0.44-0.76, p<0.00001, I^2=0%)	No difference (RR 0.66, 95% CI 0.35-1.25, p=0.20, I^2=0%)	Significant ↓ (RR 0.56, 95% CI 0.42-0.76, p=0.0002, I^2=0%)
	Overall morbidity	Significant ↓ (RR 0.67, 95% CI 0.63-0.71, p<0.00001, I^2=0%)	No difference (RR 0.71, 95% CI 0.41-1.24, p=0.23, I^2=9%)	Significant ↓ (RR 0.67, 95% CI 0.63-0.71, p<0.00001, I^2=0%)
	Development of ileus	Significant ↓ (RR 0.72, 95% CI 0.52-0.98, p=0.04, I^2=36%)	No difference (RR 0.62, 95% CI 0.14-2.67, p=0.52, I^2=50%)	No difference (RR 0.68, 95% CI 0.45-1.03, p=0.07, I^2=53%)
	Reoperation	---	---	---
	C. difficile infection	No difference (RR 0.94, 95% CI 0.55-1.61, p=0.81, I^2=37%)	No difference (RR 0.79, 95% CI 0.21-2.96, p=0.72, I^2=10%)	No difference (RR 0.97, 95% CI 0.54-1.75, p=0.92, I^2=64%)

MBP+OAB vs. OAB	SSI	No difference (RR 0.98, 95% CI 0.64-1.50, p=0.92, I^2=77%)	No difference (RR 1.36, 95% CI 0.78-2.35, p=0.28, I^2=0%)	No difference (RR 0.83, 95% CI 0.48-1.43, p=0.51, I^2=90%)
	Anastomotic Leak	No difference (RR 0.79, 95% CI 0.59-1.05, p=0.11, I^2=0%)	No difference (RR 1.39, 95% CI 0.47-4.10, p=0.55, I^2=0%)	---
	30-day mortality	Significant ↓ (RR 0.58, 95% CI 0.34-0.97, p=0.04, I^2=0%)	No difference (RR 1.02, 95% CI 0.30-3.50, p=0.97, I^2=0%)	---
	Overall morbidity	---	---	---
	Development of ileus	Significant ↓ (RR 0.83, 95% CI 0.73-0.95, p=0.008, I^2=0%)	No difference (RR 1.25, 95% CI 0.68-2.33, p=0.47, I^2=0%)	---
	Reoperation	---	---	---
	C. difficile infection	---	---	---
MBP+OAB vs. no preparation	SSI	---	---	Significant ↓ (RR 0.54, 95% CI 0.43-0.68, p<0.00001, I^2=82%)
	Anastomotic Leak	---	---	Significant ↓ (RR 0.52, 95% CI 0.45-0.59, p<0.00001, I^2=0%)
	30-day mortality	---	---	Significant ↓ (RR 0.36, 95% CI 0.17-0.76, p=0.008, I^2=46%)

	Overall morbidity	---	---	---
	Development of ileus	---	---	Significant ↓ (RR 0.72, 95% CI 0.68-0.77, $p<0.00001$, $I^2=0\%$)
	Reoperation	---	---	---
	C. difficile infection	---	---	---

CI – confidence interval; OAB – oral antibiotic; MBP – mechanical bowel preparation; RR – risk ratio; SSI – surgical site infection

--- indicates insufficient data for conduct of meta-analysis

The practice of MBP has changed significantly since the early 1980s. The regimen of Lazorthes *et al*. (Lazorthes et al., 1982) included admission three days prior to surgery and administration of a low-residue diet and standard mechanical procedures such as enemas and magnesium sulphate purges. In contrast, more modern regimens are typically administered the day before surgery and are less invasive. This is particularly important in the setting of prolonged starvation protocols in vogue prior to the more modern ones, as they resulted in increased preoperative dehydration and electrolyte disturbances which are known to have adverse effects on postoperative complications. It should, however, be considered that each study level comparison between preparation types should have been exposed to the same level of bias, thus making the results more comparable. The OAB agent, dosing and timing as well as the parenteral antibiotic details were also inconsistent between studies, with insufficient data from each differing combination to perform a meaningful analysis. Several included just one preoperative dose of OAB, or differing parenteral antibiotic regimens depending upon which preparation regimen the patient received which exerts a potential significant bias. In addition, because of limited data, we have been unable to discern conclusively whether the reduction in morbidity is a result of OAB on their own or in combination with MBP.

The definition of SSI is hugely variable within the studies included in this meta-analysis, as well as the method for reporting of SSI as either an overall incidence or split by the different classifications provided by the CDC (Horan et al., 1992). This therefore represents a large source of potential reporting bias. Where these data were quoted separately, the data provided on superficial incisional SSI were used for the meta-analysis, as the combination of different SSI locations may result in dual reporting of SSI for individual patients. The definition of anastomotic leak was also not stipulated for inclusion within this meta-analysis,

with the data from each individual study included, irrespective of whether this was based upon clinical or radiological diagnosis of anastomotic leak. However, the definition of both SSI and anastomotic leak was consistent within individual studies, thus the data from each study was comparable, partially attenuating this potential weakness.

4.4.3 Interpretation of the data in context of other recent studies

A recent meta-analysis (Koullouros et al., 2017) included 23 RCTs and 8 cohort studies published between 1980 and 2015. However, multiple cohort studies arising from the NSQIP database were included within this meta-analysis (Koullouros et al., 2017), and this probably represents multiple reporting of the same patient datasets. This previous meta-analysis (Koullouros et al., 2017) reported a significant reduction in SSI rates in patients included within cohort studies receiving MBP, OAB and IV antibiotics *versus* those receiving MBP and IV antibiotics alone (RR 0.48, 95% CI 0.44 to 0.52, p=0.00001). However, 4 of the 5 studies included within this analysis arose from the ACS NSQIP database. Bellows *et al.* (Bellows et al., 2011) previously performed a meta-analysis on the role of oral non-absorbable and intravenous antibiotics *versus* intravenous antibiotics alone in colorectal surgery, focusing on SSI. This study included 16 RCTs encompassing 2669 patients published between 1980 and 2011, with all studies including MBP within the protocol. This meta-analysis found that the combination of oral and IV antibiotics was associated with a significant reduction in wound infection rates (RR 0.57, 95% CI 0.43 to 0.76, p=0.0002), but no significant difference in anastomotic leak rates (RR 0.63, 95% CI 0.28 to 1.41, p=0.3). The findings of the currently reported meta-analysis coincide with the results of these previous meta-analyses.

4.4.4 Conclusion

The present meta-analysis is the largest and most comprehensive to date examining the role of bowel preparation prior to colorectal surgery, and supports a potentially significant benefit for OAB preparation, either in combination with MBP or alone, in the prevention of postoperative complications. Whilst evidence arising from large retrospective cohort and database studies suggests a strong positive benefit, these are tempered when evidence arising from RCTs alone is considered. However, the evidence presented would suggest a benefit from OAB preparation in terms of SSI, which represents a major source of morbidity and increased healthcare costs. Further high-quality evidence is required to differentiate between the benefits of combined MBP+OAB or OAB alone in this setting before more definitive recommendations can be made.

Chapter 5 – Goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery

5.1 Introduction

Intraoperative GDFT using measurements of stroke volume and cardiac output to inform administration of small volume of fluid (usually 200-250 ml of either a colloid or crystalloid) as well as inotropes to optimise stroke volume has been used for over two decades. The rationale for this technology is to maintain the patient in a state of euvolaemia, which optimises oxygen delivery and tissue perfusion whilst avoiding hypo- and hyper-perfusion and their associated postoperative complications. A meta-analysis published in 2014 of 22 randomised clinical trials (RCTs) that employed GDFT in a variety of elective and emergency operations showed that the risk of developing complications after surgery was reduced by 23% when compared with conventional intraoperative fluid therapy (Pearse et al., 2014). However, a recently published meta-analysis that examined 23 RCTs on 2099 patients undergoing elective major abdominal surgery (Rollins and Lobo, 2016), suggested that GDFT may not be of benefit to all patients, particularly those managed in an ERAS Pathway (Nygren et al., 2012, Gustafsson et al., 2012b) setting. Nevertheless, most guidelines for perioperative care in colorectal surgery (Nygren et al., 2012, Gustafsson et al., 2012b, Carmichael et al., 2017, Thiele et al., 2016) recommend that GDFT should be used for patients undergoing colorectal surgery. Furthermore, the UK National Institute of Health and Care Excellence has previously issued guidelines stating that intraoperative GDFT with transoesophageal Doppler monitoring should be used in ‘patients undergoing major or high-risk surgery’ (NICE, 2011), with evidence supporting both a clinical benefit and cost saving based on the literature available when the guideline was published in 2011. This guidance is based

upon 8 RCTs (Wakeling et al., 2005, Gan et al., 2002, Mythen and Webb, 1995, Venn et al., 2002, Senagore et al., 2009, Noblett et al., 2006, McKendry et al., 2004, Sinclair et al., 1997) conducted across a wide range of surgical specialities including colorectal, gynaecological, orthopaedic, urological and cardiac surgery. They found a 'clinical benefit and a cost saving when the CardioQ-ODM is used in patients undergoing high-risk surgery'.

Previous meta-analyses have been weakened by the inclusion of patients undergoing both emergency and elective surgery (Pearse et al., 2014, Som et al., 2017) and a wide range of operations (Pearse et al., 2014, Rollins and Lobo, 2016, Chong et al., 2018) and also by the fact that overall standards of perioperative care have changed over the past two decades. The device used for stroke volume and cardiac output monitoring varied across the individual RCTs (Rollins and Lobo, 2016), however there are insufficient numbers of studies for different GDFT monitoring techniques within these meta-analyses to draw meaningful conclusions. Evidence does however suggest that different GDFT monitoring techniques are not equivalent in measuring haemodynamic stability (Feldheiser et al., 2014, Nordstrom et al., 2013, Davies et al., 2013), thus this should be born in mind when interpreting the results of previous meta-analyses. Hydroxyethyl starch (HES) was frequently the colloid used in the GDFT arm and the use of this fluid has now been suspended by the European Medicines Agency (European Medicines Agency, 2018) because of the increased incidence of acute kidney injury (AKI) and the need for renal replacement therapy (Brunkhorst et al., 2008, Myburgh et al., 2012, Perner et al., 2012), thus making the results of these older trials potentially less generalisable.

The aim of this meta-analysis of RCTs was, therefore, to examine the effect of GDFT using the transoesophageal Doppler when compared with conventional intraoperative fluid therapy on postoperative outcome, including AKI in patients undergoing elective major colorectal surgery alone.

5.2 Methods

5.2.1 Search Strategy

A search of the PubMed, MEDLINE, Google™ Scholar and Cochrane Library databases was performed to identify full-text studies evaluating the impact of intraoperative GDFT on postoperative surgical outcomes in patients undergoing elective colorectal surgery published between January 1995 and July 2018. The electronic search terms used were [‘goal-directed fluid therapy’ OR ‘flow-directed fluid therapy’] AND [‘surgery’ OR ‘intraoperative’] AND [colon OR rectal OR colorectal]. No language restriction was imposed upon the search. Only studies including adult patients undergoing elective colorectal surgery were selected.

5.2.2 Selection of Articles

Following the exclusion of initial studies on the basis of article title and abstract by two independent researchers, the remaining full-text articles were screened in detail for inclusion. Studies were included if they examined adult patients undergoing elective colorectal surgery who were randomly allocated to receive either GDFT administered with transoesophageal Doppler monitoring or conventional intraoperative fluid therapy and if the study reported at least one relevant postoperative outcome. The decision to include RCTs alone rather than observational studies was based upon knowledge of the literature gained through prior work directly relevant to this area (Rollins and Lobo, 2016). Studies were excluded if any patients had undergone non-colorectal surgery, included any emergency surgical procedures, employed any other device other than the transoesophageal Doppler for the conduct of GDFT, did not include any relevant clinical outcome measures or if both groups received GDFT. Consensus was reached in cases where the manuscript was not explicit regarding their inclusion and exclusion criteria. One published abstract was identified which would be

suitable for inclusion, however the data available from the text was insufficient to include within the meta-analysis, so this was excluded (Zhang et al., 2016b).

5.2.3 Data Extraction

Study data were extracted by dual reviewer technique with any discrepancies resolved by an independent reviewer. The primary outcome measure examined was overall postoperative morbidity and secondary outcome measures included 30-day mortality, hospital LOS, time to return of gastrointestinal function (flatus and stool), incidence of paralytic ileus, acute kidney injury, and rates of SSI and anastomotic leak. Data were also collated on patient demographics [age, gender, American Society of Anesthesiology (ASA) grade], surgical variables (surgical procedure, number of laparoscopic cases, estimated blood loss) and intraoperative fluid administration (overall, maintenance and bolus fluid volumes and inotrope administration). Data were extracted on whether the patient was managed using ERAS principles (Fearon et al., 2005, Lassen et al., 2009) or traditional perioperative care, and the method of administration of GDFT was noted. If data necessary for the conduct of the meta-analysis were not available from the manuscript the corresponding author was approached to obtain this with the aim of ensuring data collection was as complete as possible, with the technique described by Hozo *et al.* (Hozo et al., 2005) used to estimate the mean and standard deviation as described in previous chapters. Where this technique was utilised, separate meta-analyses were conducted with this data both included and excluded to insure this was not exerting any significant bias upon the analysis results. The risk of bias was assessed using the Cochrane Collaboration tool as with previous chapters.

5.2.4 Statistical Analysis

Data extracted from the included studies were entered into the RevMan 5.3 software program (Cochrane Collaboration, 2014). When the Hozo technique (Hozo et al., 2005) had been used to estimate mean and standard deviation (SD) data from studies included to inform continuous data analysis, two separate meta-analyses were conducted; one including the estimated data and one excluding this data. Data were used to construct forest plots, with a p value <0.05 on two tailed testing indicating a statistically significant difference. Study heterogeneity and inconsistency were assessed using the I^2 statistic (Higgins and Thompson, 2002).

5.3 Results

From 831 studies identified initially, 11 studies (Reisinger et al., 2017, Phan et al., 2014, Srinivasa et al., 2013b, Brandstrup et al., 2012, Zakhaleva et al., 2013, Challand et al., 2012, Gomez-Izquierdo et al., 2017, Senagore et al., 2009, Noblett et al., 2006, Wakeling et al., 2005, Conway et al., 2002) were deemed eligible for inclusion (**Figure 5.3.1**). Overall the risk of bias of the studies included was low and generally the quality of the studies was medium to high (**Table 5.3.1**).

Figure 5.3.1 *– PRISMA diagram showing identification of relevant studies from initial search*

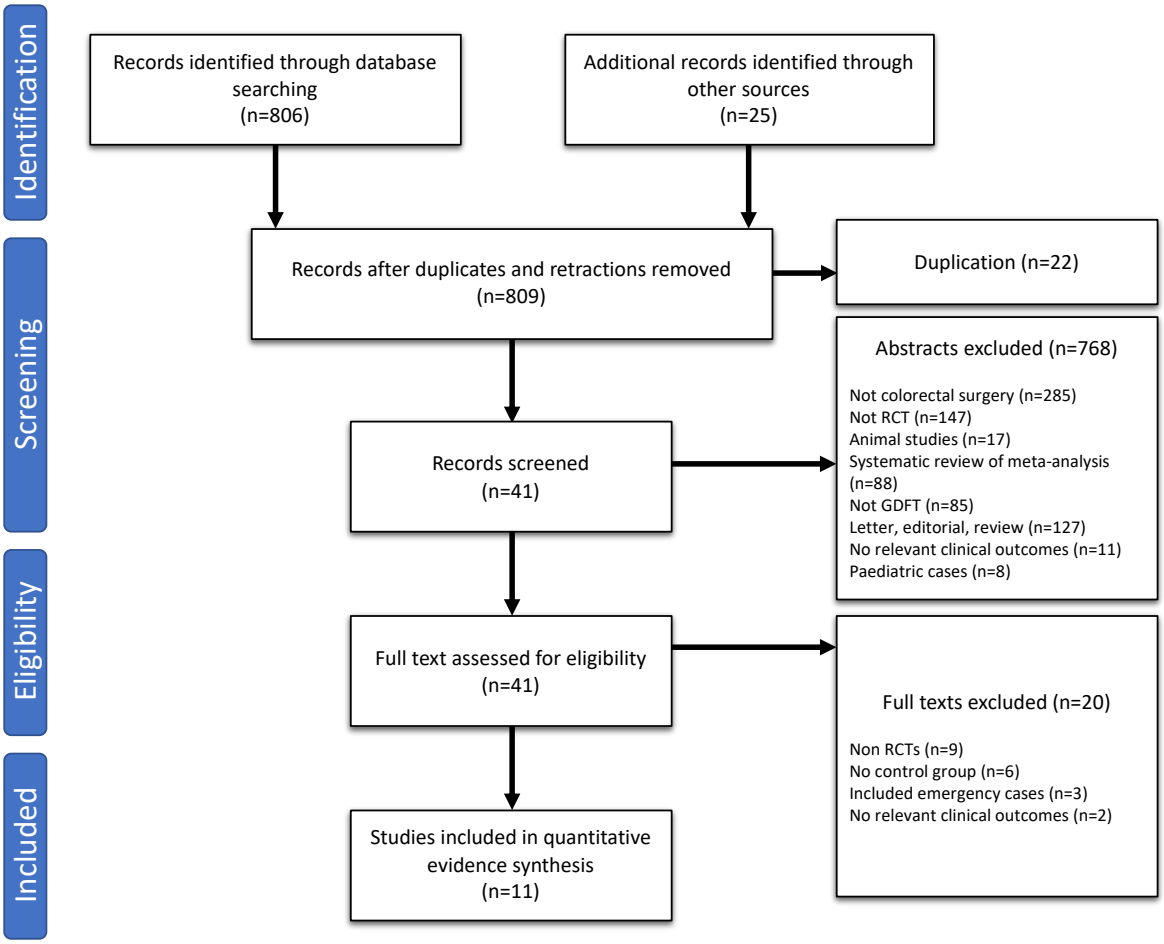


Table 5.3.1 *- Risk of bias assessment of included studies*

Reference	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other Bias
Reisinger *et al.*	+	+	-	+	+	+	?
Gomez-Izquierdo *et al.*	+	+	+	+	+	+	+
Phan *et al.*	+	+	-	+	+	+	+
Srinivasa *et al.*	+	+	-	+	+	+	+
Brandstrup *et al.*	+	+	?	+	+	+	+
Zakhaleva *et al.*	+	+	?	?	+	+	?
Challand *et al.*	?	?	?	+	+	+	+
Senagore *et al.*	+	?	?	?	+	+	+
Noblett *et al.*	?	?	+	+	+	+	-
Wakeling *et al.*	+	+	+	?	+	+	+
Conway *et al.*	?	?	?	?	+	+	-

+ Low risk of bias; - High risk of bias; ? Unclear risk of bias

5.3.1 Demographics

The 11 RCTs within this meta-analysis (Reisinger et al., 2017, Phan et al., 2014, Srinivasa et al., 2013b, Brandstrup et al., 2012, Zakhaleva et al., 2013, Challand et al., 2012, Gomez-Izquierdo et al., 2017, Senagore et al., 2009, Noblett et al., 2006, Wakeling et al., 2005, Conway et al., 2002) included a total of 1113 adult patients who had undergone elective colorectal surgery, of whom 556 were randomised to intraoperative GDFT using the transoesophageal Doppler and 557 to traditional intraoperative fluid management strategies. GDFT was administered as part of an enhanced recovery program in ten studies (Reisinger et al., 2017, Phan et al., 2014, Srinivasa et al., 2013b, Brandstrup et al., 2012, Zakhaleva et al., 2013, Challand et al., 2012, Gomez-Izquierdo et al., 2017, Senagore et al., 2009, Wakeling et al., 2005, Noblett et al., 2006) and in only one study as part of a traditional perioperative care pathway (Conway et al., 2002), thus no analysis was conducted comparing patients managed as part of these differing pathways. Data on laparoscopic surgical approach only were provided by two studies (Gomez-Izquierdo et al., 2017, Senagore et al., 2009), with no studies providing data from open only approaches. Baseline patient demographics are provided in **Table 5.3.1.1** and fluid administered during the perioperative period detailed in **Table 5.3.1.2**.

5.3.2 Overall Morbidity

Nine studies (Brandstrup et al., 2012, Challand et al., 2012, Conway et al., 2002, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Phan et al., 2014, Srinivasa et al., 2013b, Wakeling et al., 2005, Zakhaleva et al., 2013) on 487 patients managed with GDFT and 504 patients with traditional fluid management reported overall morbidity rates (**Figure 5.3.2.1**).

