Enhancing Recovery After Elective Colorectal Surgery

Stephen Ridley Smith
MB BS BSc FRACS MS
Doctor of Philosophy
July 2015
Statement of Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository, subject to the provisions of the Copyright Act 1968.

Stephen Ridley Smith

Statement of Authorship

I hereby certify that the work embodied in this thesis contains a series of published papers, of which I am a joint author. I have included, as part of my thesis, a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications. I have also included, as part of this thesis, a signed written statement from each co-author involved with each publication, presented prior to each publication.

Stephen Ridley Smith
Signature Page

This is to confirm that, to the best of my knowledge, Stephen Ridley Smith, is a joint author of the following publications, in accordance with the rules governing research higher degrees (rule 53; Rules Governing Higher Research Degrees):

a. Barrier wound protection decreases surgical site infection in open elective colorectal surgery: a randomized clinical trial
b. Pursestring closure of ileostomy wounds is superior to conventional closure for short term outcomes – a randomized controlled trial
c. Randomized Clinical Trial of Ropivacaine Wound Infusion following Laparoscopic Colorectal Surgery
d. Transversus Abdominis Plane Blocks in Laparoscopic Colorectal Surgery: A Randomized Clinical Trial
e. Sham feeding with chewing gum following elective colorectal resectional surgery: a randomized clinical trial

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To my parents: Cliff and Judy, for providing a living example of altruism.

Most of all thanks to my long suffering, and beautiful wife Lou, who took a while to realise she’d married a nerd, and my son Sambo, for providing inspiration for the future.
Dedication

In memory of Clifford Francis Smith 2/1/1943 to 3/2/2015.

The best father any son could have, and the best physician any patient could want.
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Synopsis

Enhanced Recovery After Surgery (ERAS) is terminology recently developed in order to describe clinical pathways that facilitate rapid recovery with minimal morbidity, following colorectal surgery.

The aim of this thesis was to identify areas in which recovery following colorectal surgery could be further enhanced beyond the existing ERAS pathways. In order to achieve this, a literature review was performed, to quantify existing knowledge, as well as identify deficiencies in the knowledge base.

In doing so, three broad areas of recovery were identified that appeared to result in delay or morbidity following colorectal surgery: infection, pain and delayed gastrointestinal function.

This thesis by publication, involves 5 randomised clinical trials (RCTs), all in the field of colorectal surgery. Within the above three areas of recovery, these trials addressed different aspects and attempted to identify ways to enhance recovery following colorectal surgery. All trials have been performed with patients receiving current best surgical care, in comparison with current best surgical care and intervention.

The thesis is divided into a literature review on ERAS and its science, followed by a review of the three broad areas that increase morbidity following colorectal surgery. Within each area, the randomised clinical trials are embedded.

Within the area of infection the first presented trial is an RCT assessing the role of wound protectors, in decreasing surgical site infection (SSI) following colorectal surgery. The second trial presented is an RCT assessing a form of wound closure (purse-string) in decreasing SSI following ileostomy reversal surgery.

Within the area of pain there are two RCT’s assessing the role of local anaesthetic blockade in improving pain following laparoscopic colorectal surgery: the first looks at infusions into the neuromuscular plane, while the second assesses peri-operative abdominal wall blockade.

Within the area of delayed gastrointestinal function, there is a two-armed (open and laparoscopic) RCT, assessing the role of sham feeding to improve gut function following colorectal surgery.
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADH</td>
<td>Anti-Diuretic Hormone</td>
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<tr>
<td>ASA</td>
<td>American Society of Anaesthetists (scoring system for perioperative fitness)</td>
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<tr>
<td>ASEPSIS</td>
<td>Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, inpatient length of Stay (wound scoring system for infection)</td>
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<tr>
<td>ASGBI</td>
<td>Association of Surgeons of Great Britain and Ireland</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CDC</td>
<td>Centre for Disease Control and Prevention</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>COX-2</td>
<td>Cyclo-Oxygenase 2</td>
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<tr>
<td>CPEX</td>
<td>Cardio-pulmonary Exercise testing</td>
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<tr>
<td>CVA</td>
<td>Cerebro-Vascular Accident</td>
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<tr>
<td>CVP</td>
<td>Central Venous Pressure</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DVT</td>
<td>Deep Venous Thrombosis</td>
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<td>ERAS</td>
<td>Enhanced Recovery After Surgery</td>
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<tr>
<td>ESPEN</td>
<td>European Society of Parenteral and Enteral Nutrition</td>
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<tr>
<td>FEV1</td>
<td>Forced Expiratory Volume in 1 second</td>
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<tr>
<td>FiO2</td>
<td>Fraction of Inspired Oxygen</td>
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<td>FT</td>
<td>Fast Tracking</td>
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<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
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<td>GI</td>
<td>Gastro-intestinal</td>
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<tr>
<td>HAI</td>
<td>Healthcare Associated Infection</td>
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<td>IDC</td>
<td>In-dwelling Catheter</td>
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IHD Ischaemic Heart Disease
IL-6 Interleukin 6
JHH John Hunter Hospital
LOS Length Of Stay
MA Meta-Analysis
MBP Mechanical Bowel Preparation
MD Mean Difference
MET Metabolic Equivalent of Task
MEq Milli-Equivalent
MI Myocardial Infarct
MRSA Methicillin Resistant Staphylococcus Aureus
MSSA Methicillin Sensitive Staphylococcus Aureus
NICE National Institute of Clinical Excellence (Great Britain)
NK Natural Killer
NOTES Natural Orifice Transluminal Endoscopic Surgery
NPH Newcastle Private Hospital
NRS Nutrition Risk Screening
NSAID Non Steroidal Anti Inflammatory Drug
OR Odds Ratio
p p-value: probability of obtaining a result equal or greater than was actually observed
PCA Patient Controlled Analgesia
PE Pulmonary Embolus
PEF Peak Expiratory Flow
QOL Quality Of Life
RCT Randomised Clinical Trial
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>RFT</td>
<td>Respiratory Function Tests</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>RS</td>
<td>Rectus Sheath</td>
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<tr>
<td>SAGES</td>
<td>Society of American Gastrointestinal Surgeons</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SGA</td>
<td>Subjective Global Assessment</td>
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<td>SR</td>
<td>Systematic Review</td>
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<tr>
<td>SSI</td>
<td>Surgical Site Infection</td>
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<td>SWI</td>
<td>Surgical Wound Infection</td>
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<td>TAP</td>
<td>Transversus Abdominis Plane</td>
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<td>TIA</td>
<td>Transient Ischaemic Attack</td>
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<tr>
<td>TOD</td>
<td>Trans Oesophageal Doppler</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<tr>
<td>VAT</td>
<td>Ventilatory Anaerobic Threshold</td>
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<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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<tr>
<td>VIP</td>
<td>Vasoactive Inhibitory Peptide</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thrombo-embolism</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<td>WMD</td>
<td>Weighted Mean Difference</td>
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Chapter 1.

1.1 Historical Background of Enhanced Recovery After Surgery (ERAS)

ERAS is the terminology that is used to describe the process whereby patients are placed in pathways, prior to and upon their admission to hospital, that attempt to decrease their morbidity and improve their recovery process following colorectal surgery. These enhanced pathways are also designed to result in lower health care costs.

This process has existed for decades, in its most simplistic form, however the terminology is a relatively new phenomenon. The concept of ERAS has existed in the medical literature since at least 2000, when Basse et al\(^1\) developed a clinical pathway designed to accelerate recovery following elective colorectal surgery. This pathway became known as ‘Fast Tracking’, and initial papers evaluating Fast Tracking appeared to concentrate on minimising the length of hospital stay.\(^2\)

It is interesting that Fast Tracking first appeared in the literature around the same time that laparoscopic colorectal surgery became increasingly popular. The first laparoscopic colectomy was described by Jacobs,\(^3\) in 1991 in the USA, and this was followed by rapid uptake of the procedure around the world. Not long after the first descriptions, large randomised clinical trials (RCTs) were constructed, in order to assess both the short term outcomes,\(^4,5,6,7,8\) and the oncological safety\(^9,10,11,12\) of the laparoscopic approach. Once the oncological safety of the laparoscopic approach to colectomy was established,\(^13\) and the short-term advantages had been proven,\(^14\) a platform was established whereby the laparoscopic approach was the new ‘gold standard’ for colectomy.

Colorectal surgeons, therefore, had the challenge of either adopting the laparoscopic approach, with its technical challenges and associated learning curve,\(^15\) or adopting new strategies to overcome the inherent physiological short comings associated with the impact of open colectomy. One of these strategies appears to have been Fast Tracking, with the first descriptions being for patients undergoing open colectomy,
with the assistance of epidural analgesia.\textsuperscript{1,16} Kehlet and Mogensen, from the Hvidovre University Hospital in Denmark, described a median postoperative hospital stay of two days after their patients underwent open sigmoidectomy, in a seminal paper written in 1999.\textsuperscript{16} The rationale for their paper seemed to be a response to the short length of stay laparoscopic surgery provided: “single-modality intervention to reduce these factors with laparoscopic surgery usually requires a hospital stay of 5 days”.\textsuperscript{16} The title of the paper: ‘Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme’, gives an insight into their original thought process, to decrease the length of stay. Although not described as either ‘Fast Tracking’ or ‘Enhanced Recovery After Surgery’ in this paper, a concept had emerged of a multimodal program to hasten recovery.

The initial program in Kehlet’s\textsuperscript{16} seminal paper consisted of pre-operative education about planning for a two day hospital admission, avoidance of a premedication, administration of a spinal-epidural anaesthesia that was continued as an epidural infusion for 48 hours after surgery using bupivacaine and morphine. It also consisted of small transverse incisions, early enforced oral nutrition and mobilisation, prokinetics (cisapride), multimodal analgesia, and the avoidance of nasogastric tubes. Components of this multimodal program had been described previously by Kehlet,\textsuperscript{17} interestingly in a paper describing laparoscopic surgery.

Most of the early papers on ERAS, however, concentrated on open colorectal surgery,\textsuperscript{1,18,19} while an early trial even compared laparoscopic surgery versus open surgery combined with an ERAS program,\textsuperscript{20} hinting at the early potential reason for describing ‘Fast Tracking’. This randomized clinical trial, of 60 patients, revealed no difference in postoperative morbidity, mortality or readmissions between laparoscopic colectomy alone when compared with open colectomy combined with ERAS: enhanced recovery programs had arrived!
1.2 Evolution of ERAS

The terminology of ‘Fast Tracking’ evolved rather rapidly to ‘Enhanced Recovery After Surgery’. It is unclear how or exactly why this evolution occurred, although there is speculation that the emphasis on recovery after surgery should be on minimising morbidity, rather than just on speeding up hospital stay. Most of the early literature on ‘Fast Tracking’ had originated in Europe, and in 2001 the ERAS group was established as a collaboration consisting of five specialised surgical departments from Denmark, Sweden, Scotland, Norway and the Netherlands. This group provided a consensus view on the critical components of an Enhanced Recovery After Surgery program for patients undergoing colorectal surgery.\(^{21}\)

The stated principle of the ERAS protocol drawn up by this collaborative group was that conventional peri-operative care accepted that a certain stress response to major surgery was inevitable, and that remodelling this approach to care with modern anaesthetic, analgesic and appropriate metabolic support, by utilising a multidisciplinary team, resulted in improved functional outcomes.

From this paper emerged the now well-recognised ‘hub and spoke’ picture synonymous with ERAS programs. There were 17 main elements incorporated into this protocol,\(^ {21}\) pictured below.
Figure 1: Components of the ERAS program

The stated aims of the ERAS protocol drawn up by this collaboration are to allow patients to: “recover more quickly from major surgery, avoid medium-term sequelae of conventional post-operative care and reduce health care costs by reducing hospital stay”.21

Despite the stated aims, following the introduction of the protocol, it still appeared that the most important outcome related to ERAS programs was the length of stay, and ‘Fast Tracking’ had not been entirely replaced by ‘Enhanced Recovery’. An audit looking at outcomes following the introduction of ERAS to the five collaborative centres, focussed primarily on the length of stay, with the conclusion that a protocol alone is not enough to enable discharge of patients on the day of their functional recovery.22 This audit found that the main factor that had a negative impact on the length of stay was the presence of complications, while the main positive influence on reduced length of stay was previous institutional experience with ERAS. Other factors
associated with improved length of stay were organisation of care, early mobilisation, tolerance of diet, and removal of urinary and epidural catheters on the second postoperative day. In a nutshell, the study found that if an institutional culture had been established, early discharge was possible, and if patients were slow to recover for any reason, they were slower to be discharged.

The ERAS collaborative felt that it was unethical to perform an RCT comparing ERAS with traditional care; however, they did not compare morbidity before and after implementation of ERAS, simply stating that major morbidity and mortality rates were similar to those reported before the introduction of ERAS.

It did not take long, however, before RCTs began to be published on the topic, attempting to address, scientifically, the impact of ERAS on recovery after colorectal surgery.
1.3 Elements Within ERAS

The elements that make up an ERAS pathway can broadly be classified into pre-operative, intra-operative and post-operative items.

As ERAS has evolved, the elements or items within programs have also changed. Basse et al’s original description contained nine elements: Preadmission information and counselling, pre-operative protein loading, bowel preparation, thoracic epidurals, rapid post-operative feeding, early mobilisation, post-operative gastrointestinal motility agents, early removal of indwelling urinary catheters and multimodal analgesia.

Over the 13 years since its initial introduction, the list of items has changed, such that, at last count, there are up to 27 items (some with a degree of overlap) that now make up an ERAS program in institutions around the world. These include the following, with the highlighted items being those elements routinely utilised by the author:

PRE-OPERATIVE: Pre-operative Counselling
- Pre-operative Information Packages
- Medical Optimisation
- Prehabilitation / Exercise
- Pre-operative Nutrition / Immunonutrition
- Synbiotics
- Carbohydrate Loading
- Avoidance of Mechanical Bowel Preparation
- No Premedication

INTRA-OPERATIVE: Antimicrobial Prophylaxis
- Skin Preparation
- Anaesthetic Protocol
- Thoracic Epidural
- Peri-operative Fluid Management
- Laparoscopic Surgery
- Minimal and Transverse Incisions
- Peri-operative High Oxygen Concentrations
Prevention of Hypothermia
Avoidance of Routine Peritoneal Drainage
Avoidance of Routine Nasogastric Tubes
Avoidance of Opiates

POST-OPERATIVE:
Early Mobilisation
Early Post-operative Feeding
Prevention of Postoperative Ileus
Early Removal of Urinary Catheters
Audit
1.4 Scientific Basis for ERAS

There are now a number of clinical cohort trials, randomised clinical trials, and systematic reviews on the process of ERAS programs, comparing them with standard care for elective colorectal surgery.

Despite the heterogeneity of elements that are incorporated into the different RCTs (a range in RCTs of between four and 12 elements used), and the criticism of bias related to lack of blinding, the outcome of these trials and reviews appear reasonably consistent. ERAS programs appear to reduce morbidity and length of hospital stay, may reduce hospital costs, but do not appear to reduce readmission rates or mortality.

While the latest Cochrane Database of Systematic Reviews only reports on four of the six RCTs, it essentially confirms the findings of the other published meta-analyses, and identifies a risk ratio of 0.52 reduction in morbidity favouring ERAS over conventional strategies (see forest plot below). There was no reduction in predefined major complications, however.

The same meta-analysis reveals a reduction in length of stay in the intervention or fast track group by 2.94 days (95% CI -3.69 to -2.19), while there was no difference in readmission rates between the two groups. The conclusion of this review was that, despite the outcomes suggesting ERAS was a safe intervention, the quality and quantity of the data remained low, not being able to justify the widespread implementation of ERAS as the standard of care.
Protocol compliance, blinding and the heterogeneity of ERAS regimes in different institutions remain the major problems with scientific study of these programs within randomised clinical trials. Despite the Cochrane Review suggestion that larger studies are required in order to further define the role of ERAS, it remains disputable as to whether this will add anything to the understanding of ERAS. The scientific logic and safety of current ERAS programs remain sound, and further testing of all components combined will add little to our understanding of which elements add the most ‘weight’ in improving peri-operative morbidity. In addition, many of the elements have been tested extensively, in isolation, prior to their inclusion in ERAS protocols, and were found to be scientifically valid components to peri-operative care prior to ERAS programs.

What needs to be addressed in further detail with ongoing research, is the scientific validity of each component in the ERAS programs that hasn’t been ‘fully studied’. In addition ongoing work needs to be done on new ‘breakthroughs’, or components, in peri-operative care, using a standard package of care (ERAS) as the control, in order to determine the clinical effectiveness of these components.
1.5 Scientific Basis for Elements Within ERAS

PREADMISSION COUNSELLING

Early information about the recovery process following surgery can have a profound impact on patient recovery. The combination of consistent information appears to be the key ingredient to facilitate early discharge, and may explain a great deal about the cultural differences in length of stay between different institutions. In addition to the cost-related improvements that occur in institutions with pre-operative counselling, untold psychosocial benefits occur when patients are familiar with what to expect from their post-operative journey. These benefits may extend to physical recovery, with potentially less post-operative pain, less anxiety, and improvement in GI function, all of which can also lead to improvements in morbidity and length of stay.

It appears that a vital element in constructing an ERAS protocol within an institution, is the culture that exists, whereby all surgeons involved agree on the key principles and staff within the institution follow the same principles. Once this occurs, pre-operative counselling tends to be more beneficial, as patients consistently receive the same message about what to expect from their peri-operative journey.