Table 5.3.1.1 *- Baseline patient demographics for all included studies*

		Number of Patients		Type of Surgery		Laparoscopic Approach		ASA 1:2:3:4	
Reference	ERAS or Traditional	GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control
Reisinger *et al.*	ERAS	27	31	10 right hemicolectomy, 1 left hemicolectomy, 5 sigmoid colectomy, 11 rectal resection	12 right hemicolectomy, 0 left hemicolectomy, 5 sigmoid colectomy, 13 rectal resection, 1 subtotal colectomy	7	10	8:14:5:0	4:24:3:0
Gomez-Izquierdo *et al.*	ERAS	64	64	39 colonic resection, 25 rectal resection	39 colonic resection, 25 rectal resection	64	64	6:42:14:2	8:38:18:0
Phan *et al.*	ERAS	50	50	12 right hemicolectomy, 17 anterior resection, 21 other (29 cancer surgery)	14 right hemicolectomy, 22 anterior resection, 1 abdominal/perineal, 13 other (34 cancer surgery)	31 (additional 8 converted to open)	28 (additional 8 converted to open)	Median ASA class 2 (1-3)	Median ASA class 2 (1-3)
Srinivasa *et al.*	ERAS	37	37	14 right hemicolectomy, 4 extended right hemi, 14 high anterior	17 right hemicolectomy, 5 extended right hemi, 14 high anterior resection,	5	6	5:20:12:0	5:15:17:0

				resection, 5 total/subtotal colectomy	1 total/subtotal colectomy				
Brandstrup *et al.*	ERAS	71	79	All elective colorectal	All elective colorectal	32, additional 11 converted from laparoscopic to open	38, additional 12 converted from laparoscopic to open	26:37:8:0	20:43:16:0
Zakhaleva *et al.*	ERAS	32	40	24 colectomy, 7 proctectomy, 1 small bowel resection - 16 malignant, 11 benign, 5 IBD	30 colectomy, 6 proctectomy, 4 small bowel resection - 17 malignant, 19 benign, 4 IBD	16 + 2 converted to open	19 + 5 converted to open	0:7:26:0	0:7:32:0
Challand *et al.*	ERAS	89	90	32 colonic, 57 rectal (65 carcinoma)	37 colonic, 53 rectal (68 carcinoma)	28	37	11:51:27 (3+4)	11:52:27 (3+4)
Senagore *et al.*	ERAS	42	22	All colectomy	All colectomy	42	42	Not stated	Not stated
Noblett *et al.*	ERAS	51	52	30 colonic, 24 rectal	25 colonic, 29 rectal	13	13	Mean ASA class 2.1 (0.6)	Mean ASA class 2.2 (0.6)
Wakeling *et al.*	ERAS	64	64	31 anterior and AP resection, 15 left hemi and sigmoid colectomy, 15 right	33 anterior and AP resection, 15 left hemi and sigmoid colectomy, 9 right hemicolectomy,	not stated	not stated	Median ASA class 2 (1)	Median ASA class 2 (1)

				hemicolectomy, 3 reversal of Hartmann's	4 subtotal colectomy, 2 reversal of Hartmanns, 1 Crohn's resection				
Conway *et al.*	Traditional	29	28	NOT STATED	NOT STATED	not stated	not stated	Median ASA class 1 (1-3)	Median ASA class 2 (1-3)

Table 5.3.1.2 *– Intraoperative fluid infused in the GDFT and control groups*

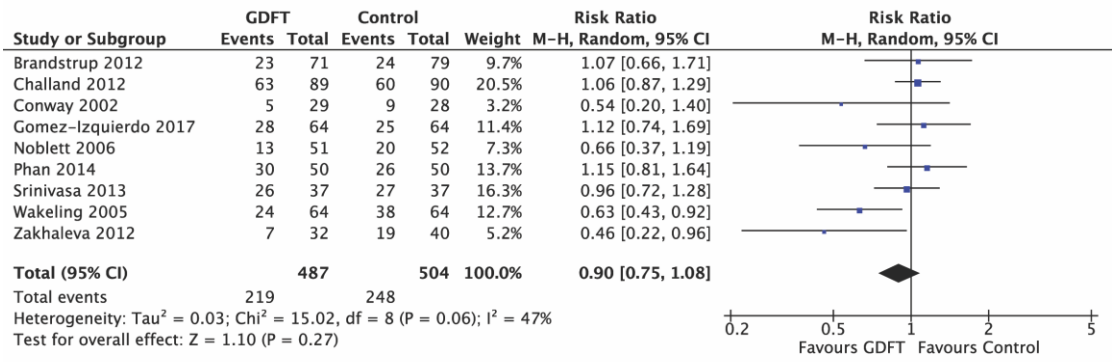
	Average Total Fluid Infused (ml)		Average Crystalloid (ml)		Average Colloid bolus (ml)		Average blood loss (ml)		Requirement for Perioperative Inotropes	
Reference	GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control	GDFT	Control
Reisinger *et al.*	Not stated	Not stated	3000+/-1093	3026+/-1307	1526+/-823	952+/-687	957+/-1880	461+/-1026	12 (44.4)	15 (48.4)
Gomez-Izquierdo *et al.*	1535 (1000-2272)	2370 (1779-3071)	NOT STATED	NOT STATED	900 (400-1400)	0 (0-500)	175 (100-400)	150 (100-400)	Phenylephrine 53 Ephedrine 40	Phenylephrine 58 Ephedrine 43
Phan *et al.*	2190 (1350-2560)*	1500 (1200-2000) *	1500 (1000-2000)	1400 (1000-1900)	500 (250-750) *	0 (0-300) *	NOT STATED	NOT STATED	NOT STATED	NOT STATED
Srinivasa *et al.*	1994 (590) *	1614 (420) *	NOT STATED	NOT STATED	591 (471) *	297 (275) *	NOT STATED	NOT STATED	31 (83.7)	34 (91.9)
Brandstrup *et al.*	1876*	1491*	Saline and LR: 483 (419)	443 (480)	810 (543) *	475 (598) *	NOT STATED	NOT STATED	NOT STATED	NOT STATED
Zakhaleva *et al.*	3100 (700-77000)	4000 (900-6200)	2700 (500-6500)	3200 (500-5600)	500 (0-2800) *	300 (0-4500) *	100 (10-650)	100 (10-500)	NOT STATED	NOT STATED
Challand *et al.*	NOT STATED	NOT STATED	3479 (1181)	3593 (1398)	1718 (446) *	336 (623) *	500 (200-1000) *	250 (100-500) *	NOT STATED	NOT STATED
Senagore *et al.*	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED	NOT STATED

Noblett *et al.*	NOT STATED	NOT STATED	2298 (863)	2625 (1004)	1340 (838)	1209 (824)	250 (40-2455)	475 (100-2900)	16 (31) *	26 (50) *
Wakeling *et al.*	NOT STATED	NOT STATED	3000	3000	2000*	1500*	500 (700)	500 (975)	NOT STATED	NOT STATED
Conway *et al.*	64.6ml/kg (36.4)	55.2ml/kg (24)	NOT STATED	NOT STATED	28ml/kg (16)	19.4ml/kg (14.7)	NOT STATED	NOT STATED	NOT STATED	NOT STATED

*Indicates statistically significant difference between GDFT and Control groups

Overall morbidity was not significantly different between these groups (RR 0.90, 95% CI 0.75 to 1.08, p=0.27).

Figure 5.3.2.1 *- Forest plot comparing overall morbidity rate for patients receiving GDFT versus traditional fluid therapy.*



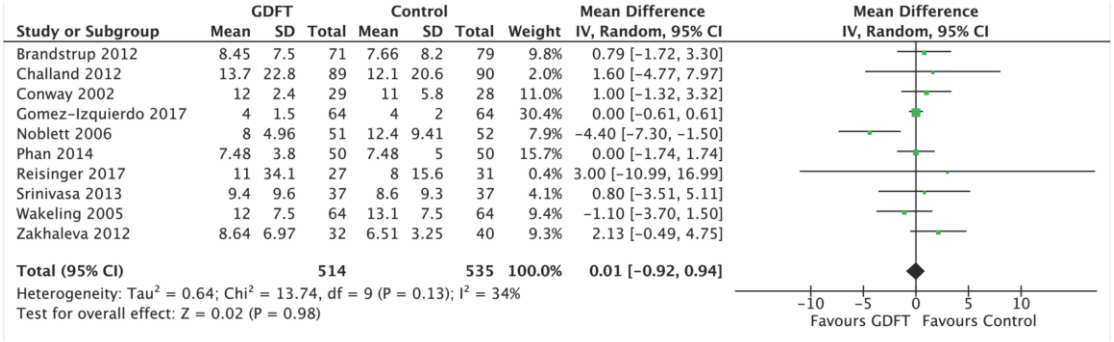
5.3.3 Hospital LOS

Overall hospital LOS was considered by ten studies included in the meta-analysis (Brandstrup et al., 2012, Challand et al., 2012, Conway et al., 2002, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Phan et al., 2014, Reisinger et al., 2017, Srinivasa et al., 2013b, Wakeling et al., 2005, Zakhaleva et al., 2013) (1049 patients; 514 GDFT and 535 traditional, **Figure 5.3.3.1**). However, two studies (Gomez-Izquierdo et al., 2017, Reisinger et al., 2017) only included median (IQR) data and did not provide the authors with mean (SD) data to include within the meta-analysis. These data were estimated using the technique described by Hozo *et al*. (Hozo et al., 2005) and all data were included in the primary analysis of hospital LOS. However, a separate meta-analysis was performed for this outcome excluding the estimated data (**Figure 5.3.3.2)**.

In the first analysis (**Figure 5.3.3.1**) which included estimated data for hospital LOS, there were 514 patients managed in an ERAS setting 535 in a traditional setting. GDFT was not

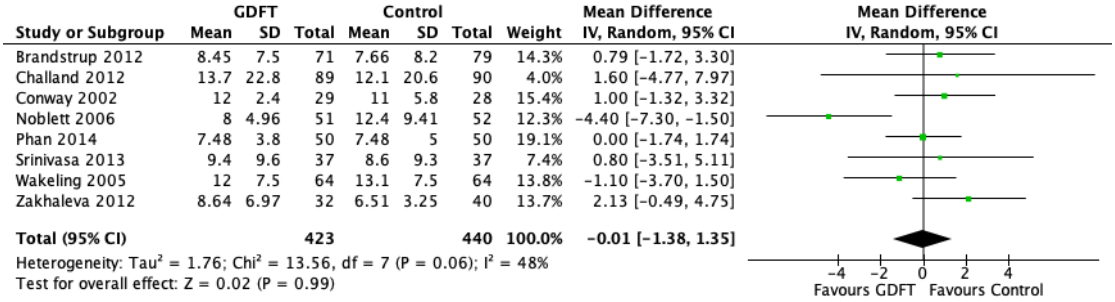
associated with a significant difference in the hospital LOS in the overall group (mean difference 0.01 days, 95% CI -0.59 to 0.61, p=0.98).

Figure 5.3.3.1 *- Forest plot comparing hospital LOS for patients receiving GDFT versus traditional fluid therapy including data calculated using the Hozo calculation*



In the second analysis which excluded the estimated data, GDFT resulted in no significant change in hospital LOS (mean difference -0.01 days, 95% CI -1.38 to 1.35, p=0.99; **Figure 5.3.3.2**).

Figure 5.3.3.2 *- Forest plot comparing hospital LOS for patients receiving GDFT versus traditional fluid therapy excluding data calculated using the Hozo calculation.*

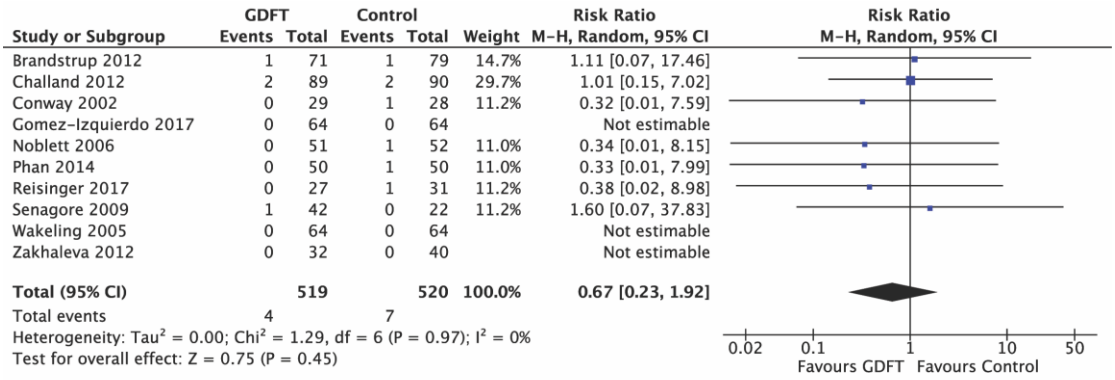


This analysis strongly suggests that intraoperative GDFT via transoesophageal Doppler is not associated with any benefit in terms of hospital LOS over traditional fluid management alone.

5.3.4 30-Day Mortality

Mortality rates were detailed in 10 studies (Brandstrup et al., 2012, Challand et al., 2012, Conway et al., 2002, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Phan et al., 2014, Reisinger et al., 2017, Senagore et al., 2009, Wakeling et al., 2005, Zakhaleva et al., 2013), including 519 patients in the GDFT group and 520 in the traditional group (**Figure 5.3.4.1**). Overall there was no significant difference in 30-day mortality between GDFT and control patients (RR 0.67, 95% CI 0.23 to 1.92, p=0.45).

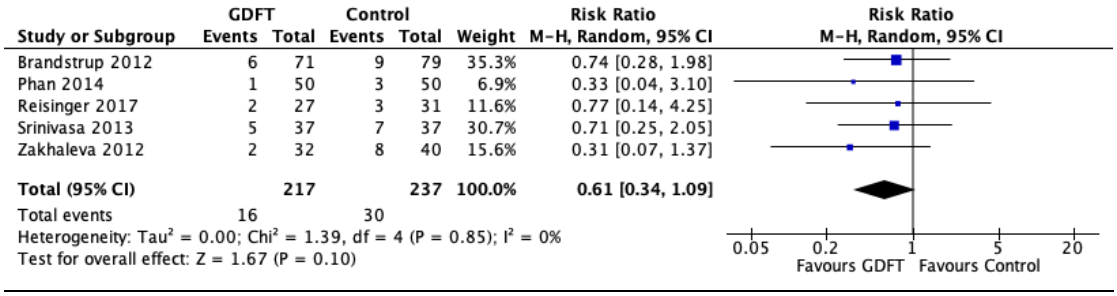
Figure 5.3.4.1 *- Forest plot comparing 30-day mortality rate for patients receiving GDFT versus traditional fluid therapy.*



5.3.5 Surgical Site Infection

Five studies (454 patients) (Brandstrup et al., 2012, Phan et al., 2014, Reisinger et al., 2017, Srinivasa et al., 2013b, Zakhaleva et al., 2013) examined the incidence of SSI in 217 patients managed with intraoperative GDFT versus 237 controls (**Figure 5.3.5.1**). The use of GDFT did not affect the incidence of SSI significantly in either the overall group (RR 0.66, 95% CI 0.35 to 1.23, p=0.19).

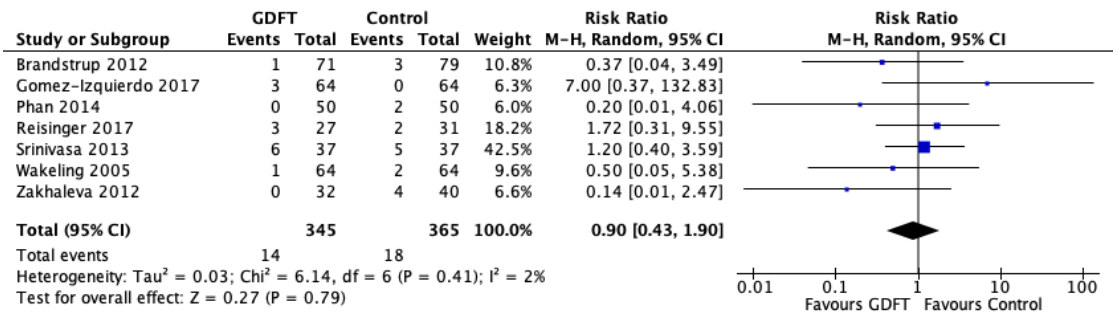
Figure 5.3.5.1 *- Forest plot comparing SSI rate for patients receiving GDFT versus traditional fluid therapy.*



5.3.6 Anastomotic Leak

Seven studies (710 patients) included data on the incidence of anastomotic leak in 345 patients managed with intraoperative GDFT versus 365 patients managed with control (Brandstrup et al., 2012, Gomez-Izquierdo et al., 2017, Phan et al., 2014, Reisinger et al., 2017, Srinivasa et al., 2013b, Wakeling et al., 2005, Zakhaleva et al., 2013) (**Figure 5.3.6.1**). Intraoperative administration of GDFT did not affect the incidence of anastomotic leakage (RR 0.90, 95% CI 0.43 to 1.90, p=0.79).

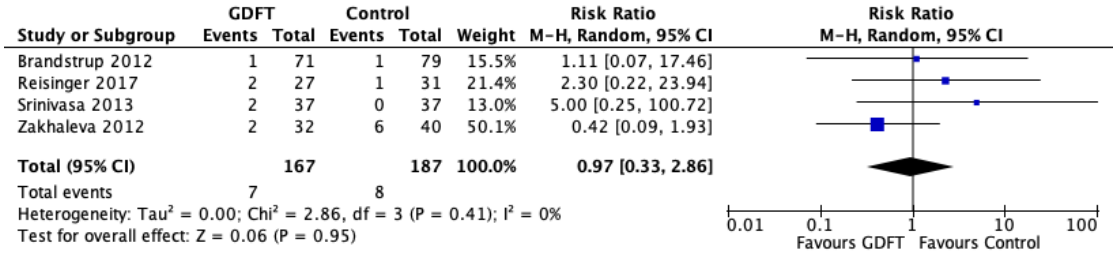
Figure 5.3.6.1 *- Forest plot comparing anastomotic leak rate for patients receiving GDFT versus traditional fluid therapy.*



5.3.7 Intra-abdominal Collection

A total of four studies (Brandstrup et al., 2012, Reisinger et al., 2017, Srinivasa et al., 2013b, Zakhaleva et al., 2013) examined the relationship between GDFT and conventional fluid therapy and the incidence of intra-abdominal collection (**Figure 5.3.7.1**). There was no significant difference in the rate of intra-abdominal collection between the two groups (RR 0.97, 95% CI 0.33 to 2.86, p=0.95).

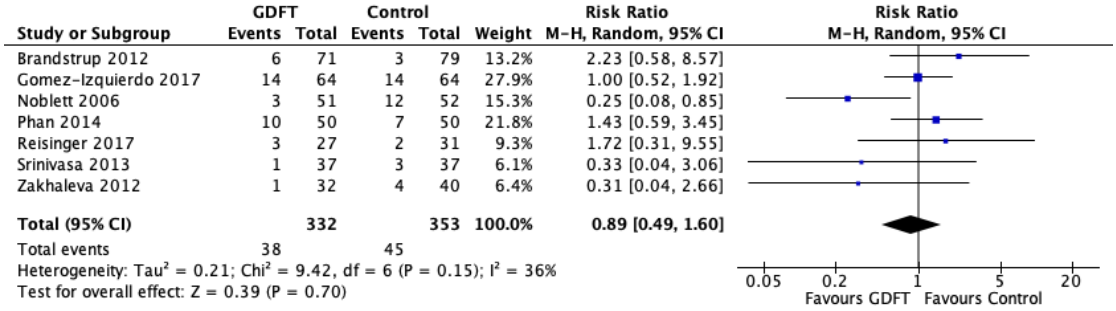
Figure 5.3.7.1 *- Forest plot comparing intra-abdominal collection rate for patients receiving GDFT versus traditional fluid therapy.*



5.3.8 Incidence of Postoperative Ileus

Seven studies (685 patients) (Brandstrup et al., 2012, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Phan et al., 2014, Reisinger et al., 2017, Srinivasa et al., 2013b, Zakhaleva et al., 2013) included data on the incidence of postoperative ileus in 332 patients managed with intraoperative GDFT versus 353 control patients (**Figure 5.3.8.1**). The use of GDFT did not significantly affect the incidence of postoperative paralytic ileus (RR 0.89, 95% CI 0.49 to 1.60, p=0.70).

Figure 5.3.8.1 *- Forest plot comparing incidence of postoperative ileus for patients receiving GDFT versus traditional fluid therapy.*

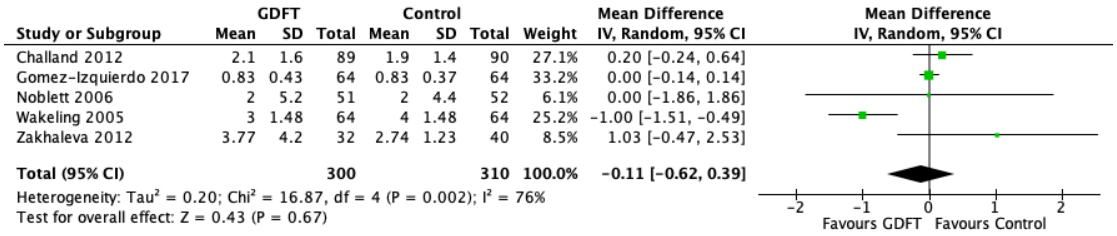


5.3.9 Return of Gastrointestinal Function

Five studies examined time to return of gastrointestinal function postoperatively, either in the form of flatus (Zakhaleva et al., 2013) or both flatus and stool (Challand et al., 2012, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Wakeling et al., 2005). Two separate analyses were performed for each outcome as in previous analyses.

Firstly considering time to flatus in all studies including those with calculated data (**Figure 5.3.9.1**), there were 300 patients who were managed with GDFT and 310 with control from 5 studies (Challand et al., 2012, Gomez-Izquierdo et al., 2017, Noblett et al., 2006, Wakeling et al., 2005, Zakhaleva et al., 2013). There was no significant difference in the time to return of flatus between the two fluid strategies (mean difference -0.11 days, 95% CI -0.62 to 0.39, p=0.67). When the planned analysis excluding data calculated using the Hozo technique (Hozo et al., 2005) was attempted, this left a total of just two studies, hence a further meta-analysis was not attempted.