Pre-operative counselling and institutional compliance provide the foundation on which the ERAS program is built, solidify expectations of the process, and may possibly be the most important components with respect to length of stay, although possibly less so with respect to morbidity. This has been emphasised by a study comparing institutions in different countries, highlighting different outcomes in length of stay, despite implementation of the same protocols.

MEDICAL OPTIMISATION

Inherent to pre-operative counselling is the advice about how the patient goes about maximising their pre-operative physical state. While reversal or improvement, with regard to comorbidities, is often beyond the ability of the peri-operative physician in the time frame provided, there remain a number of factors which should be assessed
prior to colorectal surgery. These include, but are not limited to: cardiorespiratory assessment, anaemia, nutrition, obesity, smoking and alcohol. All these factors will be addressed briefly:

**Cardiorespiratory assessment:** Assessment of cardiac risk is essential before major colorectal surgery in order to provide prognosis following surgery, avoid unnecessary dangerous surgical intervention and identify patients who require close observation or cardiorespiratory intervention pre-operatively. A detailed history and examination is important, and advances in clinical risk assessment enable a quick bedside assessment of the risk of a cardiac event, without the need for invasive and expensive tests. Risk factors include age, prior myocardial infarction (MI) or ischaemic heart disease (IHD), heart failure, cerebro-vascular accident (CVA) or transient ischaemic attack (TIA), renal dysfunction and diabetes mellitus (DM). All factors contribute one point each, according to the Lee/Goldman index, and the risk of a cardiac event or major complication following non-cardiac surgery is 0.4%, 0.9%, 7% and 11% with respective index scores of 0, 1, 2 and 3.

Functional cardiorespiratory capacity can also be assessed by history: metabolic equivalent of tasks (METs), or by physical testing: cardiopulmonary exercise testing (CPEX). METs is the clinical description of a patient’s ability to perform physically. One MET is equivalent to the resting oxygen consumption of an average adult (approximately 3.5 ml/kg/min) and the definition of poor functional capacity is usually set at less than four METs, while excellent capacity is greater than 10 METs. While this form of assessment is useful for surgical prognosis in active patients, its routine use for prediction remains somewhat controversial.

CPEX has been proposed as a way to more accurately assess functional cardiorespiratory capacity. It involves the patient exercising with the use of a treadmill or bike, and monitoring oxygen consumption, as well as carbon dioxide output. It obviously, therefore counters the problem of not being able to functionally assess the sedentary patient. A number of measurements can be performed with CPEX, but the most commonly used, from a surgical perspective is the ventilatory anaerobic threshold (VAT). The VAT is the rate of oxygen consumption at which anaerobic
metabolism occurs during exercise. This is used to assist fairly accurately with surgical prognosis, as well as to guide whether post-operative higher dependency care is required, with levels of less than 10.1 ml/kg/min being associated with higher rates of morbidity and length of hospital stay. While pre-operative CPEX testing is not considered standard care in Australia, it seems reasonable to consider this form of investigation in intermediate to high risk patients, and stands to reason that investment in this form of technology could aid the ERAS program in its ability to triage and minimise length of stay.

**Anaemia:** The World Health Organisation (WHO) define anaemia as a haemoglobin level of less than 130 g/L in males and 120 g/L in females. The potential effects of anaemia on the patient undergoing colorectal surgery are many and varied, and can be broadly divided into short and long term effects. In the short-term there is evidence that pre-operative anaemia is independently associated with an increase in peri-operative morbidity and mortality. It is also associated with the need for peri-operative transfusion, which in turn increases the risk of chronic infections, longer-term mortality, as well as an increased risk of cancer recurrence and reduced cancer-associated long-term survival. It appears that autologous blood transfusions also carry an increased risk for colorectal cancer recurrence and, in view of the poorer association with anaemia and transfusion, it is worthwhile considering iron therapy in the pre-operative preparation of the colorectal surgical patient.

Despite the obvious potential benefits of pre-operative iron therapy, there is not a great deal of evidence, data or guidelines to guide therapy in the colorectal surgical patient. Oral iron replacement is associated with minimal morbidity, but is probably mostly ineffective in the average time frame given to colorectal surgical patients between diagnosis and surgery, although one small randomised clinical trial showed a reduction in the need for transfusions associated with oral iron therapy. This trial employed a very high dose of oral iron (200mg ferrous sulphate three times daily). However, there is data suggesting the superiority of intravenous iron over oral iron, with respect to improvements in haemoglobin levels in other clinical scenarios.
Intravenous iron has been plagued with immunological-related complications in the past, but newer agents (dextran and polymaltose preparations) appear safer and have proven efficacy in increasing haemoglobin levels, as well as decreasing the need for transfusions across a wide spectrum of acute care settings. Given this efficacy it stands to reason that intravenous iron should be strongly considered in all pre-operative patients with anaemia associated with iron deficiency.

The only randomised clinical trial, utilising intravenous iron performed in a colorectal setting failed to identify an advantage associated with intravenous iron prior to elective resectional surgery. However numbers were small (n=60) and only 11 of these had pre-existing anaemia. No recorded complications occurred as a result of iron therapy in this trial. More research is clearly required in order to determine the role of intravenous iron as a routine pre-operative adjunct for colorectal surgery.

It stands to reason, however, that in the iron deficient anaemic patient, iron supplementation should be given pre-operatively as part of the ERAS package. Consideration should be given for further trials on iron therapy in this setting, in order to further define which patients stand to benefit the most, as well as which protocol is most effective.

**Nutrition:** It is well established that the surgical patient who is malnourished prior to intervention has a higher peri-operative morbidity and mortality. In this current western climate of obesity, an assessment of nutritional depletion is not always an easy task. Body mass index (BMI) alone is not a reliable indicator of nutritional status and surgical complications, and a number of scoring systems have been devised in order to both determine patients nutritional status, as well as identify those that stand to benefit most from intervention before surgery. The most commonly used scoring systems are the Nutrition Risk Score (NRS), that combines age, BMI, food intake and proportion of weight loss and the Subjective Global Assessment (SGA), that combines a quick history (weight change, dietary intake, gastrointestinal symptoms, functional capacity and disease states) and examination (nutritional related fluid balance, fat and muscle wasting). It remains difficult to know exactly where the ‘cut-off’ mark is with regard to each of these scales and, of course, there is a grey zone...
of patients who achieve marginal benefit from surgical delay and nutritional intervention. It may be that intervention for all patients in the form of immunonutrition is ample, and this will be covered in a subsequent topic.

There are clearly a group of patients at high risk of complications from malnutrition, who do benefit from intervention, however,\(^6\) and this can be in the form of either the enteral or parenteral route, with the former being the preferable option, if ‘available’.\(^6\) The exact duration and type is less understood, but it appears clear that delaying surgery for enteral feeding is beneficial for the group of patients at high risk of malnutrition (SGA grade C), while enteral feeding should be considered (without surgical delay) in patients who will not be able to eat for whatever reason for seven days or more peri-operatively (or intake less than 60% recommended for 10 days or more peri-operatively).\(^6\) Quite clearly it is not always an easy task to identify patients who may not be able to eat postoperatively, and in view of this the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines suggest a low threshold for intervention with enteral nutrition, in the form of oral nutritional supplements, a topic covered in due course under immunonutrition.

**Obesity:** Obesity, in its own right, poses an increased risk of complications following surgery that include, but are not limited to: myocardial infarction, surgical site infection, urinary tract infection, peripheral nerve injury, cardiac arrest, reintubation and mortality.\(^6\) Obese patients undergoing colorectal surgery also have an increased risk of: anastomotic leakage, particularly following rectal resection, wound dehiscence, incisional hernia, stoma complications and conversion to open surgery if undergoing a laparoscopic resection.\(^6\)

The difficulty with this knowledge is in its application. How does one go about minimising the risks associated with this factor, given the duration between diagnosis and surgery and, at what cut off BMI level should intervention occur? Very low calorie diets have been shown to provide rapid weight loss, while maintaining important parameters of nutrition,\(^6\) but have not been studied in great detail with regard to colorectal surgery. There is however very little data as to the role of weight loss surgery prior to colorectal surgery or cancer surgery in general.
**Smoking:** Smoking appears to increase post-operative complications. In addition to the standard disease conditions related to smoking, the specific post-operative complications of respiratory and wound healing are seen with higher frequency in smokers.\(^6^7\) Smokers are also more likely to end up in the intensive care unit following surgery, as well as carrying an increased risk of mortality, overall morbidity, infections not associated with the wound and neurological complications.\(^6^8\) There is probably insufficient data to identify a link between smoking and anastomotic leakage, although the association appears convincing (RR 1.42, CI: 0.96-2.09) in the light of the relationship with smoking and wound healing.\(^6^8\)

It appears logical, given the existing data, to encourage smoking cessation prior to surgery. The short time frame between diagnosis and surgical intervention, associated with a period of increased psychological stress for the patient, does make smoking cessation or reduction a difficult task, however.

There appears to be a direct relationship with the duration of smoking cessation and reduction in both respiratory and wound healing complications. It appears that post-operative respiratory complications are not reduced if smoking cessation occurs less than four weeks prior to surgery, with approximately a 25% reduction in respiratory complications if cessation has occurred at least four weeks prior to surgery, and approximately a 50% reduction if that time frame is extended to eight weeks. Abstinence from smoking at least three weeks prior to surgery results in at least a 30% reduction in wound healing complications.\(^6^9\)

There are a number of interventions to reduce smoking prior to surgery, and the most studied of these is the use of nicotine replacement therapy. This appears to be the most effective tool, to assist cessation or reduction of smoking prior to surgery, and most likely assists patients by reducing the previously mentioned post-operative complications, despite the concern that exists about nicotine being the key causative factor.\(^7^0\)

**Alcohol:** Increased alcohol consumption is a risk factor for a number of diseases, and also appears to place the surgical patient at increased risk of peri-operative morbidity and perhaps even mortality. There is considerable evidence that surgical patients who
drink five or more standard drinks per day on a regular basis, have an increased risk of hospital mortality, length of hospital stay and reoperation,\textsuperscript{71} on the basis of increased rates of bleeding, wound complications, infection and cardiorespiratory insufficiency.\textsuperscript{72} There is even a small study indicating a higher risk of anastomotic dehiscence following colorectal surgery for patients who abuse alcohol.\textsuperscript{73}

There appears to be two reasons for this increase in morbidity: the first being that of alcohol-induced organ dysfunction, with the second being the withdrawal phenomenon following abstinence, resulting in an exaggerated stress response.\textsuperscript{71,72} Studies on the pathophysiology of the effect of a moderate alcohol intake reveal that patients have ‘subclinical’ dysfunction in a number of organs, in particular, the heart, immune and coagulation systems.\textsuperscript{72,74-76} This subclinical dysfunction becomes clinically apparent under periods of stress, such as surgery.

It appears that abstinence can usually result in post-operative improvement in these subclinical parameters, although care must be taken around the peri-operative period in order to avoid the deleterious effects of withdrawal. The duration of alcohol cessation required to normalise organ function varies but, provided no permanent organ dysfunction exists, it takes approximately one to four weeks for normalisation of coagulation/haemostatic function, four weeks for cardiac function to normalise and about eight weeks for compromised immune function to return to normal. The exaggerated stress response following surgery that occurs with abstinence and withdrawal takes about three months to disappear.\textsuperscript{74-76}

In summary, there are known peri-operative risks associated with a high alcohol intake and there is evidence that stopping or reducing alcohol intake prior to surgery for this group of patients, results in improved clinical outcomes.

What is not known is how best to go about this. Although there are numerous studies assessing strategies aimed at alcohol reduction or cessation, there is not much data with which to guide the peri-operative patient. A trial performed in an Australian setting revealed no difference in alcohol consumption between two pre-operative groups of patients: one exposed to intervention (involving counselling and supplemental Disulfiram and Benzodiazepines) and the other exposed to standard
care, although both groups had a significant reduction in alcohol consumption over the course of the trial.\textsuperscript{77} A Cochrane Review on pre-operative alcohol cessation prior to elective surgery only identified two randomised clinical trials on the topic, both performed by the same clinical unit (the review was also conducted by the author of both trials, and one trial was unpublished), involving 69 patients in total. This review revealed a reduction in overall complications (OR: 0.22; 95\% CI 0.08 to 0.61; p=0.004), but no reduction in hospital stay or mortality.\textsuperscript{78} The trials used a combination of cessation interventions, and pharmacotherapy (Disulfiram and Benzodiazepines) for relapse prophylaxis and symptoms of withdrawal.\textsuperscript{79,80}

Despite the sparsity of data linking methods of pre-operative alcohol reduction to improved clinical outcomes, common sense would suggest that a detailed history pertaining to high risk alcohol intake, with associated intervention be a worthwhile component of ERAS packages.

INFORMATION PACKAGES

Preadmission counselling extends not only to a detailed medical history of the patient, pertaining to the factors listed above, but also includes counselling as to the expected ‘patient journey’, that is, their peri-operative period. In addition to the informed consent process, a guide through the expected peri-operative course, including what’s expected of the patient, is now considered a standard approach to colorectal surgery. As mentioned in the previous section, preadmission counselling has been shown to enhance the recovery process. Not all of this counselling can be given at one sitting by the one provider, and this supports the foundation for information packages to assist patients in their journey.

The simplest outcome to measure, with regard to information packages, is that of length of stay: however, there are other outcome measures of importance. Adequate pre-operative information also has the potential ability to set realistic goals, decrease anxiety levels, increase independence and autonomy, and perhaps even improve physical function and healing after surgery.\textsuperscript{81,82}
The setting of realistic goals begins with a clear expectation of what must be achieved for safe discharge from hospital. It is the belief of the Colorectal Department at John Hunter Hospital, Newcastle, that patients be able to satisfy the criteria of being able to tolerate a selective diet, perform physical activities of daily living, have evidence of gastrointestinal function (flatus or bowel motion) and having no requirement of parenteral narcotics for analgesia. It would seem reasonable for all colorectal units to have written documentation of the expected minimum requirements for safe discharge.

Once realistic goals are established, further information and education can be given to improve patient autonomy. There appears to be some evidence that the provision of this information and education results in improved outcomes with respect to symptom improvement and anxiety.\textsuperscript{81} This is probably even more important with regard to patients undergoing cancer surgery.\textsuperscript{83}

The ability to improve post-operative physical function following surgery, with the use of pre-operative education, is a fascinating observation. In particular psychotherapy has been studied with respect to wound healing.\textsuperscript{84} Research into the psychoneuroimmunology model has highlighted the roles of oxytocin, vasopressin, epinephrine, cortisol, local cytokines, matrix metalloproteinases, tissue hypoxia and leukocyte redistribution, with respect to wound healing, and the impact that coping styles, positive environment and social structures have on these pathways.\textsuperscript{84-87} In addition to wound healing, it appears that there is the potential for psychotherapy to influence cancer-related outcomes following surgery. A relationship between peri-operative stress, anxiety, depression, functional well being and Vascular Endothelial Growth Factors (VEGF-A) has been established in colorectal cancer,\textsuperscript{88} with the inference being that influencing these important cancer related cytokines with psychotherapy may have the ability to retard cancer growth and metastatic ability, and influence outcomes.\textsuperscript{87-88} The relationship between psychotherapy and cancer-related outcomes has been further established with breast cancer, where pre-operative relaxation therapy has been shown in a randomised clinical trial, to elevate levels of Natural Killer (NK) cells, and improve other immunological aspects of anti-cancer host defences.\textsuperscript{89}
What is not well established is the relationship between education and peri-operative stress, anxiety and functional wellbeing, as well as the best form of delivery of this education and information. While nothing can compare with face-to-face contact, additional information can now be delivered in multiple formats.

Telephone counselling has been proposed as one method of information and education delivery. In an Australian setting, with large distances to referral centres this would seem an ideal form of delivery. The author has participated in a large multicentre trial conducted in NSW to address this issue. The CONNECT study was a randomised clinical trial conducted across 23 hospitals involving 775 patients with colorectal cancer. Patients were randomised to ‘standard care’, or ‘standard care with intervention’ from a centrally-based nurse, and routine access in the form of telephone calls on days three and 10 post discharge from hospital, as well as calls at one, three and six months, in addition to unplanned access when required. The outcomes assessed were: experience of care coordination, unplanned readmissions, emergency department presentations, supportive care needs and Quality of Life (QOL). Questionnaires were performed at one, three and six months, with no difference found between the two groups with respect to all outcomes. The result suggests the need for a more targeted approach with respect to this group of patients. Given that the contact in this trial was with a nurse usually unknown to the patient it would be unwise to suggest, based on this trial, that this form of contact be considered unnecessary for colorectal cancer patients, although the clinical evidence for it remains patchy.

Another potential method in this day and age is, of course, an internet/web-based form of delivery. Our unit is seeking to find out whether an individualised web-based program has the ability to first of all, deliver the practical information required for colorectal cancer surgical patients, and secondly, if this will result in improved outcomes. This randomised clinical trial will follow on from a ‘listening post’ survey performed in Newcastle for colorectal cancer patients, indicating a need for a more established, coordinated approach to colorectal cancer care, followed by a review into colorectal cancer services within the region. Currently a pilot program is being undertaken in order to develop the individual web-based program, that will be used in
the randomised clinical trial. Hopefully, the ability to tailor the approach more effectively at both a regional and individual level will result in improved clinical and quality of life outcomes.

PREHABILITATION and EXERCISE

It goes without saying that poorer pre-operative fitness results in more post-operative complications following major surgery, and this has been covered earlier in the section on medical optimisation.