Figure 5.3.9.1 *- Forest plot comparing time to passage of flatus for patients receiving GDFT versus traditional fluid therapy.*



When time to stool was considered, 268 patients were managed with GDFT and 270 with control intraoperative fluid (**Figure 5.3.9.2**). GDFT resulted in no significant difference in time to passage of stool in the overall group (mean difference -0.50 days, 95% CI -1.42 to 0.43 days, p=0.29). When the data for the single study with estimated data was excluded (Gomez-Izquierdo et al., 2017), no difference in the time to passage of stool was observed (mean difference -0.76 days, 95% CI -1.88 to 0.35 days, p=0.18; (**Figure 5.3.9.3**).

Figure 5.3.9.2 *- Forest plot comparing time to passage of faeces for patients receiving GDFT versus traditional fluid therapy including estimated study data.*

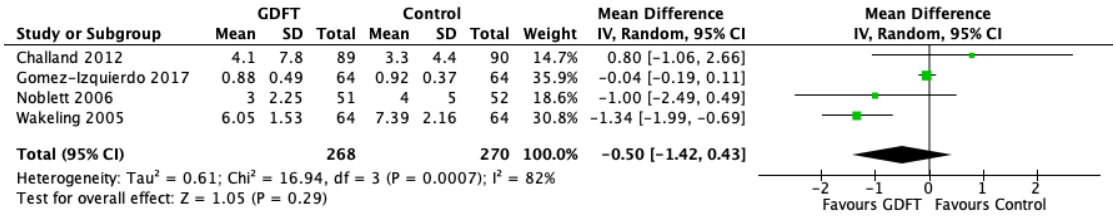
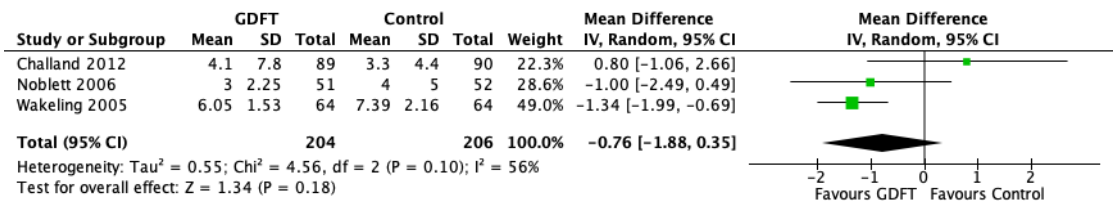


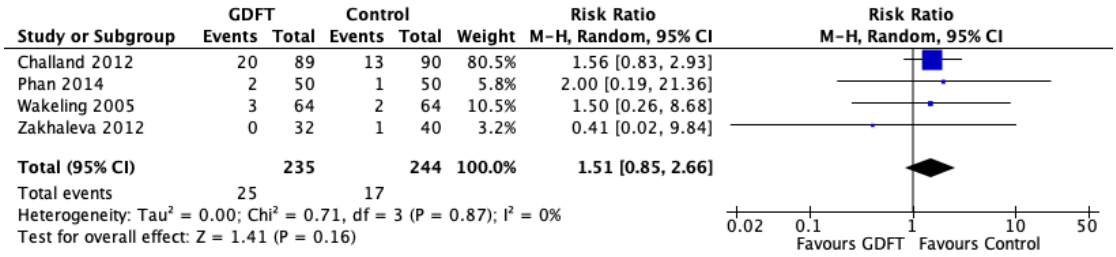
Figure 5.3.9.3 *- Forest plot comparing time to passage of faeces for patients receiving GDFT versus traditional fluid therapy excluding estimated study data.*



5.3.10 Acute Kidney Injury (AKI)

A total of four studies (Challand et al., 2012, Zakhaleva et al., 2013, Phan et al., 2014, Wakeling et al., 2005) examined the relationship between GDFT and conventional fluid therapy and the incidence of AKI. There was no significant difference in the rate of acute kidney injury between the two groups, however there was a trend towards a reduction in AKI in the control group (RR 1.51, 95% CI 0.85 to 2.66, p=0.16).

Figure 5.3.10.1 *- Forest plot comparing incidence of acute kidney injury for patients receiving GDFT versus traditional fluid therapy.*



5.4 Discussion

5.4.1 Principal Findings

This meta-analysis has demonstrated that in patients undergoing elective colorectal surgery, GDFT guided by transoesophageal Doppler monitoring was not associated with a significant difference in any of the reported postoperative clinical outcome measures when compared with conventional intraoperative fluid therapy. There was a signal in terms of a reduced incidence of SSI when patients received GDFT, and increased incidence of AKI. The demonstration of a tendency towards increased rates of AKI is interesting when considered with the recently published findings of the Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF) trial (Myles et al., 2018). This large-scale, international RCT of 3000 patients undergoing major abdominal surgery found that a restrictive intravenous fluid regimen was associated with a significantly greater incidence of AKI and renal replacement therapy over a liberal regimen. However, neither of these trends were statistically significant, although it should be considered that these analyses were based upon small patient numbers. Data on the role of GDFT in open versus laparoscopic approach for elective colorectal surgery were insufficient, hence the decision was made not to perform a meta-analysis on this variable. Further high-quality evidence is necessary to assess the potential role of GDFT between surgical approaches. In addition, just one study (Conway et al., 2002) was conducted in a traditional care setting rather than an ERAS pathway, hence it was not possible to conduct a subgroup analysis to assess the benefit of oesophageal Doppler monitored GDFT in ERAS versus traditional care settings as previous meta-analyses have (Rollins and Lobo, 2016).

These findings are more pronounced in the lack of benefit to GDFT when compared with a previous meta-analysis I conducted examining the role of GDFT in elective abdominal

surgery, although this study did not limit those papers included by the method of administration of GDFT (Rollins and Lobo, 2016). The previous meta-analysis found that overall GDFT was associated with a significant reduction in morbidity, hospital LOS, intensive care LOS and time to passage of stool, with no significant difference observed in the incidence of postoperative ileus, mortality or time to return of flatus. However, this meta-analysis separately analysed patients receiving GDFT by whether they were undergoing surgery within an ERAS or traditional care setting. In those in the ERAS setting, GDFT was not associated with a significant difference in the incidence of postoperative morbidity and mortality, hospital LOS, time to passage of flatus, or incidence of postoperative ileus. Bearing in mind that 10 of the 11 studies included in the meta-analysis conducted in this chapter were conducted within the setting of an ERAS pathway, it stands to reason that GDFT in elective colorectal surgery may not be hugely beneficial when administered as part of an ERAS pathway.

An issue raised by my previous work (Rollins and Lobo, 2016) regarding the comparison between GDFT and traditional fluid management strategies is differences in fluid management strategies over the past three decades. In the more historical studies large volumes tended to be infused in the traditionally managed group, whereas more contemporary fluid management strategies observed in the more recently published studies tend to aim for zero balance and for the patient to reach the anaesthetic room in a well hydrated state. The U-shaped relationship between fluid volume infused and perioperative morbidity which has been postulated previously (Bellamy, 2006) may suggest that in more modern fluid management strategies which advocate restrictive over liberal fluid management strategies (Doherty and Buggy, 2012, Lobo, 2009) the difference between GDFT and traditional fluid management the clinical benefit may be attenuated.

5.4.2 Strengths of Meta-Analysis

This meta-analysis is the largest to examine the impact of GDFT versus traditional fluid management strategies in elective colorectal surgery. The only other previous meta-analysis (Xu et al., 2018) published on the topic has several methodological issues, as it inadvertently included studies which were not RCTs (Jammer et al., 2010, Lin et al., 2015, McKenny et al., 2014) despite this being the stated aim, and missed several key studies on the topic (Reisinger et al., 2017, Phan et al., 2014, Srinivasa et al., 2013b), which is discussed in further detail later in this chapter. The present study included just one method for the conduct of GDFT, that of transoesophageal Doppler monitoring. This is the commonest device used for performing GDFT in the UK as well as in widespread use internationally (Srinivasa et al., 2013a) and is the methodology suggested by the National Institute for Health and Care Excellence (NICE, 2011). Evidence has suggested that transoesophageal Doppler and other methods for GDFT such as lithium dilution techniques (Feldheiser et al., 2015, Nordstrom et al., 2013), calibrated pulse contour analysis (Feldheiser et al., 2014) and pleth variability index (Bahlmann et al., 2016) are not interchangeable, hence the decision was taken to make the study population as homogeneous as possible.

Generally, the degree of heterogeneity within the analyses conducted was low, with five analyses having low levels of heterogeneity, three having moderate levels, and just two analyses having high levels of heterogeneity which were those conducted on the time to passage of flatus and stool. This large degree of concordance in study results, in addition to the relatively high study quality adds weight to the conclusions drawn.

5.4.3 Weaknesses of Meta-Analysis

This meta-analysis has a few weaknesses inherent in its design and conduct. The regimens for postoperative fluid management were poorly documented in the studies included. This may have impacted upon postoperative outcome but cannot be accounted for by the analysis undertaken and will need to be accounted for in future research by incorporation into the study design. This meta-analysis chose to focus upon just one technique for the conduct of GDFT, using transoesophageal Doppler monitoring, as this was felt to improve the homogeneity of the meta-analysis. However, this restricts the generalisability of the results to GDFT conducted using other techniques. In addition, efforts to obtain the raw data for the continuous variables were not successful. Therefore, the Hozo technique (Hozo et al., 2005) was used to estimate the mean and standard deviation data for two studies (Gomez-Izquierdo et al., 2017, Reisinger et al., 2017) in the hospital LOS analysis, three studies in the time to return of flatus (Noblett et al., 2006, Wakeling et al., 2005, Gomez-Izquierdo et al., 2017) and one study in the time to return of stool (Gomez-Izquierdo et al., 2017). To negate this potential weakness, an additional pre-planned analysis was conducted as stipulated in the methods section of this chapter. This meant a meta-analysis was conducted which included and then excluded the estimated data to ensure this did not exert any significant bias upon the results. For the hospital LOS analysis and time to return of stool excluding the estimated data, no difference was observed in the outcome. However due to the large number of studies requiring estimated data in the time to return of flatus analysis, no further analysis was conducted due to the poor strength of any conclusion drawn.

5.4.4 Comparison with Other Studies

A similar meta-analysis was published in July 2018 examining the role of GDFT in colorectal surgery (Xu et al., 2018) which included eleven RCTs. However, two of the studies included within this meta-analysis were not RCTs – the first was a comparison between a series of patients recruited to undergo GDFT and a historical series of patients managed with traditional fluid management (Lin et al., 2015), and the second was a matched cohort of patients who were not randomised (McKenny et al., 2014). In addition, several papers which should have been included as they met the inclusion criteria (Phan et al., 2014, Srinivasa et al., 2013b, Reisinger et al., 2017), were missed. These methodological flaws in this paper cast doubt over the strength of the study conclusions.

The nature of the fluid utilised for the bolus associated GDFT was variable, with hydroxyethyl starch being the documented fluid administered in 7 studies (Brandstrup et al., 2012, Challand et al., 2012, Conway et al., 2002, Gomez-Izquierdo et al., 2017, Phan et al., 2014, Reisinger et al., 2017, Senagore et al., 2009). However, there is a moratorium on the use of hydroxyethyl starch due to concerns regarding increased risk of acute kidney injury requiring renal replacement therapy (Perner et al., 2012, Brunkhorst et al., 2008) (Myburgh et al., 2012) as well as mortality (Perner et al., 2012, Brunkhorst et al., 2008) based on recent RCTs. The trend towards increasing rates of AKI in those patients receiving GDFT versus traditional fluid management strategies could potentially be related to the larger volume of HES infused in this group and the inherent increased risks. Just four studies included data on acute kidney injury rates (Challand et al., 2012, Phan et al., 2014, Wakeling et al., 2005, Zakhaleva et al., 2013), with the nature of the bolus fluid being variably reported in these. One study administered hydroxyethyl starch for boluses (Challand et al., 2012), one gave a colloid but the choice was ‘at the discretion of the anesthetist’ and included hydroxyethyl

starch, gelatin or human albumin solution (Phan et al., 2014), one gave non-HES colloid (Wakeling et al., 2005), and one did not specify which type of colloid was given (Zakhaleva et al., 2013). If just those two studies clearly receiving HES were analysed for acute kidney injury, the strength of the signal increased, however as this is based upon just two studies this is far from conclusive evidence. Future studies focusing on the role of GDFT will not include HES as the bolus agent (European Medicines Agency, 2018), and this may result in improved clinical outcomes.

5.4.5 Conclusion

This study has demonstrated no benefit for the routine use of transoesophageal Doppler guided GDFT in patients undergoing elective colorectal surgery, contrary to the National Institute for Health and Care Excellence guidance (NICE, 2011) which recommends that GDFT technology should be used 'in patients undergoing major or high-risk surgery'. However, as there were no studies on high-risk colorectal patients alone within this meta-analysis, it is still possible that GDFT may benefit high risk patients such as those with ischaemic heart disease, or those with difficult fluid balance requirements such as those with chronic kidney disease or congestive cardiac disease and those undergoing high risk surgery which is often defined as procedures carrying a mortality risk of 5% or more.

Chapter 6 - The Impact of Perioperative Intravenous Lidocaine on Postoperative Gastrointestinal Function in Elective Colorectal Surgery

6.1 Introduction

There has recently been significant interest in the potential for perioperative IVL infusion in patients undergoing abdominal surgery (Weibel et al., 2018), with increasing evidence in a range of surgical specialities including colorectal surgery (Dewinter et al., 2018), hepatobiliary surgery (Zhao et al., 2018), obstetrics (Gholipour Baradari et al., 2017) and gynaecology (Samimi et al., 2015). Studies have suggested that IVL conveys a benefit in the postoperative setting in terms of its analgesic, anti-inflammatory and opiate-sparing effects resulting in reduced postoperative pain, reduced paralytic ileus, time to first flatus and defecation and postoperative nausea and vomiting (Dunn and Durieux, 2017). In addition, there is some evidence for a beneficial effect in intraoperative parameters including blunting of the responses to airway manipulation, a reduction in anaesthetic requirement (Weinberg et al., 2017, Sloan et al., 2014) and improved recovery from general anaesthesia (Nakhli et al., 2018). There is also some evidence of an oncological benefit associated with the use of perioperative intravenous lidocaine infusion. There is evidence that IVL reduces the viability and propagation of cancer cells in vitro, and also that it enhances the activity of natural killer (NK) cells which recognise and kill tumour cells, the activity of which would otherwise be significantly impaired in the perioperative phase as a consequence of surgical stress and inflammation (Chamaraux-Tran and Piegeler, 2017).

A Cochrane Review has been recently published (Weibel et al., 2018) concerning IVL infusion versus placebo/no treatment or thoracic epidural (TEA) for postoperative pain and recovery in a total of 68 RCTs across a range of surgical specialities, including general

(oesophagogastric, hepatopancreaticobiliary, colorectal and breast), gynaecology, spinal, endocrine, and cardiothoracic surgery. This demonstrated an unclear effect of IVL versus placebo on pain scores in the early postoperative phase, on gastrointestinal recovery, postoperative nausea and overall opioid requirement, and highlighted poor quality evidence with high rates of inconsistency and imprecision.

Specific to the field of colorectal surgery, a recently published systematic review of RCTs (MacFater et al., 2017) examined the role of IVL in the setting of elective colorectal surgery concluded that this provided limited benefit in the reduction of early postoperative pain and morphine when compared with placebo, and a variable degree of improvement in pain scores when compared with epidural.

The recently published 'Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: 2018' (Gustafsson et al., 2018) have concluded that 'the use of lidocaine infusions to reduce opioid use and nausea in colorectal surgery is now well established' however the benefit in terms of reduction of postoperative ileus are unclear. Despite this, no meta-analysis has been conducted to date to assess the role of IVL in colorectal surgery specifically, and there has been substantial additional evidence (Dewinter et al., 2018, Ho et al., 2018, Beaussier et al., 2018) published since the previous systematic review (MacFater et al., 2017), hence evidence of an evidence gap which the current meta-analysis sought to fill.

The aims of this meta-analysis were:

- to examine the effect of perioperative IVL infusion upon postoperative outcome in patients undergoing elective colorectal surgery, including time to return of gastrointestinal function, postoperative pain scores, morphine consumption, hospital LOS and complications
- to examine the role of perioperative IVL infusion in laparoscopic versus open elective colorectal surgical procedures

6.2 Materials and Methods

6.2.1 Search Strategy

A search of PubMed, MEDLINE and the Cochrane Library databases was conducted in order to identify full-text studies examining the impact of perioperative intravenous lidocaine infusion in elective colorectal surgery published up to and including 5th November 2018. The electronic search terms adopted were (intravenous OR infusion) AND (lidocaine OR lignocaine) AND (colon OR rectal OR colorectal OR proctectomy OR colonic), with no limitation placed upon data or language for inclusion.

6.2.2 Selection of Articles

Studies were included if they were RCTs which evaluated the role of perioperative IVL infusion versus placebo in adult patients undergoing elective colorectal surgery within a RCT setting. Exclusion criteria included paediatric patients, non-colorectal or emergent procedures, non-RCT methodology, or lack of any relevant clinical outcome measures. The decision to only include RCTs was based upon an initial scoping literature review which revealed multiple recent RCTs published on this topic with no significant benefit to be gleaned from the inclusion of cohort studies. Studies which included more than two study arms, but had an IVL and placebo group, were included and just those groups which were pertinent to this meta-analysis were considered. The assessment of eligibility for inclusion was conducted by two independent researchers as described in chapter two. No consideration was given to how long the lidocaine infusion was continued for after surgery. However, to be eligible for inclusion the infusion had to commence prior to the surgical incision. Two studies initially identified as potentially eligible in the initial search were subsequently

excluded as the lidocaine infusion was not commenced until after the completion of surgery (Harvey et al., 2009, Beaussier et al., 2018).

6.2.3 Data Extraction

The primary outcome measure considered by this meta-analysis was time to return of gastrointestinal function, both in terms of flatus and defecation. Secondary outcome measures considered were post-operative pain scores up to 48 hours (at rest and movement scored on the visual analogue scale (VAS)), post-operative morphine requirement, incidence of prolonged ileus, SSI, anastomotic leak, signs of local anaesthetic toxicity and finally overall hospital LOS. In addition, data were also collated on patient baseline demographics (age, gender, ASA), operative variables (operating time, estimated blood loss, nature of colorectal resection and indication for surgery) and details of the lidocaine infusion (dose, starting point, duration post-operatively, and any bolus dose administered) as well as the details of the placebo administered. The studies included were divided by whether the patients underwent open or laparoscopic resection, as well as conversion rates. If the data necessary for meta-analysis of continuous variables was not available the corresponding author was approached to provide the raw data, and if the data was not available the technique described by Hozo *et al.* (Hozo et al., 2005) was employed.

Where data were only available in graphical format and the authors did not respond to the request for raw data, this was extracted in either direct or indirect form using plotdigitizer (www.plotdigitizer.sourceforge.net). Where opiate doses other than morphine were provided by the study, previously described conversion methods were used to standardise all opiates to an equivalent morphine dose (Pereira et al., 2001). The Cochrane Collaboration tool from

RevMan 5.3 (Cochrane Collaboration, 2014) was used to evaluate the risk of bias as described previously.

6.2.4 Statistical Analysis

Statistical analysis was conducted using RevMan 5.3 (Cochrane Collaboration, 2014) as described previously, with the I^2 statistic used to quantify heterogeneity within the analysis (Higgins and Thompson, 2002).

6.3 Results

The initial literature search identified a total of 107 full-text articles which were potentially eligible, which resulted in a total of 10 studies which were included within the meta-analysis (Dewinter et al., 2018, Ho et al., 2018, Ahn et al., 2015, Kim et al., 2014b, Tikuisis et al., 2014, Staikou et al., 2014, Elhafz et al., 2012, Herroeder et al., 2007, Kaba et al., 2007, Kuo et al., 2006) (**Figure 6.3.1**). Overall, the risk of bias within the included studies was moderate and the quality of the studies was similarly moderate (**Table 6.3.1**).

Figure 6.3.1 – PRISMA diagram showing identification of relevant studies from initial search

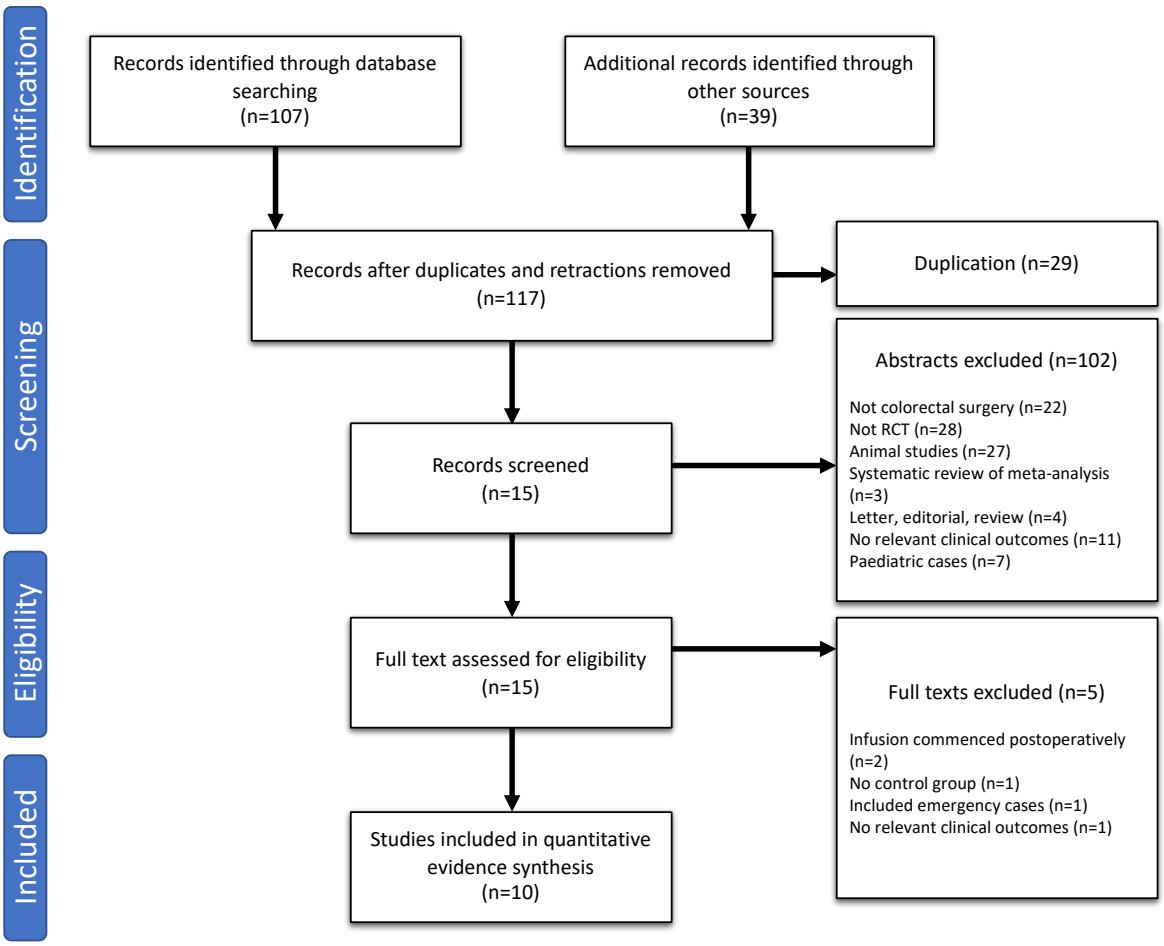


Table 6.3.1 *- Risk of bias assessment of included studies*

Reference	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other Bias
Dewinter *et al.* 2018	+	?	+	+	+	+	+
Ho *et al.* 2018	+	+	+	+	+	+	+
Ahn *et al.* 2015	+	?	+	+	-	?	+
Kim *et al.* 2014	+	?	?	+	+	+	+
Tikuisis *et al.* 2014	+	?	+	+	+	?	+
Staikou *et al.* 2014	?	?	+	+	+	?	?
Elhafz *et al.* 2012	?	?	?	?	-	?	+
Herroeder *et al.* 2007	+	?	+	?	+	?	+
Kaba *et al.* 2007	+	?	+	+	+	?	+
Kuo *et al.* 2006	+	+	+	+	+	?	+

+ Low risk of bias; - High risk of bias; ? Unclear risk of bias

6.3.1 Demographics

The 10 RCTs included in this meta-analysis included a total of 610 patients. However, several studies (Dewinter et al., 2018, Elhafz et al., 2012, Kuo et al., 2006, Staikou et al., 2014) included study groups which did not fall within the remit of the meta-analysis such as neuraxial techniques and continuous wound infusions, and as such these groups were not included. Therefore, a total of 265 patients received a perioperative IVL infusion and 243 patients received a placebo infusion. In six studies the surgery was performed laparoscopically (Dewinter et al., 2018, Kim et al., 2014b, Tikuisis et al., 2014, Elhafz et al., 2012, Ahn et al., 2015, Kaba et al., 2007), and in four via open technique (Ho et al., 2018, Staikou et al., 2014, Herroeder et al., 2007, Kuo et al., 2006). Baseline patient demographics are provided in **Table 6.3.1.1** and details of the interventions are given in **Table 6.3.1.2.**

6.3.2 Return of Gastrointestinal Function

The time to passage of flatus was considered by eight studies (Dewinter et al., 2018, Kim et al., 2014b, Herroeder et al., 2007, Kuo et al., 2006, Elhafz et al., 2012, Kaba et al., 2007, Ho et al., 2018, Staikou et al., 2014) including a total of 398 patients. Overall, IVL infusion was not associated with a significant difference in the time to return of flatus (mean difference -5.33 hours, 95% CI -11.53 to 0.88 hours, p=0.09, I^2=90%; **Figure 6.3.2.1**). When the four studies in patients undergoing laparoscopic surgery were considered, an IVL infusion (n=201) was not associated with any difference in the time to return of flatus (mean difference -3.78 hours, 95% CI -12.88 to 5.32, p=0.42, I^2= 87%), however in those patients undergoing open surgery (four studies; n=197), IVL was associated with a significant reduction to the time of passage of flatus of 8.4 hours (95% CI -13.7 to -3.1 hours, p=0.002, I^2= 31%).

Table 6.3.1.1 *– Baseline patient demographics for all included studies*

		Number of Patients		Age		Type of Surgery		Laparoscopic Approach		ASA 1:2:3:4	
Reference	ERAS or Traditional	Lidocaine	Placebo	Lidocaine	Placebo	Lidocaine	Placebo	Lidocaine	Placebo	Lidocaine	Placebo
Dewinter *et al.* 2018	ERAS	50	25	60 (49-68)	62 (59-68)	Left-sided colectomy 32, right-sided colectomy 18	Left-sided colectomy 16, right-sided colectomy 9	50	25	9:30:11:0	7:14:4:0
Ho *et al.* 2018	Not stated	28	29	57 (47-70)	66 (62-70)	Stoma formation 16 Anterior resection 14 Right hemicolectomy 4 Left hemicolectomy 1 Total colectomy 2 APR 2 Proctocolectomy 3 Other 2	Stoma formation 12 Anterior resection 10 Right hemicolectomy 10 Left hemicolectomy 1 Total colectomy 3 APR 2 Proctocolectomy 1 Other 2	0	0	1:22:5	0:19:10
Ahn *et al.* 2015	Traditional	25	25	64.48±11.68	66.2±8.88	All colectomy	All colectomy	25	25	9:13:3	8:12:5

Kim *et al.* 2014	Traditional	32	36	60.9±10.6	60.1±11.1	Right hemicolectomy 6 Left hemicolectomy 1 Anterior resection 14 Low anterior resection 10 Subtotal colectomy 1	Right hemicolectomy 8 Left hemicolectomy 3 Anterior resection 12 Low anterior resection 13 Subtotal colectomy 0	32	36	11:20:1	19:15:2
Tikuisis *et al.* 2014	Not stated	30	30	57.2±13.28	56±12.22	All left-sided colectomy	All left-sided colectomy	30 (all hand assisted)	30 (all hand assisted)	19:7:4	21:5:4
Staikou *et al.* 2014	Traditional	20	20	73.6±7.5	68.6±10.8	Right hemicolectomy 4 Left hemicolectomy 4 Sigmoidectomy 11 Low anterior resection 0 APR 1	Right hemicolectomy 4 Left hemicolectomy 0 Sigmoidectomy 10 Low anterior resection 4 APR 2	0	0	All ASA I-II	All ASA I-II

Elhafz *et al.* 2012	Traditional	9	9	61.2±11.4	59.3±12.6	Hemicolectomy 5 Total colectomy 1 Proctocolectomy 2 Sigmoid resection 1	Hemicolectomy 4 Total colectomy 3 Proctocolectomy 1 Sigmoid resection 1	9	9	2:5:2	3:5:1
Herroeder *et al.* 2007	Traditional	31	29	56.13±11.84	56.93±12.04	Ileocaecal resection 2 Right hemicolectomy 5 Left hemicolectomy 1 Subtotal colectomy 0 Proctocolectomy 1 Sigmoid resection 12 High anterior resection 2 Low anterior resection 3 Rectum exstirpation 3 Others 2	Ileocaecal resection 0 Right hemicolectomy 5 Left hemicolectomy 4 Subtotal colectomy 1 Proctocolectomy 3 Sigmoid resection 8 High anterior resection 3 Low anterior resection 1 Rectum exstirpation 2 Others 2	0	0	2:21:8	3:23:3

Kaba *et al.* 2007	ERAS	20	20	57±17	52±13	Right colectomy 3 Left colectomy 17	Right colectomy 6 Left colectomy 14	20	20	7:10:3	7:12:1
Kuo *et al.* 2006	Not stated	20	20	63 (50-75)	62 (46-85)	All colectomy for colon cancer	All colectomy for colon cancer	0	0	All ASA I-II	All ASA I-II

APR – abdominoperineal resection; ASA – American Society of Anesthesiology

Table 6.3.1.2 *– Details of IVL and placebo interventions delivered*

Reference	Point of Commencement of Intervention	Details of Lidocaine Intervention	Details of Placebo Intervention	Duration of Intervention	Any additional Intervention	Standard Postoperative Analgesia Provided
Dewinter *et al.* 2018	At induction of anaesthesia	Lidocaine bolus (1.5mg/kg) followed by a continuous infusion of 1.5mg/kg/hr	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	Until four hours after arrival in postoperative anaesthesia care unit	Both groups received a quadratus lumborum (QL) block with normal saline	Acetaminophen 15mg/kg 4/day Ketorolac 0.5mg/kg 3/day Morphine PCA IV
Ho *et al.* 2018	Immediately following induction	Lidocaine bolus over 5 minutes (1.5mg/kg; 2.5%, 0.06ml/kg) followed by continuous infusion of 1mg/kg/hr (2.5%, 0.04ml/kg/hr)	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	For 48 hours following bolus dose	Nil	Fentanyl PCA IV (20µg bolus, 5 minute lockout) for 72 hours
Ahn *et al.* 2015	Two minutes prior to orotracheal intubation	Lidocaine bolus (1.5mg/kg) followed by continuous infusion of 2mg/kg/hr	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	Infusion administered during the operation only	Nil	Fentanyl PCA IV (0.3 µg/kg bolus, 15 minute lockout)
Kim *et al.* 2014	Prior to skin incision	Lidocaine bolus (1mg/kg) followed by continuous infusion of	Normal saline bolus and infusion in equal quantities to the	For 24 hours	Nil	Relaxation therapy initially for pain management followed by meperidine 25-

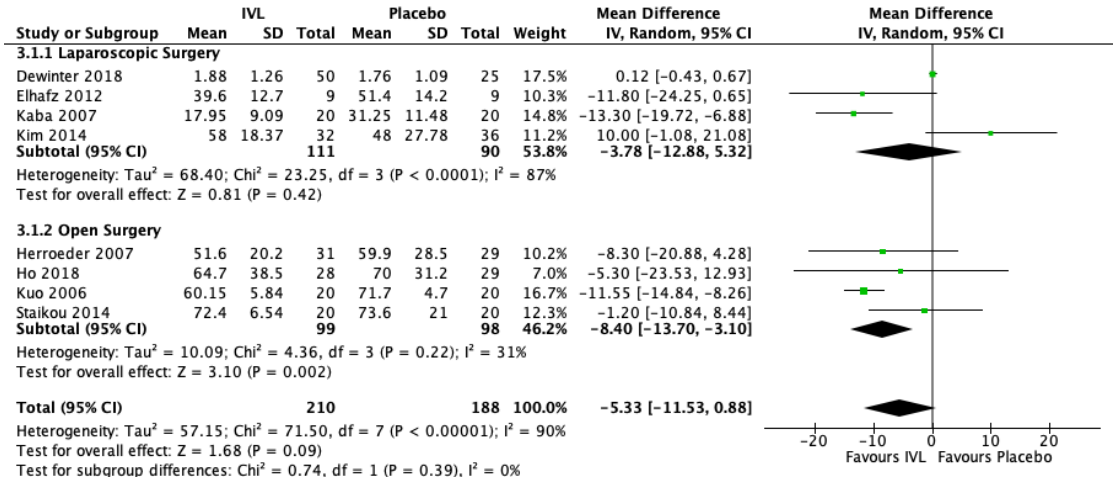
		1mg/kg/hr with 90mg ketorolac	lidocaine infusion as well as ketorolac 90mg			50mg injection as required
Tikuisis *et al.* 2014	Just before induction of anaesthesia	Lidocaine bolus (1.5mg/kg, max 100mg) followed by continuous infusion of 2mg/kg/hr	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	For 24 hours	Nil	Continuous infusion of fentanyl 0.1 µg/kg/hr for 24 hours postop If VAS >3 IV ketorolac 30mg as required
Staikou *et al.* 2014	Before induction of anaesthesia	Lidocaine bolus (1.5mg/kg) followed by continuous infusion of 2mg/kg/hr.	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	At the completion of abdominal wall closure, prior to skin closure.	Thoracic epidural inserted to all – normal saline infusion to the lidocaine infusion and placebo groups (one additional group received lumbar epidural lidocaine)	Epidural ropivacaine 10ml of 0.2% and morphine 1mg given to all patients during skin closure. Morphine PCEA with ropivacaine 2mg/min (4ml bolus, lockout 20 mins)
Elhafz *et al.* 2012	After induction of anaesthesia	Lidocaine infusion 2mg/min if body weight >70kg or 1mg/min if body weight <70kg.	Normal saline infusion in equal quantities to the lidocaine infusion	Stopped on the return of bowel function or fifth postoperative day, whichever were sooner.	Three lidocaine patches applied to the laparoscopic port sites in a separate group (not to the lidocaine or placebo groups)	Morphine PCA (2mg demand, 10min lockout)

Herroeder *et al.* 2007	Before induction of anaesthetic	Lidocaine bolus (1.5mg/kg) followed by a continuous infusion of 2mg/min commenced after tracheal intubation	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	Until four hours following skin closure	Nil	Piritamide PCA (2mg demand and 10 minute lockout) Metamizol 1g every 6 hours (or paracetamol 1g if this were contraindicated)
Kaba *et al.* 2007	Just before induction of anaesthesia	Lidocaine bolus (1.5mg/kg) followed by a continuous intraoperative infusion of 2mg/kg/hr which was reduced to a continuous postoperative infusion of 1.33mg/kg/hr	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	For 24 hours postoperatively	Nil	Propacetamol 2g IV every 6 hours for 24 hours then converted to oral paracetamol 1g every 6 hours Ketorolac 30mg IV every 8 hours for 24 hours Diclofenac 75mg twice daily Tramadol 100mg as required
Kuo *et al.* 2006	Started 30 minutes prior to surgery	Lidocaine bolus (2mg/kg) over 10 mins followed by a	Normal saline bolus and infusion in equal quantities to the lidocaine infusion	At the end of surgery	Thoracic epidural inserted to all – normal saline infusion to the lidocaine infusion and	Morphine PCEA with ropivacaine 2mg/min (4ml bolus, lockout 15 mins)

		continuous infusion of 3mg/kg/hr			placebo groups (one additional group received lumbar epidural lidocaine)	

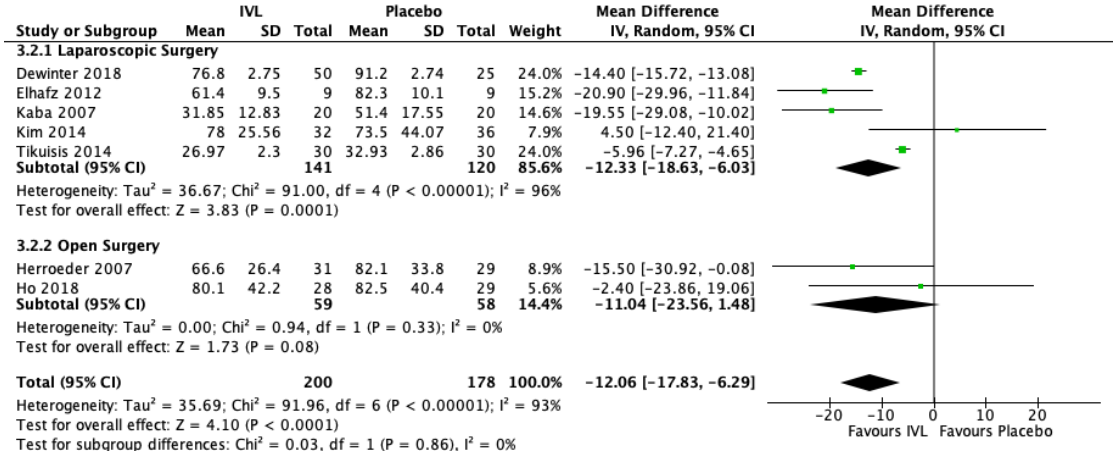
IV – intravenous; PCA – patient controlled analgesia; PCEA – patient controlled epidural analgesia QL – quadratus lumborum

Figure 6.3.2.1: *Forest plot comparing time to return of flatus for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



When time to defecation was examined, this was included by seven studies (Dewinter et al., 2018, Kim et al., 2014b, Herroeder et al., 2007, Elhafz et al., 2012, Kaba et al., 2007, Ho et al., 2018, Tikuisis et al., 2014) including a total of 378 patients. Overall, the use of IVL was associated with a significant reduction in time to defecation (mean difference -12.06 hours, 95% CI -17.83 to -6.29, p<0.0001, I^2= 93%; **Figure 6.3.2.2**). When those five studies considering laparoscopic surgery were considered (n=261), IVL was associated with a significant reduction in the time to defecation (mean difference -12.33 hours, 95% CI -18.63 to -6.03, p=0.0001, I^2=96%), however no difference was seen in those undergoing open surgery (mean difference -11.04 hours, 95% CI -23.56 to 1.48, p=0.08, I^2=0%), although this was based upon data from two studies alone including a total of 107 patients.

Figure 6.3.2.1: *Forest plot comparing time to defecation for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



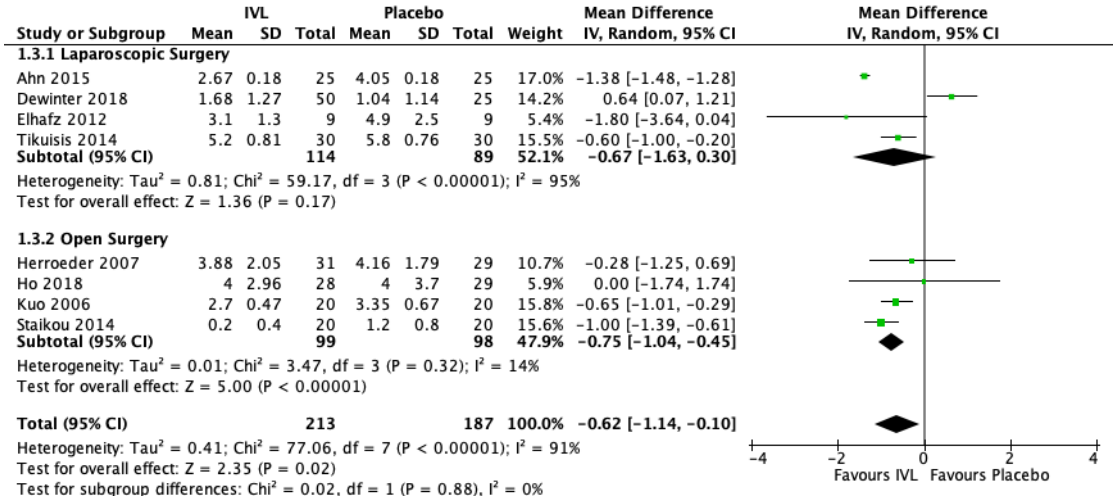
6.3.3 Postoperative Pain Scores

Postoperative pain scores were separated by whether they were measured at rest or on coughing due to significant differences in scores dependent upon this detail.

6.3.3.1 Pain Scores at Rest

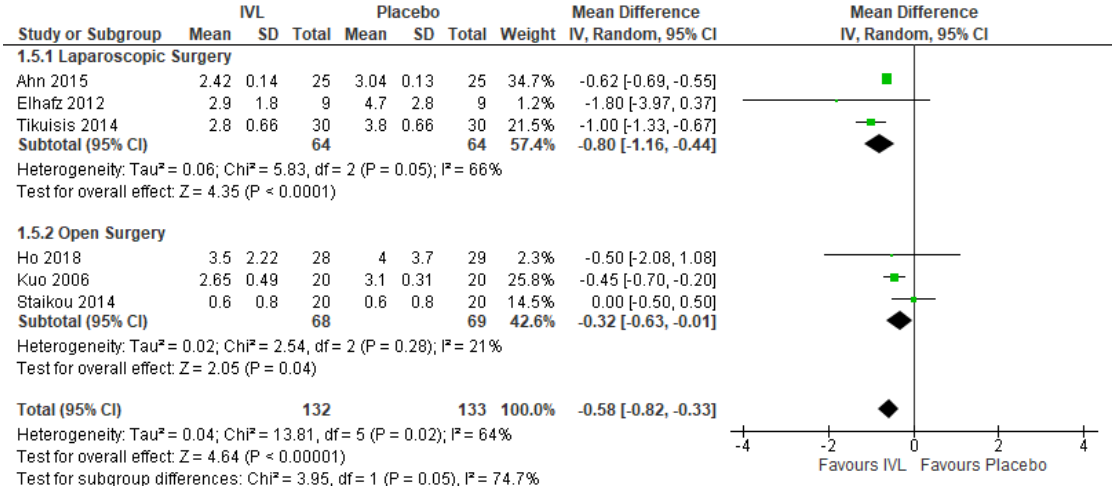
Pain scores at rest were analysed at 4, 12, 24 and 48 hours post-operatively. A total of eight studies (Dewinter et al., 2018, Ho et al., 2018, Ahn et al., 2015, Tikuisis et al., 2014, Staikou et al., 2014, Elhafz et al., 2012, Herroeder et al., 2007, Kuo et al., 2006) considered VAS pain scores at 4 hours post-operatively, four in the laparoscopic group (Dewinter et al., 2018, Ahn et al., 2015, Tikuisis et al., 2014, Elhafz et al., 2012) and four in the open group (Ho et al., 2018, Staikou et al., 2014, Herroeder et al., 2007, Kuo et al., 2006). Overall, IVL was associated with a significantly lower VAS pain score at rest (-0.62, 95% CI -1.14 to -0.10, p=0.02, I^2=91%; **Figure 6.3.3.1.1**), and in those undergoing open surgery (-0.75, 95% CI -1.04 to -0.45, p<0.00001, I^2=14%), however no significant difference was seen in those patients undergoing laparoscopic surgery (-0.67, 95% CI -1.63 to 0.30, p=0.17, I^2=95%).