Less is known, however, about the ability to influence physical function (and hence clinical outcomes) prior to elective colorectal surgery. Mayo et al performed a regression analysis on a previous randomised clinical trial they performed on colorectal surgical patients, in order to identify, firstly, whether pre-operative physical function could be improved with prehabilitation and, secondly whether change in function improved post-operative recovery. This study revealed that it was possible to influence physical function before surgery and that those patients who had an improvement in physical function were more likely to recover quicker, suffer less complications, were less likely to require intensive care unit admissions and exhibited a faster return to pre-operative baseline physical function. An association with improvements in pre-operative physical function was seen in males, those with a low baseline walking capacity, those with less anxiety, and in patients who had the perception that fitness aids recovery. Predictors of poorer recovery included: a deterioration during prehabilitation, age >75 years and high anxiety levels.

The same group from Quebec Canada, had previously sought to determine the optimal way to enhance functional capacity prior to colorectal surgery by randomising patients to one of two groups: biking/strengthening and walking/breathing. The walking/breathing group was designated as the ‘control’ group, as it was the simpler, less onerous form of activity. A higher proportion of patients in the walking/breathing group had an improvement in functional capacity, when compared with the biking/strengthening group following surgery (41% vs 11%; p=0.019), although the
outcome was somewhat biased towards the control group, with the outcome being functional walking capacity! Nonetheless, with the simple intervention of regular walking, an improvement in functional capacity was seen over a mean of 51 days prior to surgery.\(^93\)

The authors felt that this finding justified the use of walking as the preferential form of prehabilitative exercise, however, given the moderate improvement, felt that more study was required. A further study, with the implementation of nutritional counselling, protein supplementation and anxiety reduction, in addition to the walking exercise regime identified a further improvement. This pilot study showed that, with the addition of the three extra elements, further improvements were identified in walking capacity pre and post operatively. No difference was identified in post-operative complications, length of stay and quality of life.\(^94\) In view of the findings, the authors have commenced a randomized clinical trial,\(^95\) the results of which will provide for interesting reading. In the interim, given the simplicity of intervention, it stands to reason that encouraging patients to exercise regularly in the form of walking prior to elective colorectal surgery, should be undertaken, and consideration be given also for formalised prehabilitation programs in colorectal units.

PRE-OPERATIVE NUTRITION-/IMMUNONUTRITION

Pre-operative malnutrition, including its consequences, identification and treatment has been covered previously under the chapter medical optimisation. This topic deals with nutritional aspects to improve outcomes in the well-nourished patient.

While there is level 1 evidence that pre-operative nutritional support improves outcomes in patients about to undergo gastrointestinal surgery,\(^96\) this benefit is less established for those patients without malnutrition. The literature is somewhat biased, but suggests that hyperalimentation with immunonutritional supplements results in improved outcomes following gastrointestinal surgery.\(^97\) A meta-analysis of all randomised clinical trials evaluating immunonutrition identified 21 RCTs enrolling a total of 2730 patients. Immunonutrition reduced complications when used before
surgery (OR 0.48 ; 95% CI 0.34 to 0.69), without a reduction in mortality. Post-operative infection (OR 0.36 ; 95% CI 0.24 to 0.56) and length of hospital stay (mean difference -2.12 ; 95% CI -2.97 to -1.26) were reduced in patients taking pre-operative immunonutrition.97

The term, immunonutrition, was coined following the realisation that ingestion of certain compounds had the ability to influence the immune system, to the extent that both healthy growth as well as recovery from illness, surgery and trauma, could be influenced by nutritional intake. The term has historically been used in the context of Glutamine and Arginine supplementation98-99, but additional studies into the role of free fatty acids100 and nucleotides101 has resulted in an increased awareness of the role these substances have in improving tissue repair, growth, immune response, gastrointestinal circulation and reduced susceptibility to infection.

The major problems with evaluating the impact of immunonutrition are the ability to detect how much of a clinical effect it has on the well-nourished patient, as well as the difficulty knowing which, if any, component of the formula is responsible for any such clinical effect. The other key confounder is the influence and potential bias resulting from the fact that most trials have used the one formulation (Impact®, Nestle).

The available colorectal literature on immunonutrition is somewhat lacking in comparison with other forms of surgery. Of the 21 RCTs mentioned in the above meta-analysis, only two were performed in a colorectal setting only.97 One trial, consisting of 28 patients (14 control, 14 immunonutrition: Arginine, omega-3 fatty acids and RNA), identified improved immunological function (increased CD4 lymphocyte counts) in the intervention group, but no difference in any clinical outcome studied (infection, GI function).102 The other, much larger trial, consisting of 200 patients evenly randomized into four groups (no supplementation, pre-operative standard nutritional formula, pre-operative immunonutrition, pre- and post-operative immunonutrition), revealed that the groups receiving immunonutrition had significantly less post-operative infection (10% vs 30%; p<0.04), as well as an improvement in gut oxygenation and microperfusion, and improved phagocytic ability of polymorphonuclear cells.103 Another more recent trial has hinted at the potential oncological benefit of
immunonutrition. Caglayan and colleagues studied the effect of four different nutritional regimes: normal nutrition, standard enteral nutrition, total parenteral nutrition and immunonutrition, on tumour infiltrative lymphocytes. Although a relatively small study (n=28), the groups given extra nutrition showed significant increases in the tumour infiltrative lymphocytes CD4+ and CD8+. The group receiving immunonutrition had the highest rates of CD8+ tumour infiltration (p=0.01). While data regarding immunonutrition appears promising from a gastrointestinal and colorectal perspective, the factors mentioned make it difficult to interpret. Given the outcomes and the relative safety and low cost (five days Impact® Nestle, three times a day at approximately Au$ 60), one could make a valid argument for its regular use in well-nourished patients, with a view to relying on more research to identify which components are important and which patients stand to benefit the most.

SYNBIOTICS

The term, probiotics, refers to viable microorganisms that can be ingested and exert positive effects within the gastrointestinal tract. Prebiotics are those ingredients that are not microorganisms, but when ingested, change the intestinal microflora and result in a positive health effect. Synbiotics refers to nutritional supplements that contain both probiotics and prebiotics in a form of synergism, once again with the net result of a healthy outcome to the host. The concept of the use of these substances in GI surgery is that they may have beneficial effects on the immune system by attenuating the systemic post-operative inflammatory response, and likely reducing post-operative infectious complications by maintaining a ‘healthy’ intestinal microflora. An RCT comparing synbiotics in two different forms, to pre-operative bowel preparation in elective colorectal surgery, found significantly higher Interleukin 6 (IL-6) and fibrinogen levels following surgery in the patients receiving synbiotics. Another trial, conducted in the elderly population (>70 years of age) undergoing gastroenterological surgery, identified improvements in the faecal levels of Bifidobacterium and Lactobacillus, with associated decreased faecal
levels of Enterobacteriaceae, Staphylococcus and Pseudomonas. They also found increased levels of total organic acid and short chain fatty acid levels in the faecal matter of patients receiving synbiotics, whose faecal matter was also more acidic. There were less infectious complications in the group receiving synbiotics (12% vs 36%): however this failed to reach significance (p=0.06).107 A meta-analysis of combined probiotic and symbiotic use in elective surgery (13 RCTs, 962 patients) did, however, identify a reduction in sepsis overall in the group of patients receiving intervention. The incidence of sepsis was at least halved (OR 0.42; 95% CI 0.23 to 0.75: p=0.003) in the probiotic intervention groups, and maybe even with more effect when synbiotics were analysed (OR 0.25; 95% CI 0.1 to 0.6: p=0.002). Synbiotics also reduced the extent of post-operative antibiotic usage, according to this meta-analysis.108 Another meta-analysis on the subject, however, was less positive, identifying 15 clinical trials assessing prebiotics, probiotics and synbiotics. It found 10 of these trials showed a reduction in bacterial infection rates in the intervention groups, but five showed no difference in infections, one of which even showed an increase in mortality in the symbiotic arm.109 The final word on the use of synbiotics in colorectal surgery belongs to Peitsidou et al: “despite the positive results and plethora of agents, bacterial combinations and concentrations, the inconsistency in administration, the inhomogeneity of comparison groups and lack of stringent clinical endpoints remain obstacles in the effort to establish a definitive clinical strategy at this time”.110 It is quite clear that more definitive research is required in this area in order to establish any clinical value related to synbiotics, and their routine use can not be recommended at this stage.

CARBOHYDRATE LOADING

A significant change has occurred in the way pre-operative patients are managed, with regard to pre-operative fasting over the last decade. It used to be considered standard to fast patients for an operation from midnight the night before, in order to minimise aspiration risk.111 This routine pre-operative practice has been questioned for some time, but for the last decade, level1 evidence has shown it to be an unnecessary
practice. Most anaesthetic guidelines, including the Australian and New Zealand College of Anaesthetists, recommend a fasting time of six hours for solid food and two hours for liquids, prior to anaesthesia.

This change in practice, with respect to increased knowledge of aspiration risk, has resulted in patients being better prepared physiologically for the insult of surgery. Prolonged fasting results in a more catabolic state, which has significant consequences for patients undergoing surgery. Catabolism results in protein breakdown and relative insulin resistance, and while it is most often a secondary response to the surgical state of trauma, via the endogenous hormones: cortisol, glucagon, cytokines and catecholamines, the catabolic state can result in significant harm if already present at the commencement of the surgical process.

In order to minimise this state of catabolism, the concept of carbohydrate loading, already a widespread practice in competitive athletics and endurance sports, has been adapted for colorectal surgery. In the new-found knowledge that minimising fasting times is safe, and particularly so for fluids, energy rich liquids have been given as close as possible to the surgical ‘insult’, in order to maximise recovery and minimise complications following surgery.

Clinical trials have shown improvements in grip strength, muscle mass, whole body protein balance, and length of stay post-operatively, with associated reductions in time to return of gut function, insulin resistance, glucose levels, hunger, thirst and even anxiety levels.

Despite evidence existing for the beneficial effects of carbohydrate loading, most of these outcome measurements are either heterogenous in nature, or are representative of a surrogate outcome. In addition the individual trials contain small numbers, and most are of poor quality. A recent meta-analysis, identifying seven randomised clinical trials in the colorectal literature, consisting of 585 patients, revealed only significant differences in insulin and glucose levels in the first 24 hours following surgery, with no advantage seen in other clinical outcomes with pooled analysis. Quite clearly, more trials are required if a clinical advantage associated with these biochemical hormonal changes is to be teased out. Until that stage,
carbohydrate loading appears to remain a safe and simple intervention, with logical, yet unproven, improvements in clinical outcomes.

**MECHANICAL BOWEL PREPARATION**

Mechanical Bowel Preparation (MBP) has been used by colorectal surgeons for over 40 years now, and has traditionally been considered an agent to prevent anastomotic leakage. The theoretical advantage of MBP is that it cleans the colon of solid stool, thereby reducing overall bacterial count, spillage of faecal material, contamination of the wound and anastomotic leakage. This theoretical advantage was initially questioned by Irving in 1987, and has been questioned in greater detail following this publication. The reality of MBP is that it causes a great degree of patient discomfort, causes fluid and electrolyte abnormalities, has been associated with cardiac arrhythmias and death, results in a disequilibrium in anabolic to catabolic state and its safe use pre-operatively, often involves pre-operative hospital admission with intravenous fluid administration (with subsequent increase in hospital stay and infection).

A large volume of literature exists on the topic of MBP in the setting of elective colorectal surgery. Willie-Jorgensen et al initially performed a meta-analysis of the available randomised trials (nine trials involving 1592 patients) in 2003, and concluded that there is evidence that intervention with bowel preparation is associated with an increased rate of anastomotic leakage and wound complications. Since this meta-analysis, Contant et al have performed a multicentre trial involving 1431 patients undergoing elective colorectal surgery, comparing MBP with no bowel preparation. They found no difference in the rate of anastomotic leakage and concluded that mechanical bowel preparation before elective colorectal surgery can safely be abandoned. The fourth update of the Cochrane Review on ‘Mechanical bowel preparation for elective colorectal surgery’ now includes 18 RCTs with 5805 participants. This systematic review revealed no difference in anastomotic leakage between MBP (4.4%) and no MBP (4.5%), Peto OR 0.99 (95% CI 0.74 to 1.31). The
review also looked at wound infection, identifying no difference in this outcome: MBP (9.6%) vs no MBP (8.5%), Peto OR 1.16 (95%CI 0.95 to 1.42).124

Until recently, the major unresolved question regarding MBP was its role in rectal surgery where proximal ‘defunctioning’ is performed with stomas. The practical issues here are that a faecal stream is diverted proximally, and this does not appear to make logical sense if a loaded colon is left distal to the diversion. There is less data regarding MBP in this situation, and it is fair to say that most colorectal surgeons still use MBP for rectal resections, particularly where they plan to defunction with a stoma. This issue is addressed in the latest Cochrane Review, however, where a comparison was performed for low anterior resection, indicating no difference in leak rates between MBP (8.8%) and no MBP (10.3%), Peto OR 0.88 (95% CI 0.55 to 1.40). Numbers remain small in this comparison group (846) compared to the overall group, and perhaps more data is still required for this group of patients.124

A number of proponents of laparoscopic colorectal surgery propose MBP for two main reasons. The first is the concern that laparoscopic bowel graspers may cause increased trauma if the colon is faecally loaded, while the second is that small lesions may be missed in the laparoscopic approach, where palpation is not possible. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines for laparoscopic resection of curable colon and rectal cancer,125 recommend that: “mechanical bowel preparation be used routinely for laparoscopic colorectal surgery, in order to facilitate manipulation of the bowel and intra-operative colonoscopy when needed”. This is despite no reference in their guidelines to suggest bowel manipulation is easier or safer in the presence of MBP. Indeed, this author can find no scientific articles to support the subjective view that manipulation is safer, or indeed easier, with MBP. The concern regarding the inability to locate small lesions at laparoscopy, appears more valid, but is countered by the concept of colonic tattooing, performed at initial colonoscopy. This transmural, permanent, sterile, injectable tattooing technique has been described, in order to locate the lesion at the time of laparoscopic surgery. It appears to be a relatively safe technique using inert carbon, sterilised and injected submucosally at colonoscopy.126-127 Despite the description and widespread application of the technique, concern exists about its accuracy. However, if performed
carefully, by injection in the submucosal plane, and in a circumferential fashion, this can be an accurate technique. The author has personal experience with over 100 cases of laparoscopic resection involving small lesions that have been tattooed at the time of initial colonoscopy. All patients had no pre-operative MBP and accurate visualisation with segmental resection was possible, indicating the accuracy of this technique when performed carefully.

The emerging techniques involving further minimising laparoscopic colorectal surgery probably provide the best reason to give MBP. Natural Orifice Transluminal Endoscopic Surgery (NOTES) is a promising emerging technique in colorectal surgery, potentially minimising surgical impact by avoiding abdominal incisions and performing resection through the rectum. Extraction techniques have also been described through the open rectum as well, in order to minimise the size of abdominal incisions. To facilitate this MBP is obviously required.

Excluding these techniques, the scientific rationale for avoiding MBP in colonic surgery is overwhelming, and most ERAS programs involve the omission of bowel preparation. The additional practical aspect of withholding MBP is that adequate nutritional intake and carbohydrate loading, leading up until the time of surgery, can also be performed without compromise.

NO PREMEDICATION

It appears standard for most reviews on ERAS to state that premedication should be avoided prior to colorectal surgery. The intended aim is to avoid long-acting sedating agents that may impair post-operative psychomotor recovery and delay discharge. The origins of this theory appear shrouded and may have partly arisen out of the concern surrounding opiates and their effect on recovery. None-the-less, even the Consensus Review of Optimal Peri-operative Care in Colorectal Surgery, written by the ERAS Group from Europe, state that: “Patients should not receive medications known to cause long-term sedation, from midnight prior to surgery. Short-acting medications given to facilitate insertion of epidural catheter are acceptable”.

This is ranked as
Grade A evidence within the review article: however, there is a Cochrane Review on the use of premedication for anxiety in adult day surgery, that includes 17 studies revealing no evidence of impaired outcome associated with premedication. Seven of these studies looked at time to discharge, with no difference in time to discharge between patients receiving premedication or placebo. Eleven of 17 studies assessed psychomotor function: three studies showed no impairment in function with premedication, six studies showed some impairment, while two showed significant impairment.  

Given these findings, it would appear reasonable to adopt the minimal approach of avoiding anxiolytic premedication when possible: however, in patients with excessive anxiety requiring surgery, it appears that a premedication is a safe intervention with minimal effect on outcome.

THROMBOEMBOLIC PROPHYLAXIS

One of the most feared complications following on from any form of surgery is the development of Deep Vein Thrombosis (DVT), or its sinister sequel, Pulmonary Embolus (PE). The annual incidence of Venous Thromboembolism (VTE) in Australia is estimated at 0.83 per 1000 residents, and therefore affects approximately 17,000 people annually. Thirty day mortality following VTE is high: approximately 6% for DVT alone and 12% for PE. Long-term survival is also significantly impaired following VTE, with five year survival of approximately 50% and, unsurprisingly, VTE is also a major reason for inhospital mortality, accounting for approximately 10% of hospital deaths.