Figure 6.3.3.1.1 - *Forest plot comparing VAS pain scores at rest at 4 hours post-operatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



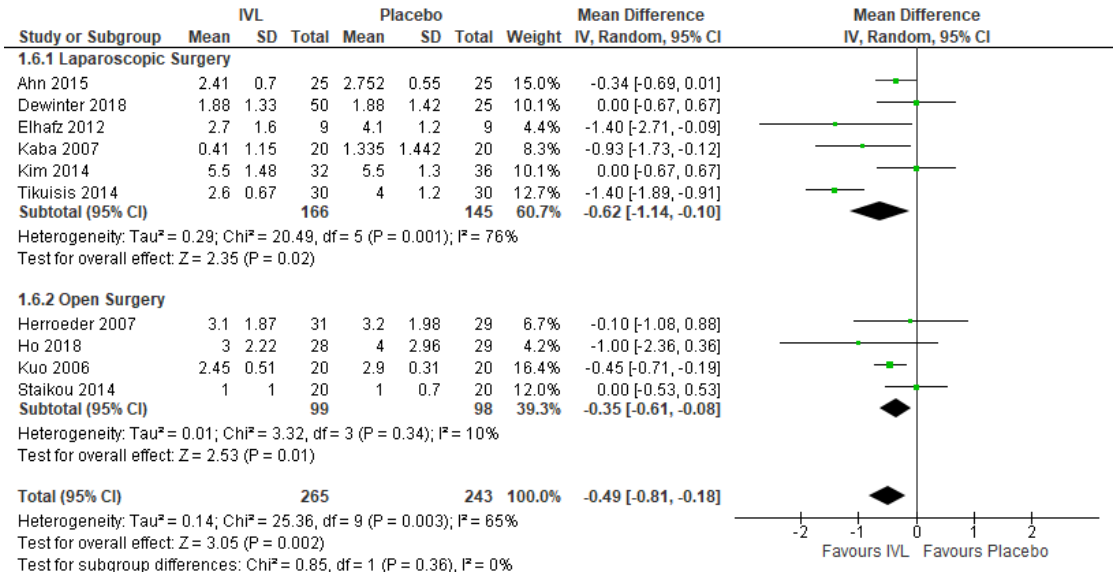
Pain at 12 hours postoperatively was considered by six studies (Ahn et al., 2015, Elhafz et al., 2012, Tikuisis et al., 2014, Ho et al., 2018, Kuo et al., 2006, Staikou et al., 2014) including 265 patients, with three studies in patients undergoing laparoscopic surgery (Ahn et al., 2015, Elhafz et al., 2012, Tikuisis et al., 2014) and three studies in those undergoing open surgery (Ho et al., 2018, Kuo et al., 2006, Staikou et al., 2014). IVL was associated with a significant reduction in pain scores at rest in the overall group (mean difference -0.58, 95% CI -0.82 to -0.33, p<0.00001, I^2=64%; **Figure 6.3.3.1.2**), as well as the laparoscopic (mean difference -0.80, 95% CI -1.16 to -0.44, p<0.0001, I^2=66%) and open (mean difference -0.32, 95% CI -0.63 to -0.01, p=0.04, I^2=21%) groups.

Figure 6.3.3.1.2 *- Forest plot comparing VAS pain scores at rest at 12 hours post-operatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



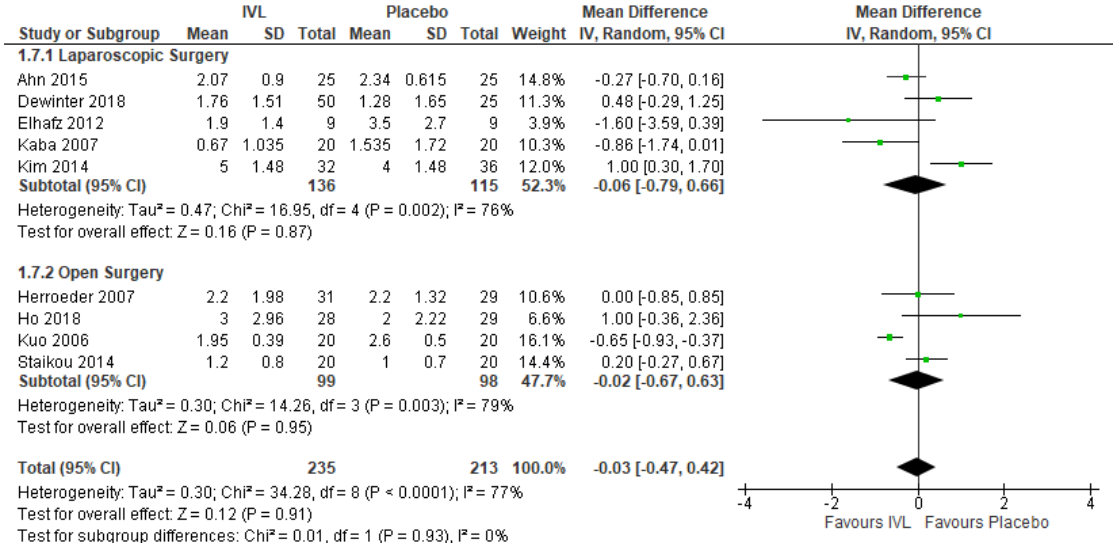
Pain scores at rest at 24 hours post-operatively were considered by all studies included within the meta-analysis (Dewinter et al., 2018, Ho et al., 2018, Ahn et al., 2015, Kim et al., 2014b, Tikuisis et al., 2014, Staikou et al., 2014, Elhafz et al., 2012, Herroeder et al., 2007, Kaba et al., 2007, Kuo et al., 2006). IVL was again associated with a significant reduction in pain scores in the overall (mean difference -0.49, 95% CI -0.81 to -0.18, p=0.002, I^2=65%; **Figure 6.3.3.1.3**), laparoscopic (mean difference -0.62, 95% CI -1.14 to -0.10, p=0.02, I^2=76%) and open surgical groups (mean difference -0.35, 95% CI -0.61 to -0.08, p=0.01, I^2=10%).

Figure 6.3.3.1.3 *- Forest plot comparing VAS pain scores at rest at 24 hours post-operatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



A total of 9 studies (Dewinter et al., 2018, Ho et al., 2018, Ahn et al., 2015, Tikuisis et al., 2014, Staikou et al., 2014, Elhafz et al., 2012, Herroeder et al., 2007, Kaba et al., 2007, Kuo et al., 2006) considered the impact of IVL on pain scores at rest at 48 hours post-operatively including 448 patients. There were no significant differences in pain scores between the IVL and placebo groups in any analysis (**Figure 6.3.3.1.4**).

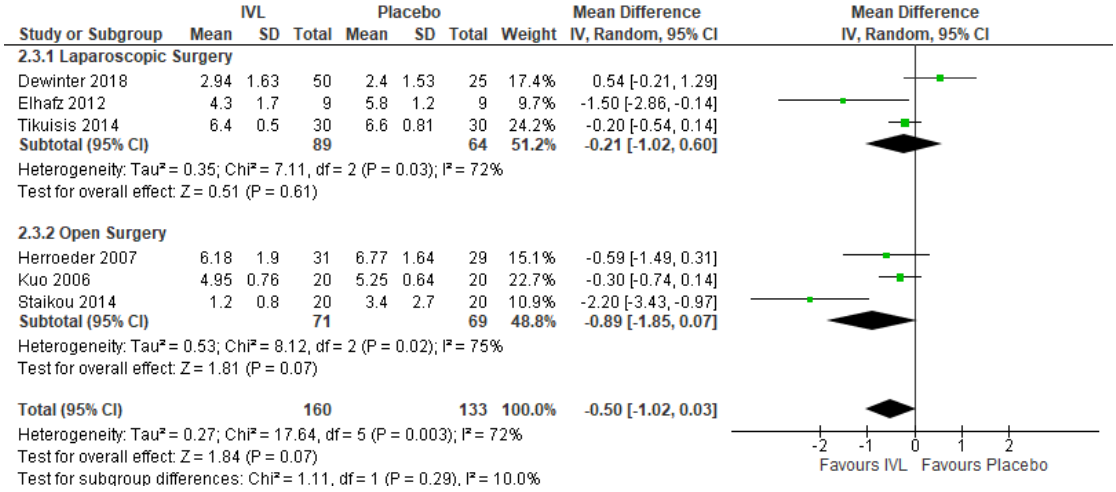
Figure 6.3.3.1.4 *- Forest plot comparing VAS pain scores at rest at 48 hours post-operatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



6.3.3.2 Pain Scores on Coughing

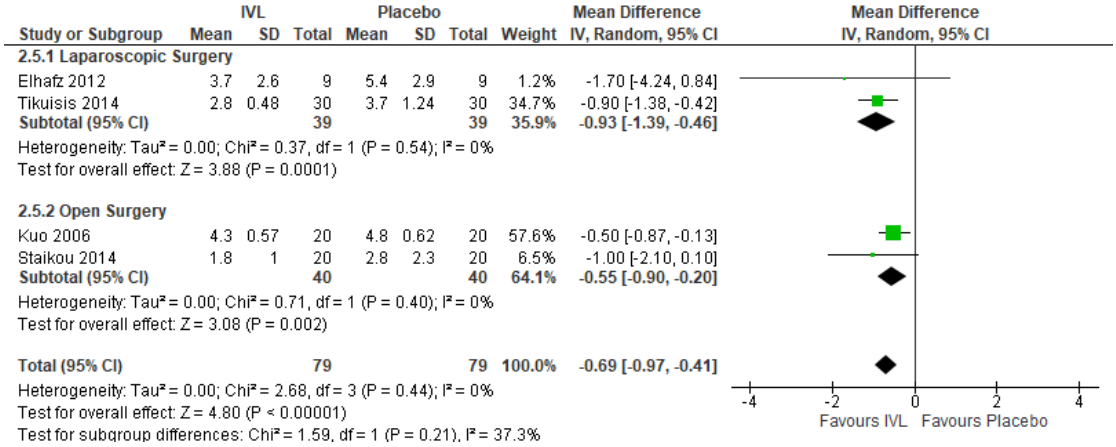
A total of six studies considered VAS pain score at four hours postoperatively (Dewinter et al., 2018, Elhafz et al., 2012, Tikuisis et al., 2014, Herroeder et al., 2007, Kuo et al., 2006, Staikou et al., 2014), three including patients undergoing laparoscopic surgery (Dewinter et al., 2018, Elhafz et al., 2012, Tikuisis et al., 2014) and three with patients undergoing open surgery (Kuo et al., 2006, Staikou et al., 2014, Herroeder et al., 2007). There was no significant difference in the VAS pain score between those receiving IVL and placebo, either overall (mean difference -0.50, 95% CI -1.02 to 0.03, p=0.07, I^2=72%) nor in those undergoing open (mean difference -0.89, 95% CI -1.85 to 0.07, p=0.07, I^2=75%) or laparoscopic procedures (mean difference -0.21, 95% CI -1.02 to 0.60, p=0.61, I^2=72%; **Figure 6.3.3.2.1**).

Figure 6.3.3.2.1 *- Forest plot comparing VAS pain scores on coughing at 4 hours postoperatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



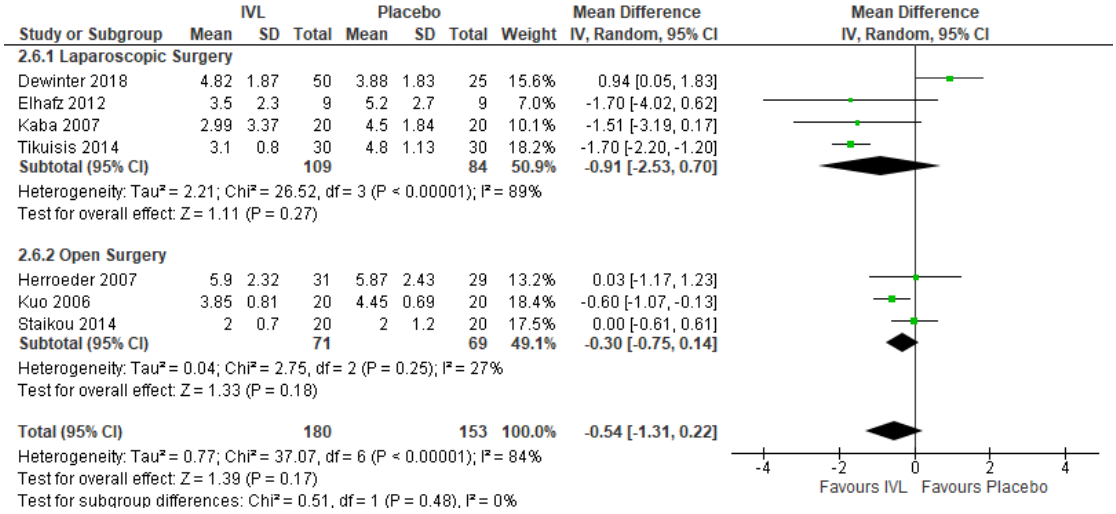
In terms of VAS on coughing at 12 hours postoperatively, four studies included data on this variable including 158 patients (Elhafz et al., 2012, Tikuisis et al., 2014, Kuo et al., 2006, Staikou et al., 2014), of which two were in open (Kuo et al., 2006, Staikou et al., 2014)and two in laparoscopic (Elhafz et al., 2012, Tikuisis et al., 2014) studies. Overall, IVL was associated with a significant reduction in postoperative pain at 12 hours versus placebo (mean difference -0.69, 95% CI -0.97 to -0.41, p<0.00001, I^2=0%). This was mirrored when just laparoscopic (mean difference -0.93, 95% CI -1.39 to -0.46, p=0.0001, I^2=0%) and open studies (mean difference -0.55, 95% CI -0.90 to -0.20, p=0.002, I^2=0%) were included.

Figure 6.3.3.2.2 *- Forest plot comparing VAS pain scores on coughing at 12 hours postoperatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



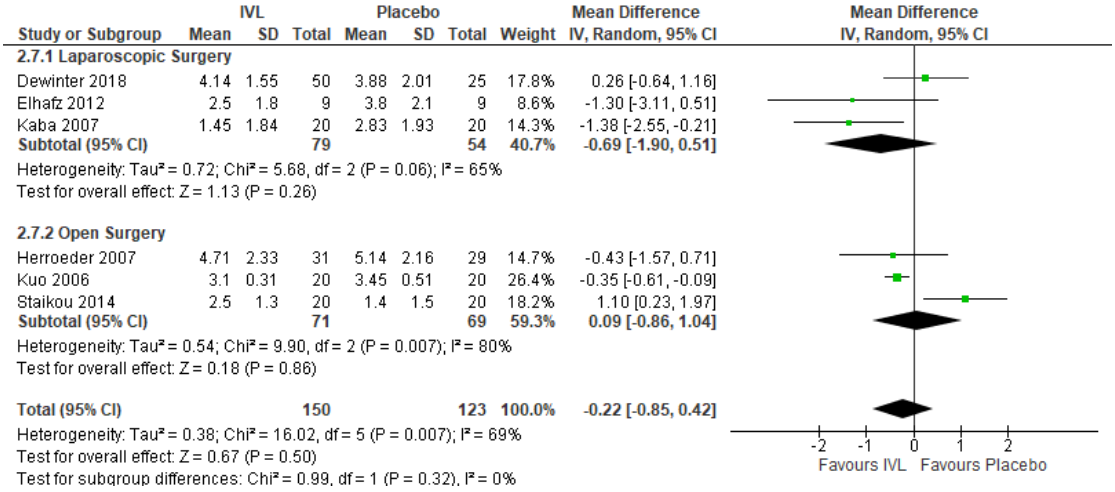
Seven studies (333 patients) (Dewinter et al., 2018, Elhafz et al., 2012, Tikuisis et al., 2014, Staikou et al., 2014, Kuo et al., 2006, Kaba et al., 2007, Herroeder et al., 2007)included data on VAS pain score on coughing at 24 hours postoperatively, of which four studies (Dewinter et al., 2018, Elhafz et al., 2012, Tikuisis et al., 2014, Kaba et al., 2007) were conducted in laparoscopic surgery and three studies in open surgery (Herroeder et al., 2007, Kuo et al., 2006, Staikou et al., 2014). IVL was associated with no significant difference in pain on coughing at 24 hours postoperatively versus placebo, both overall as well as the open and laparoscopic groups **(Figure 6.3.3.2.3)**.

Figure 6.3.3.2.3 *- Forest plot comparing VAS pain scores on coughing at 24 hours postoperatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



VAS score on coughing at 48 hours postoperatively was considered by six studies (Dewinter et al., 2018, Elhafz et al., 2012, Herroeder et al., 2007, Kuo et al., 2006, Staikou et al., 2014, Kaba et al., 2007), three in laparoscopic surgery (Dewinter et al., 2018, Elhafz et al., 2012, Kaba et al., 2007) and three in open (Herroeder et al., 2007, Kuo et al., 2006, Staikou et al., 2014). At 48 hours postop, IVL did not significantly affect VAS rated pain on coughing in any of the groups (**Figure 6.3.3.2.4**).

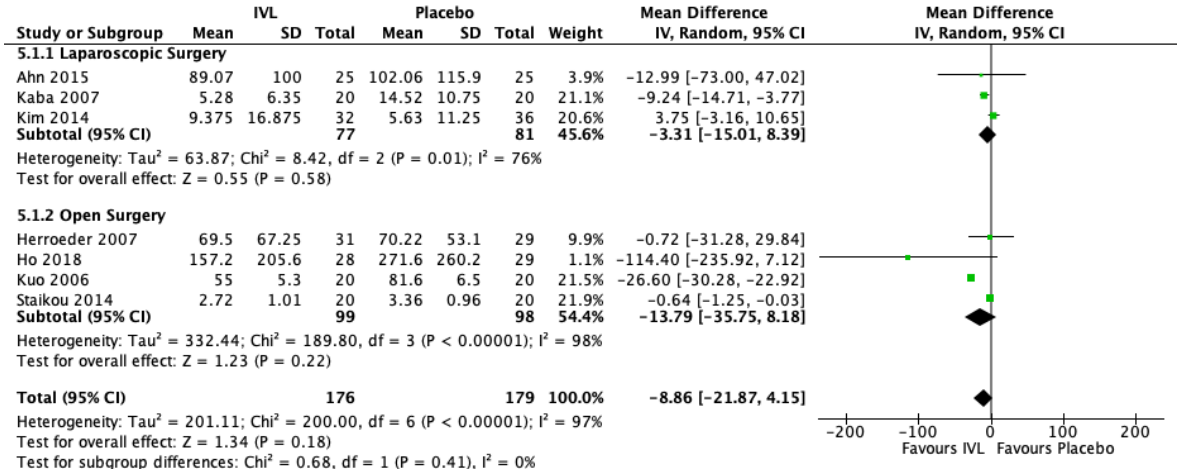
Figure 6.3.3.2.4 *- Forest plot comparing VAS pain scores on coughing at 48 hours postoperatively for patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



6.3.4 Postoperative Morphine Requirement

The most common variable considered was the overall morphine requirement which was considered by a total of seven studies (Ahn et al., 2015, Herroeder et al., 2007, Ho et al., 2018, Kaba et al., 2007, Kim et al., 2014b, Kuo et al., 2006, Staikou et al., 2014), three of which were conducted in laparoscopic surgery (Ahn et al., 2015, Kaba et al., 2007, Kim et al., 2014b) and four in open surgery (Herroeder et al., 2007, Ho et al., 2018, Kuo et al., 2006, Staikou et al., 2014). Overall, there was no difference in the postoperative morphine requirement between those receiving IVL and placebo (mean difference -8.86mg, 95% CI -21.87 to 4.15, p=0.18, I^2=97%; **Figure 6.3.4.1**), nor in those undergoing laparoscopic (mean difference -3.31mg, 95% CI -15.01 to 8.39, p=0.58, I^2=76%) or open surgery alone (mean difference -13.79mg, 95% CI -35.75 to 8.18, p=0.22, I^2=98%).