Post-surgical VTE accounts for approximately 50% of all VTE treatment episodes, and with both surgery and cancer increasing a patient’s risk of VTE, patients undergoing surgery for colorectal cancer represent a high risk group, perhaps second only to joint replacement surgery patients. Even with thromboembolic prophylaxis, the incidence of symptomatic VTE after diagnosis of colorectal cancer remains high, approximately 3.1% over a two year period, and this figure increases to approximately 25% in
patients with a diagnosis of cancer undergoing major abdominal surgery without prophylaxis.\textsuperscript{134}

There are a number of methods available to decrease the risk of VTE associated with colorectal cancer, and its associated surgery. These include: diagnosing the cancer at an early and curable stage, minimising or treating patients’ comorbidities, operating with intent to cure,\textsuperscript{135} minimising the impact of surgical intervention, mobilising patients quickly after surgery, ensuring adequate hydration peri-operatively, and using mechanical and chemical methods of thromboembolic prophylaxis.\textsuperscript{135-137}

Mechanical methods used for thromboembolic prophylaxis include: compression stockings, sequential calf and thigh compression devices and electrical stimulation devices. Generally, chemical thromboembolic prophylaxis consists of injectable forms of either unfractionated heparin or low molecular weight heparin, although aspirin has been used, and more recently, oral forms of anti-factor X have been trialled with some success.

There is significant research to suggest the peri-operative benefits of compression stockings and injectable unfractionated and low molecular weight heparin for patients at the time of major surgery, particularly for cancer.\textsuperscript{137} Less evidence is available to support the use of sequential compression devices and electrical stimulation devices have been mostly consigned to the historical library.

The larger question, currently, with regard to colorectal surgery, is how long to continue peri-operative treatment, and while level 1 evidence supports the continued use of ‘extended’ chemical thromboprophylaxis (post discharge therapy),\textsuperscript{138} the unknown is how long to continue therapy after discharge from hospital, with durations ranging from seven to 30 days in the published trials.

**ANTIMICROBIAL PROPHYLAXIS**

Antimicrobial prophylaxis in colorectal surgery is essential, if any reduction in Surgical Site Infection (SSI) is a desired outcome. There are multiple RCTs and meta-analyses demonstrating the efficacy of peri-operative antibiotics in reducing Superficial SSIs, or Surgical Wound Infections (SWIs), and through these studies, it has become apparent that the best form of antibiotic coverage for this form of surgery is a combination of aerobic and anaerobic antibiotics delivered in a timely fashion, without the need for
prolonged or repeated post-operative administration, delivered in both intravenous and oral forms.\textsuperscript{139-141}

The latest evidence suggests peri-operative antibiotics for colorectal surgery result in a reduction in SWIs (when compared to placebo) of 39% to 13% (RR 0.34, 95% CI 0.28 to 0.41). Adding aerobic coverage results in less SSI, when compared to anaerobic alone coverage (RR 0.44, 95% CI 0.29 to 0.68), and the addition of anaerobic coverage to aerobic cover also results in lower rates of SWI (RR 0.47, 95% CI 0.31 to 0.71). Combined oral and intravenous prophylaxis results in lower rates of SWI when compared with either intravenous alone (RR 0.56, 95% CI 0.43 to 0.74), or oral alone (RR 0.56, 95% CI 0.40 to 0.76).\textsuperscript{139}

The timing of the dose of intravenous antibiotics at surgery is important and, ideally, the peak tissue concentrations of antibiotics should coincide with the peak levels of bacteria in tissue. It appears the ideal timing is somewhat dependant on the type of antibiotic, but should be preferably no longer than one hour before surgery, and in most cases, just prior to or around incision time.\textsuperscript{142}

SKIN PREPARATION

The theory behind skin preparation at the time of surgery is that most post-operative infections originate from bacteria on the patient’s skin. It makes logical sense that reducing the overall load of bacteria on the skin surface prior to incision should reduce the overall risk of infection. Several antiseptic agents have been described for skin preparation and the ideal agent is one that is not toxic for the patient, but has maximal effect on skin organisms. The most commonly used agents are the iodophors, chlorhexidine agents and alcohol-containing products.

Iodophors penetrate the cell wall of bacteria, then oxidise and substitute the microbial contents with free iodine. They are effective against a wide range of gram positive and gram negative bacteria, fungi and viruses.\textsuperscript{143}

Chlorhexidine acts by disrupting membranes and is an effective antiseptic agent also against a wide range of gram positive and gram negative bacteria, yeasts and some viruses.\textsuperscript{143}
Alcohol agents work by denaturing the cell wall proteins of bacteria, and are active against a wide range of gram positive and gram negative bacteria.\textsuperscript{143}

The two physical methods of skin preparation are pre-operative washing, and immediate pre-operative painting.

Despite the fact that pre-operative washes have been shown to decrease the overall bacterial load on the skin surface, there is little evidence that performing this surgical ritual decreases SWIs. A recent meta-analysis, involving three randomised clinical trials and 1443 patients, showed no difference in SWIs between patients undergoing an antiseptic skin wash and a plain wash with soap and water (RR 1.02, 95% CI 0.57 to 1.84). Similar trials (four RCTs involving 7791 patients) also showed no improvement in SWIs when pre-operative chlorhexidine skin washes were compared with a placebo (RR 0.91, 95% CI 0.80 to 1.04). Even trials comparing pre-operative skin washes to no wash at all showed no reduction in SWIs (three RCTs involving 1142 patients), although low numbers and wide confidence intervals suggest more research needs to be performed before conclusions can be made (RR 0.82, 95% CI 0.26 to 2.62).\textsuperscript{144} Given the fact that chlorhexidine resistance has been described in gram positive bacteria (perhaps associated with increased chlorhexidine usage)\textsuperscript{145} and the above data, it would appear rational to suggest that simple washing with soap and water be the most sensible option for patients prior to coming into theatre.

The second method of skin preparation; pre-operative painting at the time of surgery, is unlikely to ever be compared with placebo or soap washes, given its ingrained nature in surgical tradition, in addition to the significant risk involved for patients in such a trial. There have been a number of comparative trials between the three main agents, however, suggesting that the addition of alcohol to the other two agents may be beneficial, and that perhaps chlorhexidine compounds are more beneficial than iodophors. This data is somewhat inconclusive, due to the heterogeneity of surgeries and differing concentrations of agents and application techniques. A recent meta-analysis, involving six RCTs with 5031 patients seems to indicate the superiority of chlorhexidine compounds over iodophors for clean-contaminated surgery, in reducing SWIs (RR 0.68, 95% CI 0.50 to 0.94; p=0.019).\textsuperscript{146}

The main problem with the trials in this meta-analysis is that three of the trials involve the addition of alcohol to the chlorhexidine arms, while none of the trials involve the
addition of alcohol to the iodophor arm. There is some evidence that alcohol-based iodophors may have superior infection prevention than aqueous-based iodophors for clean surgery,\textsuperscript{147,148} and extrapolating from this, it would make sense that the addition of alcohol to either chlorhexidine or iodophors could make comparison between the two compounds difficult.

The addition of alcohol to skin preparation in the operating theatre environment places the patient at risk of the very rare, but catastrophic outcome, of a flammable event. Although reports of flammable events exist,\textsuperscript{149} this should be avoided by the careful application of the preparation, allowing time for it to dry, and by avoiding pooling.\textsuperscript{150}

In light of this, there should be further investigation into a comparison of aqueous chlorhexidine and iodophors, as well as a comparison of the alcohol-based forms of both compounds. Until further research is conducted in this area, current data tends to suggest that alcohol-based chlorhexidine compounds are the agents of choice for SWI reduction in colorectal surgery, provided care is taken with the application process.

ANAESTHETIC PROTOCOL

Much of the work traditionally performed pre-operatively by the anaesthetic team has already been covered in previous sections, and is also covered under following sections regarding fluid management, hypothermia prevention and epidural placement.

The two areas that have received significant impetus regarding anaesthesia recently, with regard to colorectal surgery, are utilising short-acting anaesthetic agents and opiates, and attempting to minimise post-operative nausea and vomiting.

While there is no evidence to suggest the ideal anaesthetic protocol for colorectal surgery, it makes sense that replacing traditional long-acting anaesthetic agents and opiates with shorter-acting agents would potentially allow for more rapid post-operative recovery, particularly in view of the side effect profile of anaesthetic agents and opiates. Propofol and remifentanil have shorter duration and more rapid clearance, with less longer-term side effects than their more traditional analgesic counterparts, such as morphine and pethidine\textsuperscript{151-152} and, based on current data, are probably preferable agents.
Nitrous oxide is an anaesthetic adjunct agent that has been used for over 100 years for a variety of indications and has been avoided recently in colorectal surgery. It is a useful agent, as a result of its analgesic efficacy, safety and short-acting nature, but has fallen out of favour due to its potential to cause intestinal distension and post-operative disturbances in gut function. Most of the reason for this is based on a single, but well-performed trial, and while there has been some conflicting evidence, it is fair to say that nitrous oxide is very rarely used now in colorectal surgical anaesthetic practice.

Minimising post-operative nausea and vomiting following colorectal surgery can be difficult, due to a number of peri-operative factors. A proactive approach to this problem seems valuable, however, and there are certain risk predictors of post-operative nausea and vomiting that should be considered. Those at increased risk include females, non-smokers, those with a history of previous post-operative nausea and vomiting or motion sickness, and those that require post-operative opiates for pain. It is suggested that those with a moderate risk of post-operative nausea and vomiting (two of the above factors) should receive proactive dexamethasone or serotonin receptor antagonist at the conclusion of surgery, while those at significant risk (three or more factors) should have prophylactic dexamethasone at the commencement of surgery, along with a propofol and remifentanil-based anaesthetic, and receive additional serotonin receptor antagonist, droperidol or high dose metoclopramide prior to the conclusion of surgery. Caution needs to be taken when adopting such proactive strategies, however, as the science behind anti-emetic therapies in surgery still remains somewhat sketchy, and perhaps the best approach for post-operative nausea and vomiting, relies on techniques to minimise causation (opiate avoidance, epidurals, laparoscopic surgery), rather than counteracting them.

THORACIC EPIDURAL
Thoracic epidurals, when placed correctly at the midthoracic level, provide analgesia following colorectal surgery, but also, and possibly more importantly from an ERAS perspective, provide sympathetic blockade to the abdominal viscera post-operatively. The latter results in prevention of gut paralysis and attenuates both stress hormone release and post-operative insulin release.
Mostly, epidural blockade is continued post-operatively with a continuous infusion of local anaesthetic, often combined with adrenaline, or a low dose opiate, in order to improve efficacy, without evidence of increased complications. Thoracic epidurals are best placed while the patient is awake to reduce neurological associated complications.

There is significant data to suggest that post-operative analgesia is superior in patients receiving epidural analgesia over other forms of post-operative pain relief following abdominal surgery. They also provide an improvement in respiratory and possibly cardiac morbidity following abdominal surgery, as a result of both improved analgesia and less stress response. They do, however, come at a cost. There are rare but significant complications associated with epidurals, such as permanent neurological damage in the form of paraplegia, and even reported deaths. In view of these complications, certainly in the Australian environment, there has been a shift against the routine placement of epidurals for abdominal surgery. The MASTER epidural trial was also a major reason for this. It was an RCT of 915 ‘high risk’ patients undergoing major abdominal surgery, randomised to either epidural placement or routine post-operative analgesia. Contrary to other previous smaller trials, it revealed no difference in mortality (5.1% epidural vs 4.3% control; p=0.67), and identified a post-operative improvement in only one studied aspect of morbidity, that of respiratory morbidity. It is fair to say that following on from this trial, the routine placement of epidurals for major abdominal surgery, at least in Australia, has become a fairly rare event, with their placement being reserved for those patients at a high risk of post-operative respiratory complications.

The shift towards minimal access surgery has also been a driving force away from routine epidural placement generally. Laparoscopic colorectal surgery routinely involves less abdominal wall dermatomes than its open counterpart, and has been proven to be associated with fewer post-operative cardiac and respiratory complications. In addition, with respect to colorectal surgery, there has been concern regarding adequate perfusion to the anastomosis. Thoracic epidurals tend to result in a reduction in mean arterial pressure and changes in cardiac output. The concern is that this results in less perfusion of the anastomosis. This may be countered by the sympathetic blockade that prevents splanchnic vasoconstriction, but many ERAS
centres routinely suggest vasopressors to maintain systemic mean arterial pressures. This appears somewhat counterintuitive; an added intervention in order to counteract the effects of an intervention, but is backed by some evidence.\textsuperscript{128,164}

In view of the above concerns and the growing trend towards minimal access surgery, there has been a shift away from routine epidural placement for this group of patients, particularly in the more litigious countries (USA, Australia), where it is perceived that routine epidural placement for all colorectal surgery, particularly laparoscopic colorectal surgery, represents a form of ‘overkill’. Many designated ERAS centres in Europe still prefer the technique, however, based purely on its ability to block the sympathetic outflow and hasten more rapid return of gut function, in addition to minimising the need for opiates post-operatively. The Consensus Review on Optimal Peri-operative Care in Colorectal Surgery, conducted by the ERAS working group, has even stated that routine mid-thoracic epidural placement is a Grade A recommendation\textsuperscript{128} (a consensus recommendation based on at least two high quality RCTs or one meta-analysis of homogeneous RCTs).

Perhaps the longer term solution for post-operative, analgesia in a world of increasingly minimal access colorectal surgery, is to improve locoregional somatic blockade, and attempt to identify safer and simpler means of providing visceral blockade. The somatic blockade aspect of this will be covered in later chapters, describing two RCTs on abdominal wall blockade post-operatively, performed by this author and colleagues. The visceral blockade aspect requires more research, although interesting work by Andrew Hill and colleagues shows early promise on visceral blockade at the peritoneal level.\textsuperscript{165}

**PERI-OPERATIVE FLUID MANAGEMENT**

Much has changed with respect to peri-operative fluid management of the colorectal surgical patient over the last decade. Surgical dogma and established tradition meant that patients undergoing colorectal surgery arrived in the operating theatre having undergone an extended period of fasting, after receiving mechanical bowel preparation. They were therefore usually dehydrated, with potential electrolyte abnormalities. In addition, the physiological response to major surgical insult involves a release of hormones that includes catecholamines and anti-diuretic hormone (ADH),
resulting in renal hypoperfusion and fluid retention. In order to protect patients from renal impairment and subsequent acute renal failure, it was taught that patients should be managed with enough intravenous fluids to maintain a urine output of at least 0.5 ml/kg/hr in the early post-operative period, and a daily output of 400 mls.\textsuperscript{166-168} This resulted in large amounts of crystalloids being used for patients undergoing colorectal surgery, and while this may have had a protective effect on the kidneys, and have been tolerated by fit and healthy patients, it was potentially deleterious from a cardiac perspective. In addition, over recent times there has been a shift away from bowel preparation and a shift towards minimally-invasive surgery, as well as a concern that excessive fluid administration can adversely affect anastomotic healing.\textsuperscript{169}

A subsequent response was the concept of ‘fluid restriction’, which coincided with the emergence of ERAS programs. Lobo et al, in 2002, studied the effect of salt and water volumes on gastrointestinal recovery after colorectal surgery, and surmised that excessive salt and water intake and retention resulted in deleterious outcomes with respect to gastric emptying and length of stay.\textsuperscript{170} This was reinforced by a similar study around the same time frame, highlighting an association with complications and slower return of gastrointestinal function with increased amounts of intravenous fluids.\textsuperscript{171} Surgeons became aware of the concept of intestinal oedema, and also concerned about the potential association with this concept and anastomotic leakage. Fluid restriction subsequently became synonymous with ERAS programs, and an integral part of the early ERAS algorithm.

This swing in favour of restrictive fluid administration was probably, in part, due to the fact that patients were actually receiving too much salt and water in the form of crystalloids (mostly 0.9% NaCl), prior to the advent of ERAS, and subsequent studies did not show quite as dramatic an effect in favour of fluid restriction,\textsuperscript{172,173} highlighting what would seem a common sense approach of normovolaemia for the colorectal patient.

Multiple means of monitoring have been designed to achieve euvoalaemia in the surgical patient. The simplest of these include direct observation of heart rate, blood pressure, urine output and weight. More complex, and those more tailored towards intra-operative monitoring, include Central Venous Pressure (CVP), arterial line and Trans Oesophageal Doppler (TOD) Stroke Volume monitoring.
Goal-directed therapy refers to the tailored protocol-driven approach to changes in intra-operative cardiac output, with a view to maintaining tissue perfusion and euvolaemia. Most studies analysing the effect of this on surgical outcomes have used TODs as a means of monitoring, and adjust, either with a small fluid bolus, or with inotropes. A systematic review on the utility of goal-directed therapy has shown it to be beneficial with respect to return of gut function, length of hospital stay and less intensive care unit admissions. While goal-directed therapy has been included in many ERAS programs and is supported by British Consensus Guidelines, it remains poorly used within Australia, most likely as a result of skepticism surrounding the heterogeneity of trials and robustness of the data subsequently extracted.

In the post-operative period, such invasive forms of monitoring are obviously not possible and simpler methods, such as direct observations and daily weighs, are used. Research has shown that deleterious outcomes associated with hypervolaemia tend to occur when at least 2.5 to 3 kg weight gain occurs as a result of fluid excess. The simplest and least reactive way, it seems, to avoid this weight gain, would be a slow and steady approach, avoiding excessive boluses in response to urine output and blood pressure, and reacting slowly to daily weighs and electrolytes, with the exception of hypovolaemia associated with blood loss, where blood products should be used in any case. A number of other simple mechanisms exist in order to avoid the complication of overload, such as removing lines early, placing patients early on a post-operative diet so they can control their own fluid intake, and even avoiding post-operative urinary catheterisation.