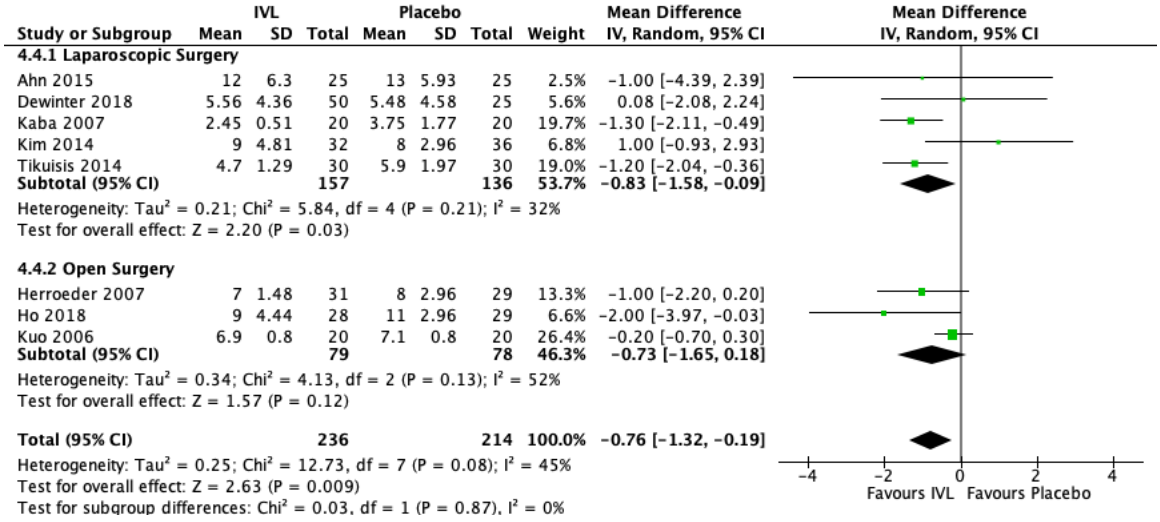
Figure 6.3.4.1 *- Forest plot comparing overall postoperative morphine requirement in patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



6.3.5 Hospital LOS

Hospital LOS was reported by eight studies included within the meta-analysis (Ahn et al., 2015, Herroeder et al., 2007, Dewinter et al., 2018, Kaba et al., 2007, Kim et al., 2014b, Tikuisis et al., 2014, Ho et al., 2018, Kuo et al., 2006), including 450 patients, of whom 293 underwent laparoscopic surgery (5 RCTs) and 157 underwent open surgery (3 RCTs). Overall, the use of IVL was associated with a significantly shorter hospital LOS (mean difference -0.76 days, 95% CI -1.32 to -0.19, p=0.009, I^2=45%; **Figure 6.3.5.1**), as well as when analysis was undertaken of those undergoing laparoscopic surgery (mean difference -0.83 days, 95% CI -1.58 to -0.09, p=0.03, I^2=32%). However, no significant difference was seen when those undergoing open surgery were considered (mean difference -0.73, 95% CI -1.65 to 0.18, p=0.12, I^2=52%).

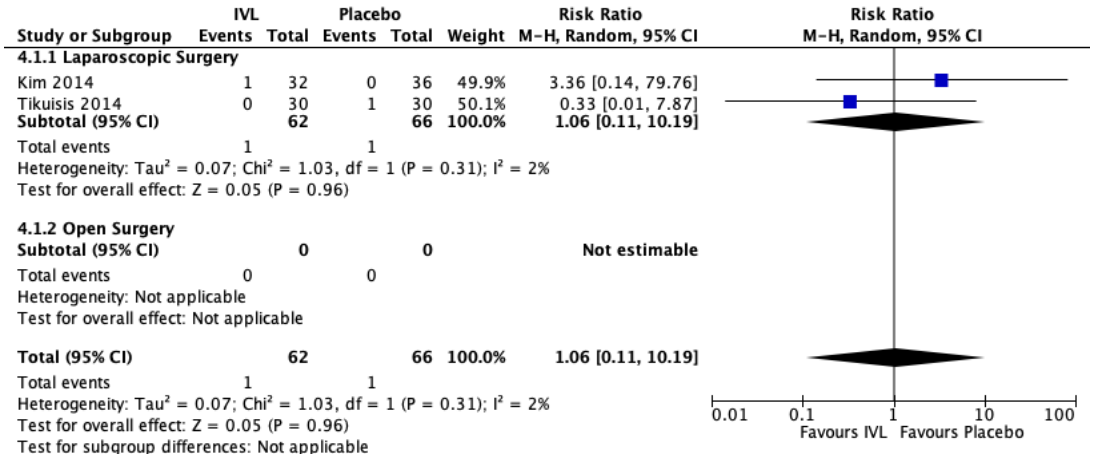
Figure 6.3.5.1 *- Forest plot comparing hospital LOS in patients receiving IVL versus not, divided by those undergoing laparoscopic versus open surgery.*



6.3.6 SSI

Only two studies (Kim et al., 2014b, Tikuisis et al., 2014) included data on the incidence of SSI, which both considered a total of 128 patients undergoing laparoscopic surgery. IVL was not associated with any difference in the incidence of SSI versus placebo (RR 1.06, 95% CI 0.11 to 10.19, p=0.96, I^2=2%), although this should be considered in the context of small patient numbers (**Figure 6.3.6.1**).

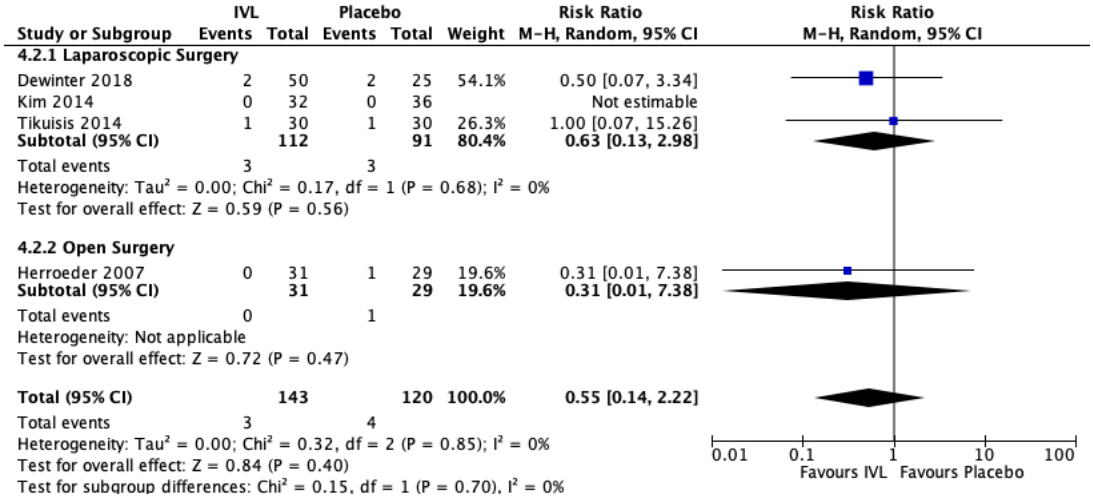
Figure 6.3.6.1 *- Forest plot comparing SSI rate for patients receiving IVL versus placebo, divided by those undergoing laparoscopic versus open surgery.*



6.3.7 Anastomotic Leak

Four studies considered the incidence of anastomotic leakage (Dewinter et al., 2018, Kim et al., 2014b, Tikuisis et al., 2014, Herroeder et al., 2007), three in patients undergoing laparoscopic surgery (Dewinter et al., 2018, Kim et al., 2014b, Tikuisis et al., 2014) and just one in open (Herroeder et al., 2007). Both overall and in those undergoing laparoscopic surgery, the use of IVL was not associated with any difference in the incidence of anastomotic leak (Figure 6.3.7.1). Due to a lack of data no meta-analysis was performed in those undergoing open surgery.

Figure 6.3.6.1 *- Forest plot comparing anastomotic leakage rate for patients receiving IVL versus placebo, divided by those undergoing laparoscopic versus open surgery.*

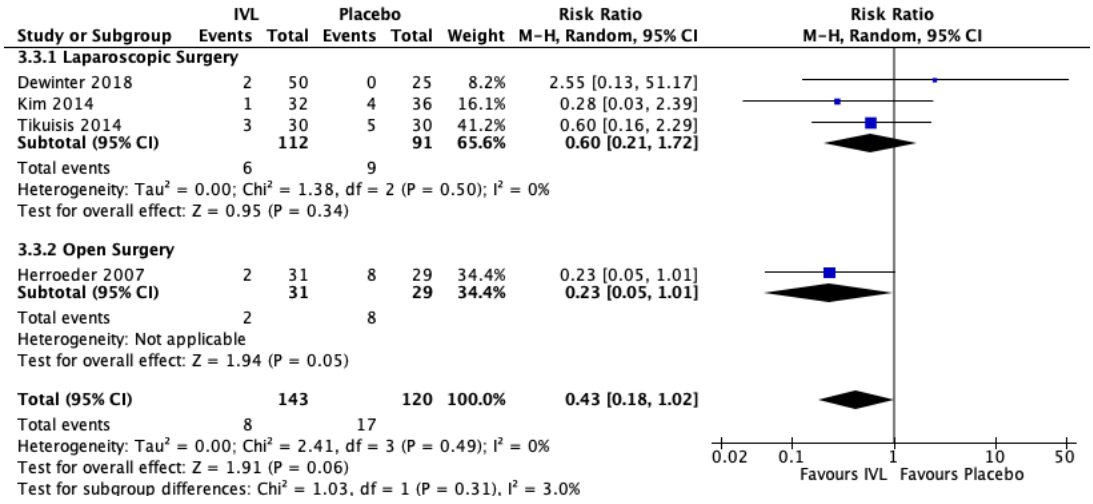


6.3.8 Prolonged postoperative Ileus

The incidence of prolonged postoperative ileus was considered by four studies (Dewinter et al., 2018, Kim et al., 2014b, Tikuisis et al., 2014, Herroeder et al., 2007), of which three studies were conducted in patients undergoing laparoscopic surgery (Dewinter et al., 2018, Kim et al., 2014b, Tikuisis et al., 2014) and one in open surgery (Herroeder et al., 2007). Overall, the use of IVL was not associated with any difference in the incidence of prolonged

postoperative ileus, nor when those patients who had undergone laparoscopic surgery were considered (**Figure 6.3.8.1**).

Figure 6.3.8.1 *- Forest plot comparing the incidence of prolonged postoperative ileus for patients receiving IVL versus placebo, divided by those undergoing laparoscopic versus open surgery.*



6.3.9 Local Anaesthetic Toxicity

Six studies examined the incidence of local anaesthetic toxicity in IVL versus placebo including 300 patients (Ahn et al., 2015, Dewinter et al., 2018, Elhafz et al., 2012, Ho et al., 2018, Kuo et al., 2006, Tikuisis et al., 2014), with four studies (Ahn et al., 2015, Dewinter et al., 2018, Elhafz et al., 2012, Tikuisis et al., 2014) conducted on patients undergoing laparoscopic surgery and two in those undergoing open (Ho et al., 2018, Kuo et al., 2006). Only one study (Dewinter et al., 2018)§ had any incidence of local anaesthetic toxicity, with all other studies reporting no events, hence a meta-analysis was not conducted on this outcome. There was only one case of local anaesthetic toxicity which was mild in nature, with a metallic taste and tinnitus. The generally reported incidence of LA toxicity is mild in 11% of patients, with 4-15% of patients exhibiting cardiovascular issues related to IVL

infusion (El-Boghdadly et al., 2018). Therefore, the patient numbers within this meta-analysis should be sufficiently powered to detect a significant difference in the incidence of LA toxicity.

6.4 Discussion

6.4.1 Principal Findings

This meta-analysis of 10 RCTs examining the impact of IVL versus placebo in elective colorectal surgery has demonstrated that IVL is associated with a significant reduction in time to defecation, VAS pain scores at rest at early time points (4,12 and 24 hours), pain scores on coughing at 12 hours only and overall hospital LOS, with a mean difference of 0.76 days. However, no difference was seen in the time to return of flatus, pain at rest at 48 hours postoperatively, pain on coughing at 4, 24 and 48 hours postoperatively, overall morphine consumption, and anastomotic leak or prolonged postoperative ileus rates (**Table 6.4.1**). When only studies considering patients who underwent laparoscopic surgery were analysed, IVL was associated with a significant reduction in time to defecation, pain at rest at 12 and 24 hours, pain on coughing at 12 hours, and overall hospital LOS, but no difference in pain scores at any other time point, time to return of flatus, morphine requirement or the surgical complications considered. When open surgery studies were considered, IVL was associated with a significant reduction in time to flatus but not faeces, pain at rest at early time points (4,12 and 24 hours) and on coughing at 12 hours only, but there was no difference in the hospital LOS or morphine requirement.

6.4.2 Strengths

This represents the only meta-analysis to date focused upon the role of IVL in patients undergoing elective colorectal surgery rather than abdominal surgery in general. The

Table 6.4.1 *– Summary of results of meta-analysis on IVL infusion versus placebo*

Outcome measure	All Studies	Laparoscopic Surgery	Open Surgery
Time to return of flatus	No significant difference (mean difference -5.33 hours, 95% CI -11.53 to 0.88 hours, p=0.09, I^2=90%)	No significant difference (mean difference -3.78 hours, 95% CI -12.88 to 5.32, p=0.42, I^2=87%)	Significant reduction in IVL (mean difference 8.4 hours, 95% CI -13.7 to -3.1 hours, p=0.002, I^2=31%)
Time to defecation	Significant reduction in IVL (mean difference -12.06 hours, 95% CI -17.83 to -6.29, p<0.0001, I^2=93%)	Significant reduction in IVL (mean difference -12.33 hours, 95% CI -18.63 to -6.03, p=0.0001, I^2=96%)	No significant difference (mean difference -11.04 hours, 95% CI -23.56 to 1.48, p=0.08, I^2=0%)
Pain at Rest – 4 hours	Significant reduction in those receiving IVL (-0.62, 95% CI -1.14 to -0.10, p=0.02, I^2=91%)	No significant difference (-0.67, 95% CI -1.63 to 0.30, p=0.17, I^2=95%)	Significant reduction in those receiving IVL (-0.75, 95% CI -1.04 to -0.45, p<0.00001, I^2=14%)
Pain at Rest – 12 hours	Significant reduction in IVL (mean difference -0.58, 95% CI -0.82 to -0.33, p<0.00001, I^2=64%)	Significant reduction in IVL (mean difference -0.80, 95% CI -1.16 to -0.44, p<0.0001, I^2=66%)	Significant reduction in IVL (mean difference -0.32, 95% CI -0.63 to -0.01, p=0.04, I^2=21%)

Pain at Rest – 24 hours	Significant reduction in IVL (mean difference -0.49, 95% CI -0.81 to -0.18, p=0.002, I^2=65%)	Significant reduction in IVL (mean difference -0.62, 95% CI -1.14 to -0.10, p=0.02, I^2=76%)	Significant reduction in IVL (mean difference -0.35, 95% CI -0.61 to -0.08, p=0.01, I^2=10%)
Pain at Rest – 48 hours	No significant difference (mean difference -0.03, 95% CI -0.47 to 0.42, p=0.91, I^2=77%)	No significant difference (mean difference -0.06, 95% CI -0.79 to 0.66, p=0.87, I^2=76%)	No significant difference (mean difference -0.02, 95% CI -0.67 to 0.63, p=0.95, I^2=79%)
Pain on Coughing – 4 hours	No significant difference (mean difference -0.50, 95% CI -1.02 to 0.03, p=0.07, I^2=72%)	No significant difference (mean difference -0.21, 95% CI -1.02 to 0.60, p=0.61, I^2=72%)	No significant difference (mean difference -0.89, 95% CI -1.85 to 0.07, p=0.07, I^2=75%)
Pain on Coughing – 12 hours	Significant reduction in IVL (mean difference -0.69, 95% CI -0.97 to -0.41, p<0.00001, I^2=0%)	Significant reduction in IVL (mean difference -0.93, 95% CI -1.39 to -0.46, p=0.0001, I^2=0%)	Significant reduction in IVL (mean difference -0.55, 95% CI -0.90 to -0.20, p=0.002, I^2=0%)
Pain on Coughing – 24 hours	No significant difference (mean difference -0.54, 95% CI -1.31 to 0.22, p=0.17, I^2=84%)	No significant difference (mean difference -0.91, 95% CI -2.53 to 0.70, p=0.27, I^2=89%)	No significant difference (mean difference -0.30, 95% CI -0.75 to 0.14, p=0.18, I^2=27%)
Pain on Coughing – 48 hours	No significant difference (mean difference -0.22, 95% CI -0.85 to 0.42, p=0.50, I^2=69%)	No significant difference (mean difference -0.69, 95% CI -1.90 to 0.51, p=0.26, I^2=65%)	No significant difference (mean difference 0.09, 95% CI -0.86 to 1.04, p=0.86, I^2=80%)

Overall Morphine Requirement	No significant difference (mean difference -8.86mg, 95% CI -21.87 to 4.15, p=0.18, I^2=97%)	No significant difference (mean difference -3.31mg, 95% CI -15.01 to 8.39, p=0.58, I^2=76%)	No significant difference (mean difference -13.79mg, 95% CI -35.75 to 8.18, p=0.22, I^2=98%)
Hospital LOS	Significant reduction in IVL (mean difference -0.76 days, 95% CI -1.32 to -0.19, p=0.009, I^2=45%)	Significant reduction in IVL (mean difference -0.83 days, 95% CI -1.58 to -0.09, p=0.03, I^2=32%)	No significant difference (mean difference -0.73, 95% CI -1.65 to 0.18, p=0.12, I^2=52%)
SSI	----	No significant difference (RR 1.06, 95% CI 0.11 to 10.19, p=0.96, I^2=2%)	----
Anastomotic Leak	No significant difference (RR 0.55, 95% CI 0.14 to 2.22, p=0.40, I^2=0%)	No significant difference (RR 0.63, 95% CI 0.13 to 2.98, p=0.56, I^2=0%)	----
Prolonged Postoperative Ileus	No significant difference (RR 0.43, 95% CI 0.18 to 1.02, p=0.06, I^2=0%)	No significant difference (RR 0.60, 95% CI 0.21 to 1.72, p=0.34, I^2=0%)	----

CI – confidence interval; IVL – intravenous lidocaine; RR – risk ratio

conduct of separate, pre-planned analyses comparing the impact of IVL in patients undergoing laparoscopic versus open surgery facilitates a better understanding of the potential benefits between the two approaches.

6.4.3 Weaknesses

The details of the lidocaine infusion differed significantly between studies included within this meta-analysis. In terms of commencement of the IVL infusion, one study commenced the infusion 30 minutes prior to the start of surgery (Kuo et al., 2006), five studies commenced this prior to induction (Kaba et al., 2007, Herroeder et al., 2007, Staikou et al., 2014, Tikuisis et al., 2014, Ahn et al., 2015), one started at the time of induction (Dewinter et al., 2018), and three commenced the infusion after induction or at the time of skin incision (Elhafz et al., 2012, Kim et al., 2014b, Ho et al., 2018). In addition, there was a degree of variability in the dosage of lidocaine administered. In terms of the bolus, all but one study (Elhafz et al., 2012) administered a lidocaine bolus prior to commencing the infusion, with the most common dosage of this being 1.5mg/kg which was used in seven of the studies (Kaba et al., 2007, Herroeder et al., 2007, Staikou et al., 2014, Tikuisis et al., 2014, Ahn et al., 2015, Ho et al., 2018, Dewinter et al., 2018), with one study administering 2mg/kg (Kuo et al., 2006), and one study 1mg/kg (Kim et al., 2014b). This was also reflected in differing doses for the IVL infusion, with the most common rate of 2mg/kg/hr being administered by four studies (Ahn et al., 2015, Tikuisis et al., 2014, Staikou et al., 2014, Herroeder et al., 2007), followed by 1mg/kg/hr in two studies (Ho et al., 2018, Kim et al., 2014b), 3mg/kg/hr in one study (Kuo et al., 2006) and 1.5mg/kg/hr in one study (Dewinter et al., 2018). One study administered the rate of infusion dependent upon body weight (Elhafz et al., 2012), and one study reduced the dose of infusion between intraoperative and postoperative stages (Kaba et al., 2007). There was also variability in the duration of infusion; three studies

administered the infusion intraoperatively alone (Ahn et al., 2015, Staikou et al., 2014, Kuo et al., 2006), and three for 24 hours (Kim et al., 2014b, Tikuisis et al., 2014, Kaba et al., 2007). Two studies discontinued the infusion at four hours postoperatively (Dewinter et al., 2018, Herroeder et al., 2007), one after 48 hours (Ho et al., 2018) and finally one (Elhafz et al., 2012) on return of gastrointestinal function or at day 5, whichever were sooner. The significant level of heterogeneity between different infusions is a potentially significant source of bias which cannot be avoided by this meta-analysis. There is insufficient evidence categorised by duration or dose of infusion to separately analyse these results and draw meaningful conclusions.