The latter has been routinely practised by the author, with data identified showing improved outcomes associated in colectomy patients, without indwelling catheters. Although this data has been collected retrospectively in the form of a historical cohort, 208 patients undergoing colectomy without an epidural were studied. This study revealed that patients without an indwelling catheter received on average 4.6 litres less intravenous fluids than their counterparts without catheterisation over the first 5 post-operative days (10.88 litres v 6.16 litres; p<0.0001). In this study, not having an indwelling catheter also resulted in a reduction in length of stay (10.1 days with an IDC vs 5.9 days with no IDC; p=0.009), with no difference in the number of complications.
While the author suggests that monitoring, in the form of indwelling urinary catheters, should be performed in the high risk patient, their routine use post-operatively may result in more morbidity in the average post-operative colectomy. The mechanism for this is probably reactive in nature, with junior medical staff being asked to react to what is considered to be poor urine output with injudicious intravenous fluid boluses. The next shift of junior staff comes along and the exercise is repeated. Post-operative ADH release compounds the problem by causing fluid retention. Urinary catheterisation is also associated with other potential complications such as infection, and also results in decreased mobility. Early removal, and even avoidance, seems logical.

The choice of which intravenous solution to use, during and following colorectal surgery, has been a source of much debate. Much antipathy currently exists towards normal saline (0.9% sodium chloride), with some authors describing it as ‘normal saline’ or, even more disparagingly, abnormal saline. Normal saline does have its drawbacks, despite being quite possibly the worlds most frequently used form of intravenous fluid. It is isotonic, and was originally formulated as a result of this, in order to prevent intravascular red cell lysis, but it is far from a balanced replacement solution. The amount of both sodium and chloride in normal saline exceeds that found in the extracellular fluid by 10 and 50 % respectively. As a result of this, excessive use can result in hyperosmolar states, hyperchloremic acidosis, decreased perfusion states and, in particular, subsequent renal impairment. These effects do not appear to be quite as pronounced when balanced solutions, such as Ringers or Hartmanns are used. Randomised clinical trials comparing normal saline and Ringers solution have shown the latter to be superior in the peri-operative period, particularly with respect to metabolic acidosis, hyperkalaemia and the need for transfusions. Other frequently used intravenous fluid solutions are the dextrose-containing solutions, with or without hypotonic saline. These have their own problems, with hypotonia and associated hyponatraemia, a significantly frequent and dangerous post-operative problem. Various types of colloids have also been used over the years, with the theory being that these are more likely to stay longer in the intravascular space, exert more of an oncotic effect and result in better flow and, ultimately, perfusion. Despite these theoretical benefits, systematic reviews comparing colloids
and crystalloids fail to show a benefit associated with the former\textsuperscript{185,186} and, given the significant cost benefit in favour of crystalloids, these seem the logical alternative at present.

It seems almost too simplistic, and perhaps has taken the surgical community too long to work it out but, ideally, the patient undergoing colorectal surgery should receive enough of a ‘balanced’ electrolyte solution in order to maintain normovolaemia. This can be achieved intra-operatively by goal-directed therapy, and post-operatively by daily weighs, aiming for ‘zero’ fluid balance in patients that do not experience post-operative complications. Most patients should receive no more than 2-2.5 litres of fluid per day of a balanced crystalloid and, ideally, in an ERAS setting, have intravenous fluids ceased as soon as is practical, once it is suitable to use the enteral route for hydration.

LAPAROSCOPIC SURGERY

No discussion about ERAS would be complete without mention of the role of laparoscopic surgery. It is almost certainly no coincidence that the timing of the emergence of ERAS (Fast Tracking, as it was previously known) coincided with the introduction of laparoscopic colectomy, almost certainly as a result of the short hospital stays reported by the latter. Most centres reporting on Fast Tracking in its early stages, appeared fixated by reducing length of stays associated with open colorectal surgery and, in the author’s opinion, this was mostly in reaction to decreased length of stay associated with laparoscopic colectomy.

The first laparoscopic colectomy was performed by Jacobs (a right hemicolectomy) in 1991, and he and his colleagues subsequently described a series of 20 patients undergoing laparoscopic colectomy.\textsuperscript{3} A number of case series followed this,\textsuperscript{187,188} but the uptake of laparoscopic colectomy was much slower than that of laparoscopic cholecystectomy. This may have been as a result of the lessons learnt from laparoscopic cholecystectomy uptake, in terms of the complications associated with the learning curve, but probably represented a degree of concern about the possibility of port site recurrences. These port site recurrences first came to light in the literature in the 1990s and dominated discussions surrounding the technique of laparoscopic colectomy. The widespread theory behind port site metastases or recurrences, centred
around insufflation that resulted in airborne cancer cells within the peritoneal cavity, but it is also quite possible that these recurrences arose from either a vascular phenomenon or a peritoneal ‘lavage’, with the trocars being dipped into fluid-containing cancer cells.

In view of the concern regarding port site recurrences, large randomised clinical trials on the short- and long-term outcomes following laparoscopic colectomy, were constructed and performed in the major colorectal training institutions around the world. In addition to this, databases were constructed in order to identify outcomes and control volume.

Prior to the results of these, data began to emerge regarding the improved short-term outcomes associated with the laparoscopic approach for colectomy, initially from trials involving polyps, diverticular disease, inflammatory bowel disease and, subsequently, for cancer. Meta-analyses of the short-term outcomes of the large randomised clinical trials on laparoscopic colectomy have subsequently revealed improvements in a substantial number of post-operative recovery aspects of clinical care. This is in stark contrast to all other laparoscopic surgical procedures, where minimal or no benefit exists, once level 1 evidence is reviewed.

The short-term benefits of laparoscopic colectomy over its open counterpart have been rigorously investigated. Laparoscopic colectomy results in an improvement in overall morbidity compared to its open counterpart, an improvement in length of hospital stay, improved analgesia, less overall infectious complications, as well as less surgical site infections, less blood loss, faster return of gastrointestinal function and less cardiorespiratory morbidity. The only two areas in which open colectomy is superior to the laparoscopic approach is operative time and intra-abdominal complications.

The fact that laparoscopic colectomy results in smaller incision lengths than its open counterpart cannot, surely, account for all the short-term advantages seen with this approach. Keeping the patient and the gastrointestinal tract warm throughout the surgery is certainly easier with the aid of laparoscopy, and minimal bowel handling or manipulation must account for some advantage as well, both potentially resulting in a lower systemic inflammatory response.
There appears to be no difference in oncological outcomes between the two approaches, despite the initial concern about port-site metastases with laparoscopy. This concern was replaced by a short-term belief that stage 3 cancers had improved survival following laparoscopic surgery, based on a Spanish trial.\textsuperscript{11} Larger numbers and meta-analyses following on from this trial refuted this finding, however.\textsuperscript{13} There does appear to be an improvement in other non-oncological long-term outcomes with the laparoscopic approach, with less episodes of bowel obstruction and less incisional herniae.\textsuperscript{197,198}

Laparoscopic proctectomy, on the other hand, is a more technically demanding procedure than its laparoscopic counterpart of colectomy. The CLASICC trial was the first large RCT that included operations for rectal cancer in addition to colon cancer, and they found a higher rate of positive margin involvement with cancer associated with the laparoscopic approach, when subgroup analysis was performed on the rectal cancers.\textsuperscript{199} One of the major criticisms of this trial was the fact that participating surgeons did not require any prior experience with regard to pelvic dissection laparoscopically. In view of the results from this trial, the uptake of laparoscopy for rectal cancer has been slower, with the suggestion that the learning curve is longer. Trials in a similar vein to those performed for colon cancer, are currently underway to further investigate the oncological aspects of laparoscopic proctectomy for cancer, and the author is a contributor to one of these.\textsuperscript{200}

Comparisons between laparoscopic colectomy with traditional care and open colectomy with ERAS programs have been made in the form of clinical trials,\textsuperscript{201} but due to the obvious heterogeneity, it is difficult to extract much in the form of beneficial information regarding this comparison. Laparoscopic colectomy and proctectomy stands to benefit with an ERAS approach, presumably in the same proportion that its open counterpart does.\textsuperscript{202}

In summary there are numerous advantages associated with laparoscopic colectomy, over its open counterpart and this approach should be used, where possible, for colon cancer, polyps and inflammatory bowel disease, while caution should be employed with rectal cancer until the results of further studies are available.

MINIMAL AND TRANSVERSE INCISIONS
Most ERAS programs blithely add the item of ‘minimal and transverse incisions’ to their list of ERAS steps, without, it would seem, due thought. ‘Minimal’ and ‘transverse’ probably need to be considered as separate components, and will be addressed so here.

It seems absurd that there is a need to consider minimising incision length in this day and age, but it bears reminding that surgical folklore used to suggest that the larger incision, the better the surgery (or surgeon!): “large mistakes are made through small incisions” and, “large incision large surgeon, small incision small surgeon”. While virtually no scientific clinical studies appear on the topic of minimising incision length (and this author does not believe these are required), it would seem logical that the correct length of incision is one that is only just large enough to permit safe operative access.

Transverse incisions, on the other hand, appear to provide patients with an early postoperative advantage. Although numbers are relatively small, there are five RCTs (n=263) that have assessed pulmonary function following abdominal surgery, comparing midline versus transverse incisions, with minor improvements, in favour of the transverse approach. Vital Capacity (VC) appears to improve by about 7-8% (Day 1: effect size 8.08, 95% CI: 5.06 to 11.10, Day 7: effect size 7.10, 95% CI: 3.21 to 10.99) with transverse incision, while similar advantages are seen in forced expiratory volume in one second (FEV1) with transverse incisions (Day 1: effect size 7.27, 95% CI: 2.90 to 11.64, last recorded day: effect size 9.97, 95% CI: 3.46 to 16.48). Lower rates of wound dehiscence are also seen with transverse incisions with eight RCTs (n=1793) comparing transverse and midline incisions, reporting a reduction in dehiscence of 45% associated with the transverse approach (OR 0.55, 95% CI: 0.25 to 1.20), as well as a reduction in incisional hernias at longer-term follow up (OR 0.49, 95% CI: 0.30 to 0.79). Analgesic use may also be slightly reduced with a transverse incision, but this outcome is difficult to assess based on the heterogeneity of studies, and length of hospital stay does not appear to differ based on the different incision types. Perhaps the technical aspect not well addressed in studies assessing transverse incisions is the difficulty reoperating and placing stomas in patients that require intervention for anastomotic leaks although, fortunately, this represents a small proportion of the colorectal surgical population.
In view of these findings, it would seem reasonable to offer a transverse incision as the superior alternative for recovery, providing access was not compromised, and the incision would not interfere with functional aspects of outcome, such as stoma siting and formation.

PERI-OPERATIVE HIGH OXYGEN CONCENTRATIONS

The role of peri-operative oxygen administered in high concentrations for patients undergoing colorectal surgery is rather controversial. The main underlying philosophy of high flow or high concentration oxygen around the time of surgery is to decrease infection rates, in particular surgical site infection, by improving the oxidative killing of bacteria by neutrophils, which are dependent on tissue oxygen partial pressure for their action.204 Another potential reason is that blood flow and angiogenesis is improved by a high partial pressure of oxygen, while higher oxygen tension has been shown to correlate with increased collagen deposition and tensile strength.205 The latter has particularly important implications in colorectal surgery, with respect to anastomotic healing and minimisation of anastomotic leak rates.

The first large trial to analyse high concentration and flow of oxygen in colorectal surgery revealed a dramatic reduction in surgical site infection, associated with higher oxygen administration. This trial, involving 500 patients undergoing colorectal surgery, performed in Austria and published in 2000, revealed a reduction in surgical site infection from 11.2% down to 5.2%, when 80% oxygen was used intra-operatively, compared with 30% oxygen.206 A subsequent trial, performed in Spain on 291 colorectal patients, revealed similar outcomes, with a reduction in surgical site infection from 25% to 11.3% when 80% oxygen was used, compared with 35%.207 The largest trial, to date, did not find similar outcomes, however. The PROXI randomised clinical trial out of Denmark assigned 1400 patients undergoing laparotomy to receive either 80% or 30% oxygen during and for two hours after surgery. They found no difference in the outcomes of surgical site infection, respiratory morbidity or mortality, between the two groups.208

Meta-analyses209-212 of all trials combined, looking at outcomes after abdominal surgery (eight RCTs, involving 4740 patients) are also quite confusing, with slightly differing outcomes, depending on whether fixed or random effects models were used.
The results indicate a surgical site infection rate of 15.5%, when supplemental oxygen is used versus 17.5% in the control arm. When a fixed effect model is used, this result is significantly in favour of supplemental oxygen (OR 0.84, 95% CI: 0.73 to 0.97), but when random effects are used, the significance disappears (OR 0.84, 95% CI: 0.61 to 1.16). The subgroup analysis of colorectal patients reveals virtually identical results. In view of the controversial nature of these outcomes, there has been a Bayesian meta-analysis performed, and this reveals a moderately high probability of a real but small clinical benefit in favour of supplemental oxygen when used for reducing surgical site infection in colorectal surgery.\textsuperscript{213} It appears unlikely that there is a large benefit associated with supplemental oxygen particularly given the heterogeneous nature of studies, implying the random effects model is more appropriate.

There is however reasonable laboratory evidence for supplemental oxygen. Oxygen tension has been shown in the animal model to correlate well with tissue healing and anastomotic strength. Hyperbaric oxygen has been shown to increase anastomotic bursting strength in rats and, conversely, hypoxia has been shown to result in inferior outcomes with respect to anastomotic healing in the animal model.\textsuperscript{214} It stands to reason that in any case of intra-operative hypoxia, the gastrointestinal tract is one of the first affected organs, and prevention of gastrointestinal ischaemia is essential in minimising anastomotic leakage. The only study that this author is aware of, addressing this issue in humans, was a Spanish trial assessing tonometry of the gastrointestinal tract,\textsuperscript{215} with a comparison between 30% and 80% intra- and post-operative oxygen. They identified lower gastrointestinal pH readings and higher pCO\textsubscript{2} readings in the patients given lower levels of oxygen, highlighting decreased gastrointestinal oxygen perfusion in this group.

The concern with high FiO\textsubscript{2} is that of absorption atelectasis, that occurs as a result of derecruitment. This occurs more frequently with higher oxygen levels, but can be potentially minimised with increase positive end-expiratory pressure.\textsuperscript{216} It appears that this concern is probably unjustified, however, given the findings from the large trials\textsuperscript{208} and subsequent meta-analyses\textsuperscript{209-212} of supplemental oxygen, at least when 80% FiO\textsubscript{2} is used.

Given the safety of supplemental oxygen seen in large numbers, combined with the probable small clinical benefit, in terms of surgical site infection reduction, as well as
the potential improvement in anastomotic healing, it seems logical to use high FiO₂. The existing data would suggest that the routine use of 80% intra-operative oxygen combined with post-operative high flow oxygen for two to six hours, be the standard of care, but further large, high quality studies are required to investigate the clinical effect on anastomotic healing.

PREVENTION OF HYPOTHERMIA

General anaesthesia affects the thermoregulatory centre in the hypothalamus, altering the ability of the body to maintain its physiological core temperature. The net result is that hypothermia is a very common outcome following surgery.²¹⁷ Added to this is the effect an open abdomen has on core body temperature, with exposure of a large surface area (the gastrointestinal tract and peritoneum) to an environment that is rarely as warm as body temperature.²¹⁸

Hypothermia produces a number of deleterious outcomes for the patient, in that it affects almost all areas of homeostasis. It can result in increased risk of: surgical site infections, bleeding, the need for transfusion, post-operative pain, and cardiac morbidity.²¹⁹ It goes without saying that the maintenance of normothermia is, therefore, of paramount importance during all forms of surgery, particularly colorectal surgery, where infection rates are high, cardiac morbidity is not insignificant given the age group undergoing surgery, and anastomotic integrity relies upon haemostasis and avoidance of regulatory disturbance.

There are a number of intra-operative methods to maintain normothermia. This begins even in the pre-operative stage, where there is evidence that pre-operative warming of the patient results in less temperature disturbance. This has been achieved in trials looking at skin surface warming with forced air warmers, where there is less reduction in core temperature drops intra-operatively when forced air warmers have been used both pre- and intra-operatively and compared with intra-operative use alone.²²⁰,²²¹

There are a number of simple methods that can be overlooked in a busy operating schedule when attempting to maintain normothermia in the surgical patient. The first is to raise the ambient temperature as much as possible (or, indeed, bearable for the operating team), while others include minimising the duration of anaesthesia and surgery by forward-planning and avoiding delays (equipment and staff checks),
minimising the incision size, minimising fluid and blood loss, avoiding cold fluids for lavage, and keeping the bowel within the abdominal cavity, where possible. Laparoscopic surgery has many advantages over its open counterpart and avoidance of hypothermia is yet another benefit with this form of surgery, but the same methods to minimise hypothermia should be employed, and active warming in the laparoscopic patient should not be overlooked. The addition of heated gas is considered standard now for most laparoscopic insufflation devices: however, despite the logic behind this, it still remains unproven, as has the addition of humidification to the same systems. Another logical, yet unproven advantage of laparoscopic surgery is the creation of minimal access platforms: for example single incision laparoscopic surgery (SILS) ports, that further maximise the available surface area for skin warming.

It was initially felt that intravenous fluid warming devices had the ability to warm patients up who were hypothermic, and while this is probably not the case, they do have the potential to minimise the development of hypothermia intra-operatively, and their routine use should be considered. Forced air warming systems are not just useful for pre-operative warming and should be used for the duration of surgery and well into the recovery period. Not only have they been shown to minimise the reduction in core temperature, they also improve clinical outcomes such as wound-related complications, earlier tolerance of diet, shorter length of hospital stay and cardiac morbidity. One of the concepts that appears to have been lost on surgeons over the ages is that of conduction versus convention as a method of heat transfer. Most scuba divers and seafarers are aware that the loss of heat is far more rapid (up to 30 times faster) when a body is submersed in water than when it is exposed to surrounding air of the same temperature. Minimising exposure to liquids that are at room temperature during surgery should be mandatory and this includes the old tradition of ‘soaked’ sponges to assist with bowel retraction. This concept of convection versus conduction has been put to the test in a clinical trial out of Tokyo, comparing circulating heated liquid with both forced hot air and a carbon-fibre resistive heating cover, as a means to keep surgical patients warm. In a three-armed trial, it was found that core temperature decreased less in the heated circulating water arm than in either of the other two
arms. While this appears to be ‘one for the future’, the current cost and potential electrical hazards limit it to the research ‘basket’ at present. While forced hot air systems remain efficacious and cost-effective, they should be considered the standard of care for the colorectal surgical patient. Their use should commence approximately one hour before surgery, continue intra-operatively while covering as much surface area as is surgically feasible, and continue in recovery until ward transfer is appropriate.