One other potential source of bias is that one study (Kim et al., 2014b) administered ketorolac in addition to the lidocaine in the perioperative infusion which was given to both the IVL and placebo groups. Thus, whilst this was a constant between the two groups, it is likely to not be comparable to other studies which provided lidocaine alone in the infusion. There were significant levels of heterogeneity observed in the meta-analyses conducted. In those overall analyses, 10 of 14 of the analyses demonstrated high levels of heterogeneity, with a similar level in those analyses concerning laparoscopic surgery (n=10/15). This was better when meta-analyses were performed on studies conducted in open surgery (n=5/12), however this also remains a significant confounder. There are also significant weaknesses associated with the use of the visual analogue scale (VAS), including that a reduction in pain score of 30-40% is needed to reflect a clinically meaningful improvement in pain (Myles and Christelis, 2011) and that is generally less reliable in elderly patients than in the young (Williams et al.). More focus is likely to be placed upon functional pain scores as core clinical outcome measures. This meta-analysis is based upon the RCTs available on the topic

and as such, use the data provided by the studies which were all in the format of a VAS-pain score.

6.4.4 Comparison with Other Studies

Only one previous systematic review (MacFater et al., 2017) has examined the impact of IVL in elective colorectal surgery, which included five RCTs comparing IVL and placebo. This demonstrated IVL provided limited benefit in the reduction of early postoperative pain and morphine consumption. This review however did not conduct meta-analysis of the available data, and since its publication an additional two RCTs (Dewinter et al., 2018, Ho et al., 2018) have been published which have been included in the current meta-analysis. The findings of the current meta-analysis and the previous systematic review are similar in their observation of an improvement in early postoperative pain in the group of patients who received IVL, reduced hospital LOS, and time to return of gastrointestinal function. However, the current meta-analysis did not find any difference in the morphine consumption rates, contrary to the previous systematic review. No conclusions were drawn regarding the relative effectiveness of IVL in open versus laparoscopic surgery by the previous systematic review, however with the additional evidence recently published, the current meta-analysis sought to evaluate this evidence.

A recently updated meta-analysis (Kranke et al., 2015, Weibel et al., 2018) examined the role of IVL in all branches of surgery which included a total of 45 RCTs, finding moderate quality of evidence on the topic. This meta-analysis found that IVL was associated with a benefit in terms of pain scores, particularly in the early postoperative phase, as well as gastrointestinal recovery, hospital LOS and opioid requirement. This study also sought to evaluate IVL versus epidural analgesia, however found just two studies (Swenson et al.,

2010, Wongyingsinn et al., 2011) (including just 102 patients) on the topic so were unable to draw any significant conclusions from the data. This Cochrane review as well as a recently published commentary article (Paterson, 2019) makes note of the significant level of heterogeneity introduced by including studies conducted in a range of surgical specialities, which is avoided in the current meta-analysis, as well as significant variability in the details of the IVL infusion, which are also relevant to the current meta-analysis and are due to a lack of standardisation in the literature.

6.4.5 Conclusion

There is ongoing emerging evidence to support the administration of perioperative IVL infusion in elective colorectal surgery, in terms of return of gastrointestinal function, early postoperative pain relief, overall hospital LOS with no difference in overall complication rates or apparent issues surrounding local anaesthetic toxicity. These findings were similar, whether patients were undergoing open or laparoscopic surgery. This meta-analysis supports the use of perioperative IVL infusion in elective colorectal surgery, however further evidence would be beneficial in light of the high levels of study heterogeneity and mixed quality of methodology to fully elucidate its potential benefits. The currently recruiting ALLEGRO trial (A placebo-controlled rAndomised trials of intravenous Lidocaine in accelerating Gastrointestinal Recovery after cOlorectal surgery' seeks to establish what impact perioperative lidocaine has upon time to return of gastrointestinal function in patients undergoing laparoscopic and open segmental colectomy, and it is hoped that this trial will add some clarity to the issue. Additional evidence is also needed regarding the optimal dosage and timing of the IVL infusion in order to standardise further studies and maximise the potential benefits of its administration.

Chapter 7 – Discussion

7.1 Summary of Results

The thesis aimed to evaluate the evidence for individual components in the enhanced recovery pathway. Following review of the literature surrounding perioperative interventions in elective colorectal surgery, four interventions forming part of the ERAS intervention were subjected to evidence synthesis in the form of meta-analysis, with the chosen topics of mechanical bowel preparation, oral antibiotic preparation, goal-directed fluid therapy and perioperative intravenous lidocaine infusion.

The second chapter of the thesis discussed the unifying methodology used in the subsequent thesis chapters for conducting a meta-analysis used for the four meta-analyses contained within this thesis which is in line with the methodology described by the Cochrane Collaboration and reporting according to the PRISMA statement (Moher et al., 2010). It also explored some of the methodological issues with meta-analysis as well as some of the pitfalls and controversies. The methodology pertinent to the individual chapters are then expanded within a study-specific methodology section in chapters three to six.

The role of MBP in elective colorectal surgery was evaluated in the third chapter in a meta-analysis of 23 RCTs and 13 observational studies. In the most comprehensive meta-analysis available to date, this demonstrated that MBP was not associated with a significant difference in any clinical outcome measure and as such should not be routinely administered prior to elective colorectal surgery. These findings are consistent with the recommendations made by the ERAS Society (Gustafsson et al., 2012a, Gustafsson et al., 2018) as well as the UK National Institute for Health and Care Excellence (NICE, 2008). However, this guidance

is not reflected in surveys of clinical practice (Devane et al., 2017, Andersen et al., 2011, Buia et al., 2019, Kang et al., 2013), which still demonstrate high rates of administration of MBP prior to elective colorectal surgery, irrespective of the use of OAB preparation. The results of this chapter should provide ongoing impetus for change in clinical practice in terms of bowel preparation prior to elective colorectal surgery.

This ties in well with chapter four which examined the role of oral antibiotic preparation, both with and without MBP, in a series of 40 studies (74,714 patients), 28 RCTs and 12 observational studies. This meta-analysis demonstrated that the combination of mechanical bowel and oral antibiotic preparation was associated with a significant reduction in SSI, anastomotic leak, 30-day mortality, overall morbidity, development of ileus and reoperation rates, with no significant difference seen in *Clostridium difficile* rates versus MBP alone. Interestingly, when the combination of MBP and OAB were compared with OAB alone, no difference was observed in the incidence of SSI, both overall and when evidence from RCTs alone were considered, suggesting a potential equivalence of the two interventions. This is an attractive option as the administration of MBP carries with it increased risk of preoperative dehydration, electrolyte disturbance and patient dissatisfaction, hence OAB alone may be a preferable option. This meta-analysis provides highly interesting results which have the potential to significantly alter preoperative protocols for bowel preparation prior to elective colorectal surgery. The most recently published ERAS Society guidelines (Gustafsson et al., 2018) make note of the recent large number of publications on the role of OAB preparation for colorectal surgery and following evidence review conclude that 'the is some evidence from randomised controlled trials to support the use of a combination of MBP and oral antibiotics over MBP alone', although this statement is associated with a weak recommendation grade and based upon low quality evidence. The evidence provided in

chapter four provides the highest quality evidence to date surrounding the use of combined MBP and OAB in the prevention of post-surgical complications including SSI in elective colorectal surgery. It has the potential to stimulate further research which is likely to result in a significant change in clinical practice, however more RCT-based evidence is necessary to differentiate between the benefits of preoperative preparation with combined MBP and OAB versus OAB alone.

Chapter five presents a meta-analysis of 11 RCTs examining the role of GDFT using transoesophageal Doppler versus traditional fluid management in 1113 patients undergoing elective colorectal surgery. This study found no benefit associated with GDFT in terms of overall morbidity, hospital LOS, 30-day mortality, SSI, anastomotic leak, intra-abdominal collection, incident of postoperative ileus, or time to return of gastrointestinal function. This is in contrast to the NICE guidelines (NICE, 2011) which recommend that GDFT technology should be used 'in patients undergoing major or high-risk surgery'. This work suggests an update to this guideline is necessary and that GDFT should not be considered a standard of care in patients undergoing elective colorectal surgery. This guidance is based upon 8 RCTs (Wakeling et al., 2005, Gan et al., 2002, Mythen and Webb, 1995, Venn et al., 2002, Senagore et al., 2009, Noblett et al., 2006, McKendry et al., 2004, Sinclair et al., 1997) conducted across a wide range of surgical specialities including colorectal, gynaecological, orthopaedic, urological and cardiac surgery. Given the vast degree of heterogeneity associated with analysis across a wide range of surgical specialities with differing complication profiles and incidences, as well as a lack of evidence synthesis behind the NICE guidance, the strength of conclusions from the meta-analysis conducted in chapter five are much greater.

The final chapter examines the role of perioperative IVL infusion in 10 RCTs which randomised a total of 610 patients undergoing elective colorectal surgery. This study demonstrated that that IVL was associated with a significant reduction in time to defecation, VAS pain scores at rest at early time points (4,12 and 24 hours), pain scores on coughing at 12 hours only and overall hospital LOS, with a mean difference of 0.76 days. However, no difference was seen in the time to return of flatus, pain at rest at 48 hours postoperatively, pain on coughing at 4,24 and 48 hours postoperatively, overall morphine consumption, and anastomotic leak or prolonged postoperative ileus rates. Given this is a relatively cheap intervention which is easy to administer with very low rates of adverse events, it should be more carefully considered as a potential standard of care for patients due to undergo elective colorectal surgery.

7.2 Implications for ERAS protocols

The introduction to this thesis explored the evidence surrounding the components considered as part of an ERAS multimodal intervention in elective colonic surgery as detailed by the guidelines published in 2012 (Gustafsson et al., 2012a) by bringing these up to date. These guidelines have recently been updated and re-published (Gustafsson et al., 2018) and reference the published version (Rollins et al., 2018b) of the meta-analysis concerning MBP from chapter three as well as data included within the OAB meta-analysis from chapter four. An updated review of the literature surrounding the interventions detailed in the 2012 guidelines allowed separation of the ERAS components into those which were foregone conclusions, those which had insufficient evidence to meta-analyse and those where further evidence synthesis would possible, with these then chosen for evidence synthesis in the current thesis. In terms of prior clear evidence, these were avoidance of prolonged preoperative fasting, use of parenteral antibiotic prophylaxis, maintenance of normothermia,

the use of minimally invasive surgery where appropriate, the introduction of early enteral nutrition, avoidance of NGT and the prevention and early treatment of postoperative nausea and vomiting. Also included were the avoidance of salt and water overload, early urinary catheter removal, routine thromboprophylaxis (however the evidence for extended prophylaxis for those undergoing cancer surgery is not well established), and early mobilisation. Interventions identified as requiring further evidence include preoperative carbohydrate loading, use of premedication and short acting anaesthetic agents, the use of mid-thoracic epidurals and their comparison with non-opioid analgesic modalities such as wound infusion catheters, rectus sheath blocks and transversus abdominis plane (TAP) blocks, and stimulation of gastrointestinal motility with agents such as alvimopam. Four topics were identified as requiring further evidence synthesis and as such were included as part of the thesis, with the results summarised above.

Since the introduction to this thesis was written and the topics for meta-analysis were chosen and performed, the ERAS Society have published updated guidelines (Gustafsson et al., 2018) for elective colorectal surgery, representing the fourth update of the guidelines. These guidelines have identified several new potential interventions as part of the ERAS pathway including prehabilitation, the management of preoperative anaemia, and pre- and post-operative fluid and electrolyte maintenance. These guidelines include the results of the third chapter concerning the use of MBP in elective colorectal surgery, as well as a previous meta-analysis (Rollins and Lobo, 2016) conducted by the author of this thesis concerning the use of GDFT in elective major abdominal surgery with particular focus upon patients receiving care as part of an ERAS pathway versus traditional care. This previous meta-analysis informed the conduct of the meta-analysis in chapter five which was specific to GDFT in elective colorectal surgery, performed to reduce the heterogeneity of inclusion of studies

from a range of specialities conducting abdominal surgery. Concerning the topic of oral antibiotic preparation in elective colorectal surgery, the updated ERAS guideline states that 'there is some evidence from RCTs to support the use of a combination of MBP and oral antibiotics over MBP alone', however the quality of evidence is quoted as low, with a weak recommendation made by the guideline. The publication of the meta-analysis performed in chapter four concerning oral antibiotic preparation (Rollins et al., 2018a) informs the evidence on this topic, although this also acknowledges that additional evidence is necessary, as detailed further below. With regards to perioperative IVL infusion, the 2018 ERAS guidelines (Gustafsson et al., 2018) have stated that 'lidocaine infusions can reduce opiate consumption after surgery, whether the treatment reduces the risk of postoperative ileus remains unclear'. The meta-analysis performed in chapter six sought to better clarify the issue of the role of IVL in return of gastrointestinal function which adds further weight to the beneficial effects associated with its use in elective colorectal surgery and is also associated with a reduction in hospital LOS. This meta-analysis has added information to the debate surrounding the perioperative use of IVL, which is far from conclusive, finding that IVL was associated with a significant reduction in the time to defecation and hospital LOS which has a knock-on effect on cost-effectiveness analysis.

7.3 Implications for evaluation of complex intervention bundles

Complex interventions such as ERAS pathways are notably difficult to assess due to the difficulties of separating all the individual components of a multimodal intervention. The concept of 'aggregation of marginal gains' which sees small gains spread over a number of clinical factors may result in a significant improvement in clinical outcome for the patient. This group of meta-analyses has provided up to date evidence for several of the interventions advocated as part of an ERAS pathway, including evidence that the combination of oral

antibiotic either with or without MBP and IVL infusion are beneficial in the setting of patients undergoing elective colorectal surgery. On the other hand, this thesis demonstrates clearly that MBP alone does not have a place prior to elective colorectal surgery and questions the previously stated benefits of GDFT in this setting. Whilst these meta-analyses evaluate the individual interventions, what cannot be controlled for is the setting in which the studies are conducted, and the presence or absence of other factors which may form part of an ERAS pathway as well as the compliance to these associated factors. The synergistic effect of the accumulation of multiple interventions is very difficult to appreciate. Factorial design studies can be employed in this setting to compare a limited number of combined interventions, such as the LAFA-study (Vlug et al., 2011) which compared laparoscopic and open surgery as well as fast-track and standard care in elective segmental colectomy in a 2x2 balanced factorial design. This type of study design allows a more direct comparison to be made between several different factors and better appreciate their interacting effects. Further RCTs in the setting of ERAS surgery may be best conducted in a factorial design rather than falsely isolating different factors. Within the field of evidence synthesis, the technique of network meta-analysis is becoming increasingly utilised (Rouse et al., 2017) to conduct a combination of both direct and indirect comparisons simultaneously to draw conclusions regarding the relative merits between multiple treatment arms. As increasing evidence develops in the comparison between different groups of bowel preparation prior to colorectal surgery, this technique will facilitate simultaneous comparisons between combined MBP and OAB, OAB alone, MBP alone and no preparation and help draw more rapid conclusions regarding the optimal method for preoperative preparation.

7.4 Literature Update

Since the literature search was conducted for the introduction of this thesis, there has been additional evidence to support the potential benefits associated with ERAS pathways as well as some progress in the literature pertaining to the topics meta-analysed.

In terms of support for ERAS programmes, a recently published meta-analysis (Greer et al., 2018) of RCTs comparing ERAS with traditional care pathways in colorectal surgery found ERAS was associated with a significant reduction in hospital LOS (mean reduction 2.6 days, 95% CI -3.2 to -2.0), and overall perioperative morbidity (RR 0.66, 95% CI 0.54 to 0.80, p). This lends ongoing support to the administration of ERAS in the setting of colorectal surgery. A recent observational cohort study (Arrick et al., 2018) of 495 consecutive patients undergoing major colorectal surgery found that those patients who had higher adherence rates to the ERAS pathway had a shorter overall hospital LOS (5.7 vs. 8.6 days, $p \leq 0.01$) and a lower rate of overall complications (11.2% vs. 19.6%, p=0.02) versus those with lower adherence rates. This has been further reinforced in a cohort of 100 patients undergoing colorectal surgery (Pecorelli et al., 2019), finding that increased adherence resulted in improved early clinical outcome measures, however late patient-reported outcome measures at 4 weeks following surgery were not significantly different according to compliance.

With regards to the topics chosen for meta-analysis within the current thesis, these are arranged in chronological order of conduct. When the literature search of MBP in elective colorectal surgery was updated at the conclusion of this thesis, the majority of the new literature has surrounded the combination of MBP and OAB preparation. There has however been a meta-analysis (Leenen et al., 2018) conducted after the publication of the work contained in chapter three which examined the impact of MBP versus no preparation in

elective colorectal surgery from eight RCTs. This meta-analysis found that the administration of MBP was not associated with any difference in the incidence of postoperative anastomotic leakage, in line with the results of chapter 3. In terms of studies which would be suitable for inclusion within the meta-analysis, an observational study of 680 patients undergoing elective colorectal resection for Crohn's disease (Iesalnieks et al., 2018) found that MBP was associated with a significant reduction in intra-abdominal septic complications as well as anastomotic leak rates. In addition, given this meta-analysis included data from observational studies, data from the ACS NSQIP database from the study by Midura *et al.* (Midura et al., 2018) would also be eligible for inclusion as this included data on clinical outcomes for patients receiving MBP alone versus no preparation.

When the work surrounding oral antibiotic preparation was brought up to date, one additional meta-analysis (Toh et al., 2018b) was published after the publication of the work contained within this thesis. This was conducted as a network meta-analysis of 38 RCTs including a total of 8454 patients and found that the combination of MBP and OAB was associated with the lowest risk of SSI, followed by the use of OAB alone. This study included RCT evidence only rather than that derived from many of the large observational database studies recently published such as the ACS-NSQIP data. In addition, not all studies considered the administration of parenteral antibiotics as a criterion for inclusion in the meta-analysis, whereas the meta-analysis in chapter four did. Given this is a standard of care due to overwhelming evidence that this significantly reduces the incidence of SSI, this is a weakness associated with the network meta-analysis performed by Toh *et al*. In terms of new evidence which would be suitable for inclusion within the meta-analysis, there have been three studies which support the beneficial effects of the combination of MBP and OAB in elective colorectal surgery (Ambe et al., 2019, 2018, Mulder et al., 2018). There have

additionally been three further papers arising from the ACS-NSQIP database (Toh et al., 2018a, Kaslow et al., 2018, Al-Mazrou et al., 2018b), however these are all smaller than the largest study included in the meta-analysis in chapter four. These studies either focus upon open elective restorative colorectal surgery with and without faecal diversion (Toh et al., 2018a), compared only MBP and OAB versus OAB alone (Kaslow et al., 2018), or only compared those received OAB with those who did not (Al-Mazrou et al., 2018b), hence it would not displace the study by Midura *et al.* (Midura et al., 2018).

A literature review on GDFT in patients undergoing elective colorectal surgery identified a meta-analysis published after the completion of this work based upon 11 RCTs (Xu et al., 2018). This found that perioperative GDFT did not impact upon 30-day mortality, hospital LOS, or rates of ITU admission, in line with the results of chapter 5. These included 10 RCTs with GDFT administered via transoesophageal Doppler as per chapter 5 and one study via systemic central venous oxygen saturation (Scv02)(Jammer et al., 2010) which adds an element of heterogeneity to the analysis. Despite the inclusion criteria stating that this meta-analysis would include RCTs alone, two studies were included, one of which was a comparison between a prospective collated cohort of patients receiving GDFT versus a historical cohort without GDFT (Lin et al., 2015), and one of which was an audit (McKenny et al., 2014). This therefore represents a major methodological flaw and casts doubt upon the conclusions of this meta-analysis.

Finally, the use of perioperative IVL was the most recently conducted meta-analysis contained within the thesis and at the conclusion of writing this thesis no additional data has been published which supersedes that included within the chapter.

7.5 Suggestions for Future Work

The meta-analyses contained within this thesis have identified a number of gaps within the literature studied which require additional evidence to draw more meaningful conclusions from.

The first major topic for future work concerns that of bowel preparation prior to elective colorectal surgery. The combination of MBP and OAB or OAB alone appears to convey a significant benefit in terms of SSI rates based upon analysis based upon RCTs alone. However, evidence from RCTs made up just 9.4% of the study population in this meta-analysis due to the inclusion of several large observational and database studies. These were included as much of the newly available literature surrounding the potential benefits of OAB have arisen from large database studies. What is now required is a large, high quality four arm RCT in elective colorectal surgery comparing the administration of MBP and OAB, MBP alone, OAB alone and no preparation with a primary outcome measure of the incidence of SSI.

In terms of GDFT, the ideal infusion fluid solution is not currently well validated. Historically, many studies utilised hydroxyethyl starch (HES) as the agent for bolus fluid administration which has now been withdrawn due to its association with increased rates of acute kidney injury and requirement for renal replacement therapy (Brunkhorst et al., 2008, Myburgh et al., 2012, Perner et al., 2012). Recent research has examined the best fluid for use as the bolus agent in GDFT (Cvetkovic et al., 2018, Hiltebrand et al., 2009, Yates et al., 2014). However, no definitive data to support the use of one agent over another has been presented to clarify which may result in superior clinical outcomes. A definitive answer regarding the best infusion solution for bolus will help optimise the GDFT intervention and

more clearly define the potential benefits associated with its administration. In addition, there has been significant speculation that GDFT may be best administered to high-risk patients, or patients undergoing high-risk surgery, however this is not based upon a large amount of data specific to this study population. It is recommended that additional RCT-based evidence surrounding GDFT use in high-risk patients undergoing elective colorectal surgery be conducted to more conclusively answer this question.