AVOIDANCE OF ROUTINE PERITONEAL DRAINAGE

The rationale for routine peritoneal drainage in the presence of a gastrointestinal anastomosis was to drain fluid collections that were potentially harmful to the patient (or to the anastomosis), or to detect if enteric fluid was present, thereby alerting the surgeon to an early anastomotic dehiscence. Billroth was a champion for the cause of routine drainage back in the late 19th century and it continued as standard practice for decades.

Over the last two to three decades, this practice has slowly changed as more data has emerged confirming either non-inferiority or superiority of a no-drainage policy for almost all forms of gastrointestinal surgery. Colorectal surgery is no exception, with a Cochrane meta-analysis performed in 2004 (six RCTs, 1140 patients), revealing no difference in mortality (3% no drain vs 4% with drain), clinical anastomotic leak rate (2% vs 1%), radiological anastomotic leak rate (3% vs 4%), wound infection (5% vs 5%), reintervention (6% vs 5%), and extra-abdominal complications (7% vs 6%). In addition to a lack of ability to reduce complications, drainage also does not seem to achieve its other aim of alerting the surgeon to anastomotic leakage, with only one in 20 patients with anastomotic leakage having evidence of leakage in the drain (purulent or enteric contents).

For some time now this data has been accepted for intraperitoneal anastomoses, and the widespread practice now is to avoid routine drainage for these anastomoses. Extraperitoneal, or pelvic anastomoses, however, have been thought to represent a different scenario. Low pelvic anastomoses have a higher leak rate, and a total mesorectal excision of the rectum also leaves a large raw surface on the side walls of the pelvis. This raw surface, like many other surgical dissection surfaces of its type, is
associated with the production of serous and lymphatic fluid, as well as blood. The anastomosis in the pelvis is also usually well-contained by the confines of the pelvic wall which, in theory at least, makes for easier drainage of a collection or enteric leak. Many surgeons have also postulated that collections confined within this space are likely to cause a ‘pressure’ effect on the anastomosis, and potentially burst through the suture or staple line. All these theories appear logical and sound and, until recently, drainage of extraperitoneal anastomoses was considered standard care.

This standard of care appeared to be supported by the Dutch total mesorectal excision trial involving 924 patients undergoing rectal cancer surgery, randomised to either pre-operative radiotherapy followed by surgery, or surgery alone. An analysis of anastomotic leak rates in this trial revealed a 9.6% anastomotic leak rate in patients with pelvic drains, and a staggering 23.5% leak rate without drains, in addition to a significantly higher reoperation rate in the group without drains. These results were obviously seen to favour the routine use of drainage: however, not being a randomised trial, with the placement of drains being left up to surgical decision, in addition to the fact that defunctioning was also performed at surgical discretion, the results need to be interpreted with some caution.

The recent randomised clinical evidence does not seem to back up the findings of the Dutch trial, however, which is probably unsurprising in the light of other data regarding drains. The French Association for Surgical Research, headed by Merad, was the first large scale RCT assessing pelvic drainage for rectal anastomoses. It randomised 494 patients to drainage (248) or no drainage (246), and found no difference in overall leak rate (6.8% with drainage vs 6.0% without drainage), mortality (eight patients with drainage vs 10 without drainage), mortality from leak (three with drainage vs two without drainage) or reoperations for leakage (11 with drainage vs four without drainage). This finding is supported by two smaller RCTs (n=100, n=60), with the same findings. No meta-analysis has been performed solely on the role of routine pelvic drainage for extraperitoneal anastomoses.

The debate about whether drains are useful or not in pelvic anastomoses, also centres around the type of drain used and the duration of drainage. Proponents of drainage in order to prevent fluid accumulation argue for a short duration of drainage, which has been poorly studied. Proponents of large bore suction/irrigation drains argue that they
may minimise complications of a leak, despite the fact that it appears these drains may be associated with a higher leak rate as a result of their bulky and rigid structure. Proponents against drainage argue that drains are associated with increased rates of infections and complications (pain, trocar injuries, misplacement, enteric and vascular trauma) and inhibit mobility. This population of surgeons maintains that, in order for drainage to be considered routine, there must be strong evidence that they reduce anastomotic leak-related complications.

Certainly the debate over pelvic drainage will continue until a large-scale trial using modern, safe, low-level suction for a short duration, is performed. It is the authors practice to ‘first do no harm’, and not routinely place drains for pelvic anastomoses, with a view to having the level of equipoise to participate in a high quality trial on this topic. With regard to anastomoses above the pelvic brim, there can be no debate: routine drain placement is unjustified and should not be performed.

AVOIDANCE OF ROUTINE NASOGASTRIC TUBES

Like drains, the routine placement of nasogastric tubes has long been a traditional aspect of colorectal surgery. There have been many potential reasons touted for the routine placement of nasogastric tubes following colorectal surgery. These include: the prevention of post-operative ileus, the decompression of a distended stomach, prevention of vomiting, minimising anastomotic leakage due to upstream decompression, and minimising early wound dehiscence and hernia formation by abdominal decompression. With so many potential reasons, it is no wonder that an old surgical consultant’s adage was: “I’d rather have a resident with a nasogastric tube in their pocket than a stethoscope”.

The counter arguments against routine nasogastric tube placement include: the potential for significant harm during placement, irritative rhinitis and pharyngitis, increased gastric distension due to impaired swallowing, respiratory complications, significant discomfort, and the fact that a number of tubes need to be placed in asymptomatic patients, in order to treat that patient that may benefit.

Studies suggesting that nasogastric tubes may not be as beneficial as they were first thought to be, began to emerge in the late 1970s. The first meta-analysis on the subject was performed in 1995 (26 trials with 3964 patients), and this revealed a
higher rate of respiratory complications associated with routine nasogastric tubes after laparotomy. In addition this meta-analysis calculated that at least 20 nasogastric tubes needed to be inserted at the time of elective abdominal surgery, in order to treat one patient thought to require one based on postoperative symptoms.\textsuperscript{240} Subsequent larger meta-analyses have confirmed the finding that routine nasogastric tube placement was unnecessary. The latest meta-analysis from the Cochrane collaboration on the routine use of nasogastric tubes after abdominal operations performed in 2007, revealed 37 RCTs on the subject, comprising 5711 patients.\textsuperscript{242} They identified that patients having routine tube placement had an increase in pulmonary complications (RR 1.45: 95% CI 1.10 to 1.92; \( p=0.008 \)) and a slower return of gastrointestinal function (MD 0.51: 95% CI 0.45 to 0.56; \( p<0.00001 \)). This was countered by a decreased rate of vomiting (OR 0.64: 95% CI 0.46 to 0.90; \( p=0.011 \)), while there was no difference seen in anastomotic leak rate (\( p=0.70 \)), wound infection (\( p=0.39 \)), ventral herniation (\( p=0.09 \)), and length of hospital stay (\( p=0.26 \)). No analysis was performed on the level of discomfort caused by the tubes, but one only has to ask a patient who has had a nasogastric tube inserted in order to determine the answer! Interestingly, out of 2866 tubes placed in the context of this meta-analysis, there was not a single adverse event reported, related to direct trauma from tube insertion, although it must be pointed out that most tubes were inserted in the anaesthetised patient.

A separate analysis was performed on colorectal surgery in this review (five RCTs comprising 873 patients), with very similar findings: a slower return of gastrointestinal function associated with routine nasogastric tube placement (MD 0.47: 95% CI 0.07 to 0.87; \( p=0.02 \)), a trend towards increased pulmonary complications (OR 1.93: 95% CI 0.56 to 6.63; \( p=0.30 \)) and no difference in anastomotic leakage (OR 1.13: 95% CI 0.46 to 2.74; \( p=0.79 \)).\textsuperscript{242} Based on these outcomes, there can be no debate that the placement of nasogastric tubes should not be performed routinely in the elective colorectal surgical patient. Given the poorer outcomes associated with elective placement of nasogastric tubes, there needs to be research performed on whether or not they are actually beneficial for the patient with a post-operative ileus or bowel obstruction. It is extremely unlikely that they will hasten the recovery from either ileus or obstruction, given the findings
that they retard gastrointestinal function in the elective setting. This is despite the widespread theory amongst gastrointestinal surgeons that they are beneficial in terms of treatment for those two conditions. The main question, therefore, that needs to be posed for further research is: does placement of a nasogastric tube decrease aspiration risk in the patient with an ileus or obstruction? It may be that for the post-operative patient with a distended stomach, significant pain requiring opiates, and a potential for decreased level of consciousness, a nasogastric tube is beneficial, while for the alert, healthy patient with recurrent small bowel obstruction, or post-operative ileus in the presence of a non-distended stomach, a nasogastric tube does more harm than good. In the ERAS setting, nasogastric tubes should be avoided.

**OPIATE AVOIDANCE**

Opiates have been the mainstay of analgesia during and following major abdominal surgery for decades now. Despite the concern that exists regarding their ‘addictive capacity’, they are extremely effective at abolishing pain perception, by their action on the opiate receptors: delta, kappa and mu. The patient controlled analgesic (PCA) device has been the most widespread mechanism for post-operative opiate delivery since its inception in the early 1970s, and it has been shown to be the safest and most effective form of post-operative opioid delivery. The main concern regarding the use of opiates in colorectal surgery pertains to the common side effect of delayed gastrointestinal transit, which is one of the key factors involved in delaying recovery and discharge of the post-operative colorectal patient. Efforts made to minimise opioid analgesia in the recovery process after colorectal surgery, began well over a decade ago when the terms ‘opiate sparing’ and ‘multi-modal’ analgesic regimes started to become commonplace in the anaesthetic and surgical literature.

There are a number of methods available in order to attempt to minimise opiate usage after colorectal surgery. These include: using the laparoscopic approach, utilising simple analgesia in the form of paracetamol and non-steroidal anti-inflammatory medications, peripheral opiate receptor blockade (alvimopan), infiltration of local anaesthetics into the wound, locoregional nerve and field blocks, intravenous local anaesthetic and, finally, neuro-axial anaesthesia.
The laparoscopic approach has proven benefits, in terms of reducing opiate analgesic requirements and as a result, along with many other factors associated with the laparoscopic approach, this helps promote more rapid recovery of gastrointestinal function after laparoscopic surgery.\textsuperscript{249} This is particularly interesting as other studies have shown no effect on improving rates of ileus by decreasing incision size, and correlation of size and opiate use is poor.\textsuperscript{248} This highlights both the fact that there must be more to the laparoscopic approach than merely the smaller incisions, and that opiate use should not be liberally encouraged based on surgeons’ perception of incision size and its relationship to post-operative opiate requirements. Paracetamol is a relatively safe, and frequently used drug for the purposes of recovery from surgery. It is only useful in its own right for mild to moderate pain, but commonly used as an adjunct in the multimodal approach to analgesia following colorectal surgery. It has a central serotonergic effect, probably through cannabinoid receptors\textsuperscript{250} and, usually in combination with NSAIDs, has a significant opiate-sparing effect.\textsuperscript{251} Given its safety profile with minimal gastrointestinal side effects, it seems logical to use this as an analgesic in this instance. Cyclo-oxygenase inhibition, following major surgery seems logical, given the cascade-type release of prostaglandins and cytokines following the trauma of major surgery. Non-steroidal anti-inflammatory drugs (NSAIDs) and Cyclooxygenase Type 2 inhibitor (COX-2) medications achieve this inhibition and, at first glance, appear to be the ideal solution for post-operative analgesia. Their side effect profile is large,\textsuperscript{252} however, and potentially more so in the post-operative patient. Increased rates of gastrointestinal bleeding are a well known side effect and post-operative patients are at higher risk of this effect. Renal dysfunction is another common side effect and patients, post-operatively, may already be predisposed to this, in view of hypovolaemia. Long-term use is associated with an increase in cardiac events, although this is probably not a problem in the post-operative period. Finally, there is the concern, only fairly recently raised, of increased risks of anastomotic leakage,\textsuperscript{253} possibly by inhibition of the inflammatory response required for healing. Despite all these potential problems, short term NSAID or COX-2 use post-operatively is effective at reducing opiate requirements and improving postoperative gastrointestinal function, following colorectal surgery.\textsuperscript{254-255} Care should be taken to ensure that these drugs are used in
the non-fasted and well hydrated patient who has no history of peptic ulcer disease or renal dysfunction. Alvimopan is a peripherally acting mu opioid receptor antagonist that does not cross the blood-brain barrier. It is ideal therefore, in combination with opiates in that it does not interfere with the central analgesic properties of these drugs, but does counteract the peripheral effects they have on the gastrointestinal tract. Although not yet commercially available in Australia, RCTs have shown it to be effective in hastening the return of gastrointestinal function following colorectal surgery, when opiates are used for analgesia.256

Wound infusions of local anaesthetics have been used in order to minimise post-operative pain and opiate usage. Although not studied well in the laparoscopic era, there is a meta-analysis on RCTs performed in midline laparotomy colorectal resections (five RCTs involving 542 patients),257 showing a reduction in opioid consumption in patients receiving continuous local anaesthetic infusions post-operatively (WMD -40.13 MeQ, 95% CI: -76.74 to -3.53; p=0.03). There was, however, no difference seen in length of hospital stay or return of gastrointestinal function. Locoregional blockade, in the form of nerve or field blocks are gaining momentum, in the era of laparoscopic colorectal surgery. The transversus abdominis plane (TAP) block is the most popular of these, and will be discussed in much greater detail in chapter 3, but there is evidence that they assist with post-operative analgesia and have been shown to decrease the need for opiates following laparoscopic abdominal surgery. A meta-analysis of ten RCTs involving 633 patients, revealed that TAP blockade was associated with a fairly minimal reduction of approximately 6mg in morphine-equivalent usage.258

Post-operative infusions of local anaesthetic seem to be rarely used in practice following surgery (perhaps for fear of toxicity), but are frequently used for chronic pain, and research into their use for post-operative recovery is encouraging. Although used for a variety of surgical operations in order to dampen down the systemic inflammatory response, they seem to be most effective following major abdominal surgery.259 First employed under anaesthesia as far back as the 1950s,260 there is now level 1 evidence showing efficacy of these infusions for post-operative pain and recovery. At least 29 RCTs have been performed on the topic, involving 1754 subjects,
revealing a significant reduction in opioid analgesia, when compared to standard care (WMD -8.44mg morphine, 95%CI -11.32 to -5.56). There are significant improvements in early post-operative rest pain, movement pain, time to first flatus, time to first bowel motion, nausea, vomiting and length of hospital stay. Although eight studies detected toxic plasma levels of lidocaine, in the 12 studies that screened for adverse events, these were not increased in the intervention arm. Similar outcomes have been found with respect to lidocaine infusions in colorectal surgery, with significant favourable outcomes in terms of: gastrointestinal function following laparoscopic colectomy, gastrointestinal function and length of hospital stay in open surgery, and gastrointestinal function, length of hospital stay and analgesic consumption in hand-assisted laparoscopic surgery. These outcomes certainly highlight the potential advantages of this modality to assist with post-operative recovery.

Spinal infiltration prior to colorectal surgery is becoming more popular recently, as it can be applied fairly safely, with a one-off injection, using opiates, local anaesthetic, or a combination of the two. Unlike a thoracic epidural, it lacks the potential advantage of sympathetic blockade but, theoretically, should cover most of the dermatomal territory of laparoscopic resections. When used for laparoscopic surgery in the presence of an ERAS program, it has been shown to be superior to PCA alone in providing analgesia, with significantly less opiate consumption over the first 72 hours following surgery. It may also be equivalent to epidural analgesia, according to a three-armed trial performed, comparing epidural, spinal and PCA alone. Consisting of 91 patients, randomised to one of the above, they identified a more rapid return of gastrointestinal function and shorter length of hospital stay in the spinal analgesia group, compared to the epidural group. There is much to be said for considering this rather simple, but elegant technique, for laparoscopic colon surgery.

Epidural analgesia has been the mainstay of analgesia following colorectal surgery in the ERAS environment. Much of this has already been discussed in the previous section on thoracic epidurals, and while there are some reservations about the use of epidurals in the laparoscopic era, with respect to providing the best form of analgesia following abdominal, or specifically, colorectal surgery, an epidural, expertly-placed, with a good dermatomal block, is the gold standard. It has proven efficacy with respect
to minimising opiate use post-operatively and providing superior analgesia, when compared to PCA.\textsuperscript{266}

In addition to the techniques mentioned above, medications being trialled to improve post-operative analgesia and minimise opioid usage, include: magnesium, gabapentin and glucocorticoids, amongst others.

There are many techniques available, to decrease opiate usage after colorectal surgery. The wide variation of opiate use seen in the literature fascinates this author and, although there is definitely a correlation between opiate analgesic use, and both impact of surgery, as well as means to minimise this impact, there also seems to be a large cultural component associated with opiate use and the expectation of adequate analgesia following surgery, that needs to be studied in more detail.

**EARLY MOBILISATION**

Bed rest was a fairly standard post-operative order for some time and, indeed, a treatment for many medical conditions. This strategy began to be questioned some time ago and was even found to, potentially, do more harm than good.\textsuperscript{267} Since then, it has been known that early mobilisation assists with: prevention of deep venous thrombosis, prevention of pulmonary complications, and earlier discharge from hospital.\textsuperscript{268}

In addition there are physiological problems with lack of mobilisation including: decreased muscle bulk, increased insulin resistance and poorer pulmonary function. Although there is a paucity of clinical trials on the subject of post-operative mobilisation, common sense dictates that, within reason, depending on the degree of post-operative pain experienced by the patient, early mobilisation is a positive strategy.

There are a number of ways to achieve this. A multidisciplinary approach is essential, with physiotherapists, nursing staff, occupational therapists and a surgical team on the same page with respect to physical progression and criteria for daily progress and discharge. Another aspect is ensuring that the patient is aware of what is expected of them regarding their physical progress post-operatively. This can be achieved by both prehabilitation and the use of a diary to record progress. Early removal or avoidance of as many tubes and lines as possible, is helpful, particularly the urinary catheter.
Mobilisation to an outside courtyard, toilet and dining facilities as well as avoiding bedside television screens have been suggested options as well. Adequate, but not excessive analgesia, is another important aspect, and requires a fine balance in order to achieve good mobility.

Finally, mobility scores are one way of assessing progress objectively, guiding patients as to where they should be up to and comparing outcomes within and across units, as well as in trials.  

EARLY POST-OPERATIVE FEEDING
The traditional approach to recovery after colorectal surgery was to keep patients ‘nil by mouth’ until there was evidence of gastrointestinal function. Progression to a normal diet would often follow incremental steps: sips of water, graduated fluid intake (30, 60, 90 mls per hour of fluid), clear fluids, full fluids, light diet and, finally, selective diet. The 1990s saw the commencement of trials looking into more rapid progression of diet. This followed on from the knowledge, gleaned over the previous two decades, that keeping the stomach empty using nasogastric tubes was detrimental. It was logical therefore, to explore whether the opposite practice of ‘filling’ the gastrointestinal tract, resulted in superior outcomes.

There are a number of physiological reasons why early enteral feeding should be beneficial. Short periods of starvation, particularly in periods of stress, result in release of cortisol, increased insulin resistance and muscle breakdown. Providing early nutrition has the potential to counteract this, improve healing and provide better muscle function. In addition, it appears to have the ability to potentially reduce septic complications, in light of data suggesting this is the case, when comparing enteral versus parenteral nutrition.

After initial studies were performed, revealing the safety of early post-operative feeding, more studies came to light suggesting the clinical benefits associated with this approach. A number of meta-analyses have been performed on the subject. Zhuang et al looked at seven RCTs in colorectal surgery, consisting of 587 subjects, identifying a reduction in length of stay associated with early feeding (WMD -1.58 days, 95% CI -2.77 to -0.39; p=0.009). Osland et al identified 15 studies in patients undergoing gastrointestinal surgery with 1240 subjects, and found a significant
reduction in complications in patients who were fed earlier (OR 0.55, 95% CI 0.35 to 0.87; p=0.01).\textsuperscript{275}

Finally, the Cochrane group analysed 14 RCTs on gastrointestinal anastomoses, comprising 1224 patients, looking specifically at complication rates. They found a trend in favour of early feeding for the complications of surgical site infection, intra-abdominal abscesses, anastomotic leakage, length of hospital stay, acute myocardial infarction, thrombosis and pneumonia but, most importantly, found significantly lower mortality in the early feeding group (RR 0.41, 95% CI 0.18 to 0.93; p=0.033).\textsuperscript{276}

There is significant data suggesting early feeding is safe and beneficial following colorectal surgery, and it should be the standard of care.

PREVENTION OF POST-OPERATIVE ILEUS

It goes without saying that post-operative ileus is a frustrating and costly problem following colorectal surgery, and it will be discussed in greater detail in chapter 4. Simply put, ileus is the absence of peristaltic activity within part of the gastrointestinal tract. More complex is the time frame in which the ‘normal’ absence of gastrointestinal activity becomes defined as ileus. Different anatomical parts of the gastrointestinal tract regain their normal activity at differing times post-operatively. The small intestine is usually the first, within 24 hours, followed by the stomach over the next 24 hours, while the colon is usually the last to function following surgery.\textsuperscript{277}

This time frame, of course, is quite variable,\textsuperscript{248} dependant on the myriad of external factors that influence gastrointestinal function following surgery. These include, but are not limited to: surgical trauma, influence of opiates, systemic inflammation, sepsis (particularly intra-abdominal) and immobility, but the most potent cause appears to be direct bowel manipulation.\textsuperscript{278} This is probably the most underestimated aspect that is able to be directly influenced by the surgeon. A laparoscopic approach is the best way to achieve this, and it makes logical sense that approximating the usual environment that the bowel is exposed to, by providing heated and humidified gas, is the best way to minimise this trauma, although there is no direct evidence for this approach currently. Even during laparoscopic colectomy, the avoidance of bowel manipulation can be underestimated. Most bowel handling can be avoided by tilting the operating table and, with the assistance of fixed shoulder pads and padded side supports, this
can be achieved by 5-10 degrees of side tilting, and up to 30 degrees of trendelenberg and reverse trendelenberg. In addition, using a non grasping technique to ‘swing’ the mesentery or omentum is easy to achieve and can move large sections of intestine out of the operating field. Traumatising the bowel at open surgery was one area of historical surgical neglect as well, in the anecdotal opinion of the author, during his training. Trying to keep the bowel within the peritoneal cavity during surgery can only be a good thing, provided vision is adequate, and this can usually be achieved with a dry sponge and table tilt, with minimal external forced retraction. Fixed rigid retractors on the bowel cause visible trauma to the bowel and mesentery and can usually be avoided, while handling bowel with wet sponges can only make the bowel and patient quickly colder at room temperature, according to the physics of convection and conduction.

Avoiding opiates has been discussed earlier, as has the concept of a thoracic epidural to minimise sympathetic response. Alvimopan has also been discussed in the context of opiate usage. Early feeding stimulates more rapid return of gastrointestinal function and sham feeding with chewing gum has shown promise, but this will be discussed in greater detail in chapter 4. Minimising incisions and local anaesthetic blocks, as well as lidocaine infusions have also been discussed and all contribute to decrease the rates of ileus.

Medical therapies have been largely unsuccessful in the treatment of this surgical complication, most aiming to target motility receptors in the gastrointestinal tract. Cisapride has probably been proven to be the most successful of these with both metoclopramide and erythromycin having been trialled without success. The main concern about cisapride is its association with arrhythmias, particularly if used with other serotonergic medications, and it is rarely used as a result.

In lieu of the fact that sympathetic stimulation is responsible for ‘shutting down’ gastrointestinal tract activity, attempts have been made to identify pharmacological ways to block sympathetic activity. A study performed in the rat model indicated that a longer duration of ileus was associated with a larger incision. Believing that this longer duration of ileus was associated with higher sympathetic activity, the researchers attempted to dampen down the activity by trialling beta-blockade (propranolol), catecholamine inhibitors (guanethidine) and alpha-2 adrenoreceptors (yohimbine) in
the same model. They showed that the inhibitory effect of laparotomy on GI transit was reversed by yohimbine and guanethidine, but not propranolol, highlighting the fact that sympathetic stimulation causing ileus, occurs as a result of catecholamine release and via the alpha-2 adrenoreceptors, but not via beta-receptors. Further research on sympathetic blockade is required in the post-operative patient.

Blockage of acetyl-choline breakdown using the acetyl-cholinesterase inhibitors neostigmine or pyridostigmine, is useful for colonic pseudo-obstruction but once again, concerns about arrhythmias preclude the routine use of cholinesterase inhibitors post-operatively. Laxatives have been mentioned in ERAS programs, but data too suggests these have no known beneficial effect on post-operative gastrointestinal function. The one concern that all colorectal surgeons share regarding mechanisms used to stimulate the gastrointestinal tract, particularly the colon following colorectal surgery, is the effect this may have on the anastomosis. While this may not be articulated in the literature, many such surgeons believe that ileus occurs for a reason in a number of post-operative patients, namely to rest the colon if there has been a ‘subclinical’ leak. Mechanisms to counteract this may be detrimental to the healing of small defects in the anastomosis, and is one reason to avoid the routine use of bowel stimulants.

In summary, ileus is a major post-operative problem in colorectal surgery. Minimising it is essential while avoiding it altogether is impossible. Medicinal therapies have been disappointing and simple surgical manoeuvres make logical sense, to decrease the rate and impact of post-operative ileus.

EARLY REMOVAL OF URINARY CATHETERS

Catheters have traditionally been used post-operatively in abdominal and colorectal surgery. The principal reason has been one of monitoring urine output as a surrogate for renal function. In much the same way that post-operative observations are undertaken of temperature, blood pressure, heart and respiratory rates, urinary output has been measured as a sign of recovery after surgery. While this is founded in solid principles and monitoring urine output is vitally important in a number of surgical and medical conditions, there has possibly been a degree of harm caused by an overemphasis on urine output as vital in recovery after colorectal surgery. As
previously mentioned, possibly a higher than necessary urine output used to be considered desirable following surgery (at least 0.5 ml/kg/hr in the early post-operative period, with a daily output of at least 400 mls).\textsuperscript{166-168} In the era of avoidance of bowel preparation, replacement crystalloids are not really required, and in the era of rapid post-operative feeding, maintenance crystalloids are also excessive. With the surgical insult causing excessive release of anti-diuretic hormone (ADH), in order to ‘chase’ urine output to maintain 0.5 ml/kg/hr (more than most surgeons probably maintain in the same time period), a large volume of crystalloids has usually been required. This has resulted in the average colorectal surgical patient being overloaded with fluid (averaging 3 litres/kg excess) in the early post-operative period.\textsuperscript{169} Chasing an ideal urine output has probably, therefore, done more harm than good in the average colorectal surgical patient, and is one strong argument for early removal, or even avoidance of, an indwelling catheter.

Catheters have also been traditionally employed to assist keeping patients comfortable in bed after surgery, in order to prevent discomfort associated with mobilisation to the toilet. This also helps to minimise the nursing care required to assist patients without a catheter. While this is a practical consideration, once again, early mobilisation after surgery has been shown to be beneficial, and early catheter removal certainly helps achieve this from a practical perspective.

Rectal dissection, associated with rectal cancer surgery, has been thought to be a risk with regard to post-operative urinary retention, another reason catheters have been left in for extended periods post-operatively. An RCT on this topic, involving 126 patients undergoing rectal resection, randomised patients to have their catheters either removed on post-operative day one or day five. While those in the former group had a higher rate of urinary retention (25% vs 10%; \textit{p}<0.05), the risk of urinary tract infection was significantly higher in the group with the longer duration of drainage (42% vs 20%; \textit{p}<0.01).\textsuperscript{286} Likewise a cohort study on the same topic showed it feasible, and potentially safer to have the indwelling catheter removed on day one, when compared with day three or day five post-operatively.\textsuperscript{287}

Finally it has been thought that urinary catheters should be left in while epidurals are functioning, due to the risk of retention and, given the high significance of the role of epidurals in ERAS programs, this is an important concept. Once again, however,
research has shown that patients tolerate early removal of the catheter in this group as well,\textsuperscript{288} with less risk of urinary tract infection if removed early.\textsuperscript{289} With no convincing reason to keep catheters in, and increased risk of local complications associated with the longer duration of catheterisation, it appears early removal may be beneficial for patients, and this is backed up by a review, performed by the Cochrane collaboration. This looked at all inpatient medical reasons for catheterisation, and identified 13 RCTs (1442 participants) comparing early versus standard removal of indwelling catheters, with less urinary tract infections and shorter hospital stay in the group of patients having earlier removal.\textsuperscript{290} It is the authors practice to avoid post-operative indwelling catheters altogether, as stated in the previous section on fluid therapy.\textsuperscript{177} This practice has been performed without significant complication over the last five years. All rectal resections have an intra-operative catheter to help pelvic visualisation and assist with anatomy, while all colonic cases do not have one inserted. If inserted, the catheter is removed upon completion of surgery, prior to recovery. The major exception to this rule is if a single shot spinal, or epidural is used (rare occasions in the laparoscopic era for the author), where the catheter is kept in until post-operative day one. In summary, early removal of an indwelling urinary catheter for the colorectal surgical patient is associated with superior outcomes and should be considered as first line therapy, rather than an afterthought.

AUDIT

“Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care, and the implementation of change”.\textsuperscript{291} This is the definition of clinical audit endorsed by the National Institute of Clinical Excellence (NICE), the board of audit process and review in the UK. The clinical audit process has been described as a cycle, although it’s difficult to find the origins of where this cycle was first described. The first stage in this process involves identifying an area of clinical practice that needs to be reviewed. The second part of the cycle is comparing this area against an appropriate set of standards and determining if further action is required. Most audits will stop at this stage if the standards have been felt to be met. The third stage involves the implementation of
suitable changes in order to improve the studied area of practice. The fourth, and final process, is that of re-audit (hence the concept of cycle), in order to determine if the process of implementation has been successful.\textsuperscript{291} Clinical audit makes logical sense and has been an integral part of regular clinical practice since the days of Florence Nightingale, who audited mortality rates in the Crimean War (the Sanitary Commission), which resulted in a reduction from 42\% to 2\% after the implementation of the change phase.\textsuperscript{292} In a sense, for a competent physician, audit is simply part of the day to day activities required of a clinician. One audits the ability to correctly diagnose, perform repetitive tasks (eg, cannulation, intubation), rapidly source information and change clinical outcomes, amongst many other aspects of a daily practice. In a sense, the best clinician is in a constant phase of audit cycles, without necessarily realising it! This type of audit evolves into a more formal process, whereby the clinician audits a regular aspect of their practice (eg, colonoscopy: completion rate, polypectomy rate), and progresses to a group or unit practice audit and, finally all the way through to a nationwide audit into practice, where mostly the audit outcome measure is mortality rates.

It can be said that most of the literature, with respect to audit, regarding ERAS programs, has been obsessed with length of stay as an outcome measure.\textsuperscript{23} This, in the author’s eyes, is one of the lesser (although still important) outcome measures that should be employed when directly comparing unit outcomes and assessing that good clinical progress is being made within units. The other outcomes that have been assessed include compliance with protocol outcomes\textsuperscript{293} and, probably most importantly, complication rates.\textsuperscript{294} Complication rates have been shown, in the context of clinical trials, to be reduced with the introduction of ERAS programs.\textsuperscript{30,33} An audit performed by the ERAS Consensus Group has gone one step further. It revealed a significant improvement in symptoms and post-operative complications (OR for complications 0.73, 95\% CI 0.55 to 0.98) when audit was performed across two time periods at the one institution in Stockholm, after the introduction of an ERAS program there.\textsuperscript{294} This improvement coincided with an improvement in adherence rates to the ERAS program as well, delineating nicely the combination of the improvement in clinical care that can be
identified with good clinical audit, and that can be facilitated with adherence to ERAS principles.
1.6 Potential areas for research and improvement

The advent of ERAS has been important for a number of reasons. As mentioned many times previously, it has resulted in improvements in patient care, particularly with respect to morbidity and length of hospital stay. It has also led to an increased awareness by the colorectal surgical community, of the physiological aspects involved with patient recovery from surgery to the point that a good surgeon is no longer just an operator, but a coordinator of peri-operative process and care. If all of this began merely as a reaction to laparoscopic colorectal surgery, then it can be said that this form of surgery has achieved far more than simply provide a superior operation.

The critics may argue that ERAS is no more than a clinical pathway (which nursing personnel have been using in this country for many years), but it is one that is also becoming increasingly conversed about, studied and implemented. In essence, therefore, as well as providing individual units with an improved process and care, it is shifting the culture of national surgical care as well, which can only result in positive outcomes for patients. In this author’s short career, there are a number of traditional aspects of colorectal surgical care that have been found to provide no benefit, and even do harm to patients, that have been abandoned, not just in ‘centres of excellence’, but in most colorectal units around the country. These aspects include: mechanical bowel preparation, drains, nasogastric tubes, extended pre- and post-operative fasting, extended indwelling urinary catheters and post-operative bed rest, to name a few.

The other significant finding to arise following the widespread implementation of ERAS, is the number of scientific articles published around aspects of peri-operative care. To date there are now over 3,000 articles (MEDLINE), and at least 25 systematic reviews on the topic (which seems reasonably excessive, in view of the fact that there are only 56 RCTs performed on the same subject). This increased rate of publication around the science of the topic can only be a good thing for the colorectal surgical community and its patients.

The counter-argument against ERAS is that it is essentially terminology for what should be the standard of care, not ‘enhanced’ care. David Urbach, the professor of surgery and health policy at The University of Toronto states: “We would argue that the
immediate challenge to improving the quality of surgical care is not discovering new knowledge, but rather how to integrate what we already know into practice.” This quote summarises part of the problem with ERAS; first of all, that of slow implementation of the aspects involved with ERAS into practice, but also, the argument that once an aspect of ERAS is found to be beneficial (e.g., antimicrobial prophylaxis, which has at least three decades of proven efficacy), it should really be considered the standard of care, not enhanced care. The problem with an RCT comparing ERAS with standard care is that the ‘standard care’ should be the intervention or, alternatively, and more correctly, the intervention should be standard care. It is this problem that is highlighted by the wide variation in the number of aspects incorporated in the ERAS, or interventional arms of the individual RCTs (ranging between four and 12!) It is this variation that results in significant heterogeneity, making interpretation of results difficult.