For perioperative IVL infusion, Chapter 6 has provided good early evidence of a potential benefit associated with infusion in terms of early postoperative pain relief, hospital LOS and time to defecation. One major issue identified from the RCTs included within this meta-analysis was a huge degree of variation in the timing and dosage of the lidocaine infusion. At present, there is a lack of evidence to support the optimal dosage of lidocaine, both in terms of bolus as well as infusion rates, and also of duration of infusion postoperatively. There was insufficient literature available within the studies included in the meta-analysis to conduct separate subgroup analyses of differing doses and duration of infusion. Therefore, there need to be two focuses to the literature going forward with regards to IVL infusion. The first is a RCT which seeks to evaluate the optimal dose of lidocaine, varying between 1 and 3mg/kg/hr. All these infusion rates were included in studies included within the meta-analysis with no significant incidence of local anaesthetic toxicity. Reported threshold serum plasma concentrations associated with local anaesthetic (LA) toxicity are hugely variable, with mild toxicity seen at 6 μg/mL and progression to serious toxicity at levels exceeding 10 μg/mL (Eipe et al., 2016). The generally reported incidence of LA toxicity is mild in 11% of patients, with 4-15% of patients exhibiting cardiovascular issues related to IVL infusion (El-Boghdadly et al., 2018). Therefore, the patient numbers within this meta-analysis should be sufficiently powered to detect a significant difference in the incidence of

LA toxicity. In addition, a RCT should be conducted to investigate the optimal duration of IVL infusion, varying between cessation at the end of surgery, 4 hours postoperatively, 24 and 48 hours. Only once the optimal dose and duration of IVL infusion has been established can there be standardisation within future RCTs which will help to more definitively answer the question of the role of IVL infusion in elective colorectal surgery.

One final point for future work concerns the fact that despite all the evidence in support of ERAS pathways, it is not being uniformly being followed. There have been a number of studies which have attempted to understand the challenges associated with ERAS pathways and identify methods to facilitate the adoption, implementation and embedding of ERAS within perioperative care pathways (Herbert et al., 2017, Cohen and Gooberman-Hill, 2019, Gotlib Conn et al., 2015). Despite these studies, the implementation of ERAS pathways lags somewhat behind the evidence to support their use, and this remains a topic which must be addressed in future research.

7.3 Conclusion of Thesis

This thesis has provided additional high-quality evidence on four individual components which all contribute to ERAS pathways in elective colorectal surgery. This thesis has provided evidence to suggest that MBP combined with OAB, or OAB preparation alone should be included within ERAS pathways as a standard of care for the reduction of SSI, although further high-quality evidence is needed to clarify whether the combination of MBP and OAB is superior to OAB alone. MBP alone does not have a place due to its potentially deleterious effects and lack of clinical benefit. Perioperative IVL similarly should be considered for routine administration due to its beneficial effects in reduction of postoperative pain, time to defecation and hospital LOS. GDFT via transoesophageal

Doppler does not appear to have a role in low risk patients undergoing elective colorectal surgery, however further evidence is required to establish whether high-risk patients, or those undergoing high-risk surgery should undergo fluid administration using this methodology. The thesis has also demonstrated the beneficial effects of evaluation of single components within a multimodal, complex intervention such as ERAS pathways, such that all included interventions do indeed provide 'aggregation of marginal gains' which culminate to form a significant clinical benefit to patients.

One meta-analysis within this thesis has already contributed to international guidance for the ERAS Society, with one other meta-analysis on OAB preparation resulting in two invited lectures at the World ERAS Congress. All of the meta-analyses represent high quality evidence synthesis which are on topics currently in evolution and are suitable for inclusion within future consensus statements and international guidance. The findings of this work are likely to result in significant changes in clinical practice and stimulate future research to more definitively conclude some of the unanswered questions surrounding the perioperative care of patients undergoing elective colorectal surgery.

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Appendices

Appendix 1 - PROSPERO Record for Mechanical Bowel Preparation Meta-Analysis

UNIVERSITY of York
Centre for Reviews and Dissemination

1) Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The role of mechanical bowel preparation in elective colorectal surgery: a systematic review and meta- analysis

2) Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title

3) Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

05/08/2015

4) Anticipated completion date.

Give the date by which the review is expected to be completed. 30/11/2015

5) Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence

of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

The review has not yet started: No

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

6) Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record. Dr Rollins

Named contact email: krollins@doctors.org.uk

Named contact address

Nottingham Digestive Diseases Centre, E floor, West Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH

Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)1158231144

7) Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Nottingham Digestive Diseases Centre, E Floor, West Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH

8) Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team.

Dr Katie Rollins. Nottingham Digestive Diseases Centre, E floor, West Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH
Dr Hannah Javanmard-Emamghissi. Nottingham Digestive Diseases Centre, E floor, West Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH
Professor Dileep Lobo. Nottingham Digestive Diseases Centre, E floor, West Block, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH

9) Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review.

No funding source

10) Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

11) Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

12) Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Meta-analysis of bowel preparation techniques in elective colorectal surgery on clinical outcomes

13) Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Search will be conducted of the PubMed, MEDLINE, Web of Science, GoogleTM Scholar and Cochrane Library databases.There will be no language or publication period limitations.
Search terms used will be: bowel preparation OR bowel cleansing AND surgery.
The bibliography of studies that meet the inclusion criteria will also be searched for other relevant articles and conference abstracts to ensure study inclusion is as comprehensive as possible

14) Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Elective colorectal surgery

15) Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Adult patients undergoing elective colorectal surgery

RCT or observational study

Prospective or retrospective

At least two comparative groups from:

Mechanical bowel prep (any form of oral preparation to cleanse bowel)

Enemas

Systemic antibiotics

Luminal antibiotics

16) Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Mechanical bowel prep (any form of oral preparation to cleanse bowel)

Enemas

No bowel preparation

17) Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Mechanical bowel prep (any form of oral preparation to cleanse bowel)

Enemas

No bowel preparation

18) Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

RCT and cohort study Prospective and retrospective.

19) Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurements are made, if these are part of the review inclusion criteria.

Surgical site infection.

20) Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate

to the review

Anastomotic leak

Systemic sepsis

Other complications

Mortality

Length of stay

Also note other endpoints described in the papers

21) Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

PubMed, Cochrane Collaboration, MEDLINE, Google Scholar. Two researchers will screen for eligibility with any queries being resolved by the senior author.

22) Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

GradePRO software analysis.

23) Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

RevMan analysis - quantitative.

24) Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co- morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Mechanical bowel prep (any form of oral preparation to cleanse bowel)

Enemas

No bowel preparation

25) Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Interventional

Health area of the review

Digestive diseases

26) Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error. English

27) Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

28) Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

International meeting presentation followed by peer reviewed publication

29) Do you intend to publish the review on completion? Yes

30) Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

bowel preparation colorectal; surgical site infection; elective surgery; anastomotic leakage

31) Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing.

Please provide anticipated publication date Review_Completed_published

32) Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Rollins KE, Javanmard-Emamghissi H, Lobo DN. Impact of mechanical bowel preparation in elective colorectal surgery: A meta-analysis. World J Gastroenterol 2018; 24(4): 519-536

Give the link to the published review. https://www.wjgnet.com/1007-9327/full/v24/i4/519.htm doi: 10.3748/wjg.v24.i4.519

Appendix 2 PROSPERO Record for Oral Antibiotic Meta-Analysis

UNIVERSITY of York
Centre for Reviews and Dissemination

1) Review title.

The role of oral antibiotic bowel preparation in elective colorectal surgery: a meta-analysis of randomised controlled trials and cohort studies

2) Original language title.

Not applicable

3) Anticipated or actual start date.

14/05/2018

4) Anticipated completion date.

16/07/2018

5) Stage of review at time of this submission.

The review has not yet started: No

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

6) Named contact.

Katie Rollins

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence: Miss Rollins

7) Named contact email: krollins@doctors.org.uk

Named contact address: NIHR Nottingham Digestive Diseases Centre BRC, Nottingham University Hospitals NHS Trust
Named contact phone number: +44 (0)7929 353455

8) Organisational affiliation of the review.

Nottingham University Hospitals NHS Trust and NIHR Nottingham Digestive Diseases Centre BRC

9) Review team members and their organisational affiliations.

Miss Katie Rollins. Nottingham University Hospitals NHS Trust
Professor Dileep Lobo. Nottingham University Hospitals NHS Trust and NIHR Nottingham Digestive Diseases Centre BRC
Miss Hannah Javanmard-Emamghissi. Nottingham University Hospitals NHS Trust
Mr Austin Acheson. Nottingham University Hospitals NHS Trust and NIHR Nottingham Digestive Diseases Centre BRC

10) Funding sources/sponsors.

None.

11) Conflicts of interest.

None

12) Review question.

This meta-analysis is planned to compare the role of different combinations of bowel preparation, focusing upon the role of oral antibiotic preparation. A meta-analysis has been recently published comparing mechanical bowel preparation (MBP) with no MBP including 36 studies (23 RCTs and 13 cohort studies) and a total of 21,568 patients undergoing elective colorectal surgery. When all studies were considered, MBP versus no MBP was not associated with any significant difference in anastomotic leak rates (OR 0.90, 95% CI 0.74 to 1.10), surgical site infection (OR 0.99, 95% CI 0.80 to 1.24), intra-abdominal collection (OR 0.86, 95% CI 0.63 to 1.17), mortality (OR 0.85, 95% CI 0.57 to 1.27), reoperation (OR 0.91, 95% CI 0.75 to 1.12) or hospital LOS (overall mean difference 0.11 days, 95% CI -0.51 to 0.73), when compared with no MBP, nor when evidence from RCTs only were analysed.

13) Searches.

MEDLINE, Embase and Cochrane Library will be searched for RCTs and cohort studies including oral antibiotic preparation in adult patients undergoing elective colorectal surgery. No language or date restrictions to be imposed.

14) Condition or domain being studied.

Elective colorectal surgery.

15) Participants/population.

Adult patients aged over 18 years

Elective colorectal surgery - to include resection with or without primary anastomosis and including the creation of a defunctioning stoma

Open and laparoscopic procedures

Cohort studies can be prospective or retrospective.

Exclusion:

Paediatrics

Inflammatory bowel disease.

16) Intervention(s), exposure(s).

Oral antibiotic preparation is the exposure of interest - non-absorbable, luminal antibiotics.

17) Comparator(s)/control.

Combined OAB and MBP versus OAB

Combined OAB and MBP versus MBP

Combined OAB and MBP versus no preparation

OAB versus MBP

OAB versus no preparation

Intravenous antibiotics are now considered a standard of care, thus all groups will receive intravenous antibiotics, including the no preparation groups.

18) Types of study to be included.

Randomised controlled trials and cohort studies will be included within the analysis, although separate analyses will be conducted according to study design.

No restriction on the basis of language or time in the initial search.

19) Main outcome(s).

Surgical Site Infection (SSI).

20) Additional outcome(s).

Hospital LOS

Anastomotic leakage

Postoperative ileus

Intraabdominal collection 30-day mortality

21) Data extraction (selection and coding).

Dual literature search and screening by KR and HJE, with discrepancies resolved in conjunction with the senior author (DNL). Data extraction similarly by both KR and HJE to ensure validity. Extracted into Excel spreadsheet format.

22) Risk of bias (quality) assessment.

The risk of bias will be assessed using the Cochrane Collaboration tool for assessing bias risk in RevMan 5.3, which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). This will be performed by KR and HJE.

23) Strategy for data synthesis.

Data from included trials will be entered into RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Dichotomous variables will be quoted as a risk ratio with 95% confidence intervals and analysed using the Mantel-Haenszel random effects model. Continuous variables were quoted as a mean difference using a random effects model with 95% confidence intervals and analysed using the inverse-variance random effects model. Forest plots will be constructed from the data, with a p value 0.05 on two tailed testing used to signify a statistically significant difference. Study heterogeneity and inconsistency will be assessed using I^2 statistics..

24) Analysis of subgroups or subsets.

Subgroup analysis comparing laparoscopic versus open surgery

Subgroup analysis comparing outcomes from RCTs and observational studies.

25) Type and method of review.

Type of review

Intervention Yes

Health area of the review

Digestive system Yes

26) Language.

English

27) Other registration details.

None

28) Dissemination plans.

Planned presentation and peer-reviewed publication.

Do you intend to publish the review on completion? Yes

29) Keywords.

bowel preparation; antibiotic; oral; colorectal; surgical site infection; anastomotic leak

30) Current review status.

Please provide anticipated publication date Review_Completed_published

31) Details of final report/publication(s).

Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: a meta-analysis. Ann Surg (2019); Epub ahead of print

Give the link to the published review.

https://journals.lww.com/annalsofsurgery/Abstract/publishahead/The_Role_of_Oral_Antibiotic_Preparation_in.95298.aspx

Appendix 3 PROSPERO Record for Goal-Directed Fluid Therapy Meta-Analysis

UNIVERSITY of York
Centre for Reviews and Dissemination

1) Review title.

Goal directed fluid therapy using transesophageal doppler in patients undergoing elective colorectal surgery: a meta-analysis of randomized controlled trials

2) Original language title.

Not applicable

3) Anticipated or actual start date.

02/07/2018

4) Anticipated completion date.

22/10/2018

5) Stage of review at time of this submission.

The review has not yet started: No

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

6) Named contact.

Katie Rollins

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence: Miss Rollins

7) Named contact email.

krollins@doctors.org.uk

Named contact address: Nottingham Digestive Diseases Centre, E Floor, West Block, Queen's Medical Centre, Derby Road, Nottingham
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8) Organisational affiliation of the review.

Nottingham University Hospitals NHS Trust and NIHR Nottingham Digestive Diseases Centre BRC

9) Review team members and their organisational affiliations.

Miss Katie Rollins. Nottingham University Hospitals NHS Trust
Professor Dileep Lobo. Nottingham University Hospitals NHS Trust
Mr Neil Mathias. Nottingham University Hospitals NHS Trust and University of Exeter Medical School

10) Funding sources/sponsors.

No funding necessary for this study

11) Conflicts of interest.

None

12) Collaborators.

None

13) Review question.

This review aims to establish the role of intra-operative oesophageal doppler guided goal-directed fluid therapy (GDFT) versus traditional fluid management in elective colorectal surgery, particularly when combined with an Enhanced Recovery After Surgery (ERAS) pathway or traditional care pathway.

14) Searches.

A search of the PubMed, MEDLINE, GoogleTM Scholar and Cochrane Library databases will be performed to identify full-text studies evaluating the impact of intraoperative goal-directed fluid therapy on postoperative surgical outcomes in elective colorectal surgery

published between January 1995 and July 2018. The electronic search terms employed are [‘goal-directed fluid therapy’ OR ‘flow-directed fluid therapy’] AND [‘surgery’ OR ‘intraoperative’] AND [colon OR rectal OR colorectal]. No language restriction will be imposed upon the search, with studies including adult patients undergoing elective colorectal surgery only. The bibliographies of all studies that meet the inclusion criteria will be hand searched for any additional suitable articles and relevant conference abstracts to ensure study inclusion was as complete as possible.

15) Condition or domain being studied.

Elective colorectal surgery

16) Participants/population.

Adult patients aged over 18 years undergoing elective colorectal surgery

17) Intervention(s), exposure(s).

Inclusion:

Human studies

Randomised controlled trials

Goal directed fluid therapy delivered by transoesophageal Doppler versus traditional perioperative fluid management

Major elective abdominal surgery

Clinically relevant outcomes

Exclusion:

Cohort studies

RCT where only haemodynamic parameters are reported

Other methods of conduct of GDFT other than transoesophageal Doppler

Emergency surgery

Sepsis

Trauma resuscitation

18) Comparator(s)/control.

Traditional perioperative fluid management for elective major abdominal surgery

19) Types of study to be included.

Randomised controlled trials only

20) Main outcome(s).

Primary outcome measure is overall postoperative morbidity assessed at 30 days

21) Additional outcome(s).

Secondary outcome measures of 30-day mortality, hospital length of stay, incidence of paralytic ileus, rates of surgical site infection, anastomotic leak, and acute kidney injury.

22) Data extraction (selection and coding).

Dual paper review by two independent researchers (KR and NM), with any discrepancies resolved by the senior author (DNL). All data extraction also performed independently by KR and NM to ensure this is thorough and complete.

In addition to the primary and secondary outcome measures, data will also be collated on patient demographics [age, gender, American Society of Anesthesiology (ASA) grade], surgical variables (surgical procedure, number of laparoscopic cases, estimated blood loss) and intraoperative fluid administration (overall, maintenance and bolus fluid volumes and inotrope administration). Data will be extracted on whether the patient was managed using enhanced recovery after surgery (ERAS) principles or traditional management.

23) Risk of bias (quality) assessment.

The risk of bias will be assessed using the Cochrane Collaboration tool for assessing bias risk in RevMan 5.3, which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias).

24) Strategy for data synthesis.

The data will be aggregated at single patient level.

Data will also be analysed by whether the patient was managed in the setting of an ERAS pathway or traditional postoperative management

25) Analysis of subgroups or subsets.

None planned

26) Type and method of review.

Type of review

Intervention

Health area of the review

Digestive system

27) Language.

English

28) Other registration details.

None

29) Dissemination plans.

Submitted for peer reviewed publication: Yes

Do you intend to publish the review on completion? Yes

30) Keywords.

Colorectal; Fluid Therapy; Humans; Surgical Procedures, Elective

31) Current review status.

Review_Completed_not_published

32) Any additional information.

None

33) Details of final report/publication(s).

Rollins KE, Mathias NC, Lobo DN. Meta-analysis of goal-directed fluid therapy using transoesophageal Doppler in patients undergoing elective colorectal surgery. BJS Open (2019); Epub ahead of print.

Appendix 4 PROSPERO Record for Intravenous Lidocaine Meta-Analysis

UNIVERSITY of York
Centre for Reviews and Dissemination

1) Review title.

The role of perioperative intravenous lidocaine infusion in patients undergoing elective colorectal surgery: a meta-analysis

2) Original language title.

None

3) Anticipated or actual start date.

01/11/2018

4) Anticipated completion date.

03/02/2019

5) Stage of review at time of this submission.

The review has not yet started: No

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

6) Named contact.

Katie Rollins

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7) Named contact email: krollins@doctors.org.uk

Named contact address: Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals and University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK
Named contact phone number: +44 (0)1158 231144

8) Organisational affiliation of the review.

Nottingham University Hospitals NHS Trust

9) Review team members and their organisational affiliations.

Miss Katie Rollins. Nottingham University Hospitals NHS Trust
Professor Dileep Lobo. Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals and University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK

10) Funding sources/sponsors.

None.

11) Conflicts of interest.

None

12) Collaborators.

None

13) Review question.

The review aims to examine the role of intravenous lidocaine infusion in adult patients undergoing elective colorectal surgery, in terms of postoperative pain levels, hospital length of stay, overall complications and time to return of gastrointestinal function.

14) Searches.

Searched will be conducted on PubMed, EMBASE and the Cochrane Library. The initial search was conducted on 1st November 2018. No language or date restrictions will be placed

upon the search. The search strategy employed was: (intravenous OR infusion) AND (lidocaine OR lignocaine) AND (colon OR rectal OR colorectal OR proctectomy OR colonic).

15) Condition or domain being studied.

Elective colorectal surgery.

16) Participants/population.

Inclusion:

Adult patients undergoing elective colorectal surgery for any pathology

Intravenous lidocaine infusion in the preoperative setting, irrespective of duration post-operatively Evidence from RCTs alone

At least one relevant clinical outcome

Exclusion:

Not RCT methodology

Not colorectal surgery

No relevant clinical outcome measures.

17) Intervention(s), exposure(s).

Intravenous lidocaine infusion in the preoperative setting, irrespective of the time period the lidocaine was carried on for post-operatively.

18) Comparator(s)/control.

Placebo control, with saline infusion commenced at the same rate as the intravenous lidocaine infusion, and ideally blinded.

19) Types of study to be included.

Randomised controlled trials only.

20) Main outcome(s).

Time to return of gastrointestinal function (flatus and defecation).

21) Additional outcome(s).

Postopertaive pain scores at rest and dynamic (with VAS, up to 48 hours post-operatively)
Hospital LOS
Postoperative morphine requirement (overall and split into 24/48/72 hours post-op) Mortality at 30 days
Morbidity including surgical site infection and anastomotic leak rates Postoperative ileus rates.

22) Data extraction (selection and coding).

Dual study screening will be conducted by two independent researchers, with any discrepancies resolved by the senior author. Data extraction will also be performed by two independent researchers and compared. Extracted data will include study details (author, year of publication, methodology, patient numbers, details of the intervention and control groups, details of randomisation), patient demographics (numbers in intervention and control groups, age, ASA, gender, reason for colorectal resection), surgical demographics (number of different types of resection, op time, estimated blood loss) and the post-operative outcomes mentioned above.

23) Risk of bias (quality) assessment.

Will be performed using standard methodology using the GradePRO software.

24) Strategy for data synthesis.

Quantitative meta-analysis conducted using RevMan software from the Cochrane Collaboration if the I^2 statistic (testing for heterogeneity) permits this.

25) Analysis of subgroups or subsets.

Planned subgroup analysis will be conducted between those undergoing laparoscopic versus open procedures, and those patients who underwent lidocaine infusion only to immediately post-operatively versus those who had the infusion to 24-48 hours post-op.

26) Type and method of review.

Type of review

Intervention

Health area of the review

Digestive system

27) Language.

English

28) Other registration details.

None

29) Dissemination plans.

Plan for submission for publication and presentation

Do you intend to publish the review on completion? Yes

30) Keywords.

colorectal surgery; lidocaine; infusion; ileus; gastrointestinal function

31) Current review status.

Review_Complete.

32) Any additional information.

None

33) Details of final report/publication(s).

None yet