The large number of meta-analyses on the topic, previously alluded to, also represents a form of bias, not previously well studied. Some authors have even produced more than one meta-analysis on the topic, involving minor variations, and an overview of systematic reviews and meta-analyses of ERAS programs in colorectal surgery, published in the British Medical Journal was quite harsh in its assessment of these meta-analyses: “Systematic reviews of enhanced recovery programs show a high level of research waste” and “We identified limitations in reporting as one of the main barriers to understanding differences between reviews. These reporting issues often limited our ability to comment on whether decisions taken by review authors appear to be ‘right’ or ‘wrong’.”

It is with these thoughts in mind that the author has felt that research focussing on ERAS should not compare a ‘so-called’ ERAS program, with ‘so-called’ standard care, and that future RCTs of this nature should not be undertaken. The author’s view, however, is that, in addition to an ERAS program enabling comparison of outcomes across institutions, it provides the ideal structure, with which to investigate new interventions. By providing a consistent clinical pathway which all elective surgical patients are expected to follow, the detailed study of an intervention becomes easier, with less variables interfering with the impact of the chosen intervention. An ERAS pathway, when presented as part of such an RCT, allows the reader to also interpret,
for themselves, the clinical impact of a certain intervention based on the knowledge they have of their own patients’ journey through such a pathway. It also allows for such RCTs to be implemented in a multicentre fashion, with less need to exclude the usual variables that confound trials of this nature, provided similar ERAS pathways are chosen.

When analysing both the ERAS research and pathways, in addition to the knowledge gleaned by the colorectal surgical community over the last three to four decades, it appears obvious to the author that there are three main areas of surgical recovery that consistently hamper the patient recovering from colorectal resectional surgery. These (not in level of importance) are: Infection, Pain and Ileus. More specifically, the main hindrances are surgical site infection, post–operative surgical pain and slow return of gastrointestinal function. While there are many complications, too numerous to list, that can occur during recovery from this surgery, it is these three that consistently delay discharge, or even more thought provokingly, these three factors that prevent colorectal resectional surgery from being a day procedure. Attempts to minimise the impact that each of the three have upon the recovery process will no doubt lead to improvements in patient comfort, recovery and well being. With long-term cancer outcomes being linked to this shorter-term process, the search for improvements becomes even more intense.

With this in mind, and the author’s belief that clinical trials should be performed in conjunction with an ERAS program so that the only difference between the control and intervention arms is the comparator, the following trials in this PhD have been constructed. The trials in chapter 2 deal with superficial surgical site infection. The trials in chapter 3 deal with post-operative analgesia, while those in chapter 4 deal with improving post-operative gastrointestinal motility. All trials are randomised clinical trials and all have been performed within the umbrella of an ERAS-style program. Although different aspects of ERAS have changed within the institutions over time, at the time of each trial, the program was standard. All trials were designed, constructed and performed at the time of commencement or after commencement of the author’s PhD and at the outset were designated as being a component of this PhD thesis. They will be presented on paper as they have been accepted for publication; however, with additional data included.
Chapter 2.

2.1 Importance of Surgical Site Infection in Colorectal Surgery

The importance of SSIs cannot be underestimated following any form of abdominal or colorectal surgery. They represent a major form of morbidity, both for the individual patient, as well as for the surgical community, and also represent a significant financial burden on the community as a whole.

There have been various definitions described for surgical site infection but most simply, it has been defined by the World Health Organisation as: “any purulent discharge, abscess, or spreading cellulitis at the surgical site during the month after the operation”.\textsuperscript{297} This simplistic definition, has been expanded somewhat by the Centre for Disease Control (CDC) and divided into superficial, deep and organ space SSIs, depending on the location of infection, in relation to the depth from the skin surface. This is pictured below, as adapted from the CDC description,\textsuperscript{298} and subsequently described:

![Diagram of types of SSIs](image)

Figure 3: CDC description of types of SSIs
Superficial SSIs involve skin and subcutaneous tissues only, while deep SSIs involve fascia or muscle, and organ space SSIs are related to the surgery and involve the deep surgical or organ space (e.g., anastomotic leaks). The full definition, as described by the CDC, is depicted below:

**Superficial incisional SSI:** occurs within 30 days after the operation, and involves the skin or subcutaneous tissue only of the incision. Additionally, it must have any one of the following:
- Purulent discharge from the superficial incision;
- Organisms isolated and cultured from the incision (tissue or fluid) using aseptic technique;
- Clinical signs and symptoms of infection and/or inflammation: redness, pain, localised swelling or heat, and in conjunction with this the surgeon must have deliberately opened the superficial incision. If the incision is culture negative, it is not categorised as a superficial incisional SSI.
- The diagnosis of deep incisional SSI is made by the surgeon, or by a consultant physician.

**Deep incisional SSI:** occurs within 30 days after the operation with no implant, or within 1 year with an implant in situ, and the infection appears to be related to the operation. Additionally, it must involve deep soft tissue layers of the incision (muscle, fascia) and have at least one of the following:
- Purulent discharge or drainage from the deep incision, but not from the organ or organ space component of the surgical site;
- A deep incision that either spontaneously dehisces or is surgically and deliberately opened by a surgeon, in the instance where the patient has at least one of the following signs or symptoms (unless infection site is culture negative):
  - A fever of >38°C;
  - Localised pain;
  - Tenderness.
- An abscess that is either identified on physical examination, on operative re-
- Opening of the incisional site, on radiological examination or on histopathology.
- The diagnosis of deep incisional SSI is made by the surgeon, or by a consultant physician.

In addition, any SSI that involves both the superficial and deep layers should be classified as a deep incisional SSI. Any organ/organ space SSI that drains through the deep incisional layers should also be classified as a deep incisional SSI.

**Organ/space SSI:** occurs within 30 days after the operation with no implant, or within 1 year with an implant in situ, and the infection appears to be related to the operation. Additionally, it must be the organ or organ space that was opened or manipulated during an operation and have at least one of the following:
- Purulent discharge from a drain that is placed through an incisional site into the organ/space.
- Organisms isolated and cultured from the organ/space using aseptic technique.
- An abscess or other evidence of infection involving the organ/space that is found on: direct examination, on reoperation, or by histopathological or radiological examination.
- The diagnosis of deep incisional SSI is made by the surgeon, or by a consultant physician.

Figure 4: CDC definition of SSIs

Despite the fact that these definitions have stood the test of time, there has been criticism of them, particularly the fact that a physician can decide the diagnosis of an SSI without the need for the other criteria of SSI to be fulfilled. In view of this there have been modifications or variations proposed. The main variation proposed has been the ASEPSIS scoring method,\(^{300}\) which generally gives a lower estimate of SSI than the CDC classification.\(^{301}\) Despite these concerns, the CDC definition is certainly the one most frequently cited in the literature.

The risk of SSI varies a great deal depending on a number of factors, but the one that appears to have the most influence is the degree of potential ‘contamination’ the incision has at the time of surgery. In view of this, the CDC has also created a
classification system for wounds depending on this degree of contamination. Based on this classification, one can estimate (it must be emphasised, estimate), depending on the degree of contamination and based on years of audit and research, the proportion of wounds that can become infected. The classifications are as follows: clean (an uninfected, non traumatic wound where the respiratory, alimentary, genital or urinary tracts are not entered and primary closure is achieved), clean/contaminated (an operative wound where the respiratory, alimentary, genital or urinary tract is entered without unusual contamination), contaminated (open, fresh traumatic wounds or operations with major breaks in sterile technique or gross spillage from the tracts, or incisions in which non-purulent inflammation is encountered), dirty/infected (old traumatic wounds, wounds with devitalised tissue, or wounds where existing purulent infection or perforated viscous is encountered).

In addition to the degree of contamination an incision or wound has, there are a number of other factors that contribute to the risk of an SSI. These have generally been classified in one of two ways. They can be described as either patient factors or external factors, with the inference being that the patient factors are less easily influenced by the peri-operative team than other external influences. Another, and possibly more common way to classify the risk factors for SSI, is to divide them arbitrarily into pre-operative, intra-operative and post-operative factors, and a list (by no means exhaustive) of these factors appears below.

<table>
<thead>
<tr>
<th>PREOPERATIVE FACTORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Nicotine / Smoking</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Increased Age</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Immunosuppression</td>
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<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Pre-existing Skin Infection</td>
</tr>
<tr>
<td>Pre-existing Intra-abdominal Infection</td>
</tr>
<tr>
<td>(Poor) Glycaemic Control</td>
</tr>
<tr>
<td>Shaving</td>
</tr>
<tr>
<td>Methicillin Resistant Staphylococcus Aureus (MRSA) Carriage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTRAOPERATIVE FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics (Omission)</td>
</tr>
</tbody>
</table>
Hypothermia
Duration of Surgery
Break in Aseptic Technique
Hypoxia

<table>
<thead>
<tr>
<th>POSTOPERATIVE FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Contamination</td>
</tr>
<tr>
<td>Poor Glycaemic Control</td>
</tr>
<tr>
<td>‘Cross’ Contamination</td>
</tr>
<tr>
<td>Post-operative Sepsis</td>
</tr>
</tbody>
</table>

Figure 5: Table of risk factors for SSI

In terms of the impact that SSIs have in the Australian health care context, it is difficult to give precise estimates. The main difficulty is the division between inpatient and outpatient settings, both from a data as well as a financial perspective. Each different state too has its own resources, limitations and different ways of capturing data, making estimates even more complex. Each different surgical procedure, in addition to different rates of SSI, are associated with different costs. An infected joint replacement is vastly more morbid and expensive than a superficial SSI following minor skin surgery.

Nonetheless, there is data available concerning the amount of Healthcare Associated Infections (HAIs) that occur annually in Australia. There are around 200,000 HAIs that occur annually in acute healthcare settings making it the most common complication affecting inpatients. Of these HAIs, it is estimated that about 13% are related to surgical wounds, according to possibly the only national survey performed on this topic. Any attempt at cost extrapolation from this data is folly, however.

Regardless of the estimated overall impact, economic or otherwise on the community, SSIs remain a significant source of personal morbidity for the sufferer. Sepsis, the need for repeat procedures, increased mortality, long-term antibiotics (and their sequelae), delays in other forms of treatment, increased risk of poor cosmesis and increased risk of long-term herniation, are just some of the potential complications that can arise following an SSI. Any intervention known to minimise them, provided harm is minimised, would appear justified.
2.2 Strategies to Minimise Surgical Site Infections

HISTORICAL BACKGROUND

Surgical Site Infection is not a modern phenomenon, with the Roman physician, Cornelius Celsus, describing the four principal signs of inflammation around the time 30-40 AD.\textsuperscript{304} His description of inflammation and infection is still in use today. Galen, another Roman physician about a century later, unfortunately probably retarded progress with regard to treatment of SSIs, describing what is now called the ‘laudible pus’ theory\textsuperscript{305} that suggests pus in the wound is part of the healing process.

Ambroise Pare in the 16\textsuperscript{th} century, was one of the fathers of surgical treatment of infected wounds, encouraging the suppuration of such wounds,\textsuperscript{306} but it wasn’t until the time of Semmelweis in the 18\textsuperscript{th} century, that the concept of prevention, in the context of wound infection, came into being. Ignaz Semmelweis, a Hungarian physician, has been described as the ‘saviour of mothers’ after introducing hand disinfection in obstetric clinics. Semmelweis, while working in Vienna, observed a higher mortality rate from puerperal sepsis in the clinic wards run by doctors, when compared to that run by midwives. Observing the differences in practice, he surmised that the difference was in part due to poor hand hygiene and, as a result, he advised the practice of hand washing with disinfectants (chlorinated lime solution).\textsuperscript{307} Unfortunately, initially Semmelweis’ theory was not accepted by the medical community and he met a fairly tragic end, being sacked from his post in Vienna at the time of the Hungarian revolution and eventually being admitted to a mental asylum, where he died after a brutal beating by the prison guards there (ironically dying from sepsis related to his injuries).\textsuperscript{308} Despite initial indifference with respect to his theory of ‘cadaveric transmission’, word had spread and it wasn’t long until the ‘Germ Theory of Disease’ developed. John Snow was described as the ‘leader of epidemiology’ after his description of ‘the mode of contamination of cholera’ and the ‘dot map’ that he used to describe an outbreak of cholera in London around the Broad Street water pump in 1854. His efforts in describing the outbreak were enough to make authorities close the pump but he never isolated or saw the causative organism, despite observations of the water at fault.\textsuperscript{309} Louis Pasteur, however, is credited with being the
father of the ‘germ theory’ after he not only identified and cultivated organisms, but came up with initial therapies for them, including boric acid to treat puerperal sepsis. Unlike Semmelweis and Snow, Pasteur’s theories and work were well respected at the time, almost certainly partly due to the fact that he saved the French silk industry from oblivion by identifying a method to screen for the disease of silkworms, known as pebrine. Pasteur suggested that there were three ways to eliminate organisms causing infection: filtration, exposure to heat and exposure to chemical solutions. Joseph Lister, around the same time in the UK, was taking a great interest in Pasteur’s work. Lister went on to become known as the ‘father of sterile surgery’, after taking the ‘germ theory’ one step further, and identifying a means of sterilisation using carbolic acid (phenol) to both sterilise surgical instruments and clean contaminated wounds. From Lister’s time on, the focus with regard to surgery, began to become that of prevention rather than just treatment of surgical site infections.

The focus of prevention in modern times is not just at the surgical interface, but is also aimed at addressing general aspects of patient physiology, and begins from the time the peri-operative team become aware that a patient will undergo this form of surgery.

**PRE-OPERATIVE PREVENTATIVE STRATEGIES**

It goes without saying that obesity is constantly becoming a ‘larger’ problem in the western world, with the average BMI in Australia rapidly rising annually, and obesity appears to be overtaking smoking as the major cause of health related morbidity and mortality in this country. As a risk for so many morbidities following surgery, it is no coincidence that the rate of SSIs are increased in the obese. This, in part, relates to the development of type II diabetes and the inherent problems this creates, but also the environment that adipose tissue creates for the growth of deleterious organisms with a low partial pressure of oxygen and a poor blood supply. Always a difficult problem to address in the short time frame available prior to surgery, more elective procedures may benefit from contemplation of anti-obesity surgery, while less elective cancer-type procedures may benefit from short-term weight loss strategies, such as an opti-
fast diet, done in conjunction with dietitian input. Strategies aimed at enriching the subcutaneous tissue with oxygen include hyperoxygenation, which has been shown to be effective at increasing the partial pressure of oxygen in that tissue, although there is still debate as to how effective this is in reducing SSIs. Certainly, it stands to reason that lavaging exposed subcutaneous fat after intra-abdominal, and particularly, gastrointestinal surgery, would be beneficial. Lavage has the potential to remove fat debris from the wound, preventing necrosis and removing a nidus for infection. It also is capable of diluting the potential pathogen load present in the subcutaneous tissue. While it is a practice that is performed fairly widely by surgeons following fascial closure and has been suggested as a practice to reduce infection, there is surprisingly little prospective clinical data to ascertain whether or not this practice is beneficial. The rate of SSIs following abdominal surgery does not appear to be decreasing at a great rate, despite the recent advances in strategies to reduce them, and it is almost certainly the relative problem of a rapidly rising average BMI in this population that is responsible for this phenomena. Further strategies with regards to reducing SSIs certainly need to target the problem of obesity.

Nicotine reduction prior to surgery is essential to reduce the risk of SSIs in this group of patients. Fortunately, this is a societal issue that is on the improve with reduction in the overall rate of smokers in Australian society. Much has been discussed regarding cessation of smoking prior to surgery in the previous chapter and won’t be repeated, but given the vaso-constrictive and anti-healing properties of nicotine, it goes without saying that any attempts to minimise overall nicotine intake prior to abdominal surgery, are worthwhile.

Many other pre-operative risk factors with regard to SSIs are difficult or impossible for the peri-operative team to influence. Age is certainly one aspect that can’t be influenced, but malnutrition on the other hand, is open to a certain amount of manipulation. This can be achieved in the form of either enteral or parenteral (in the case of significant malnutrition) nutrition. Occasionally, admission is required for the former, and almost always for the latter, and the enteral route is always the preferable one, where possible, due to the inherent risk of increased sepsis associated with the latter.
Tight peri-operative control of blood sugar levels is essential for healing and for minimising SSIs. High post-operative blood sugar levels have been implicated in both poorer wound healing and a higher rate of wound infections, and tighter control leading into and following surgery is essential to maximise patients’ chances of recovery by minimising complications. This is mostly achievable with good compliance and appropriately designed intravenous insulin protocols.

Pre-operative shaving was traditionally, routinely performed, most commonly with a razor blade in order to remove hair from the operative field. The rationale behind this was to make visualisation easier, as well as to minimise trapped hair in the surgical wound. While this appeared to make logical sense, recent data suggests that shaving possibly increases surgical site infection. It is thought that razors cause micro-abrasions to the skin surface that enable skin surface micro-organisms to both enter the subcutaneous tissue, as well as to multiply. This theory is backed up by evidence revealing lower rates of surgical site infection when clipping hair is performed instead of shaving with razors. A number of trials exist comparing other forms of hair removal and different timing of hair removal prior to surgery. Apart from the fact that clipping is superior to shaving, no other definitive finding has emerged from the trials. In view of this, the CDC have made the recommendation that hair not be removed unless it interferes with the operation, and if hair is to be removed, it should be done immediately prior to surgery with electric clippers. This seems an entirely reasonable recommendation, given the available research, and should be routinely adopted.

Pre-operative screening for MRSA makes rational sense based on both an individual as well as a public health perspective. The infections that result from MRSA are generally associated with a higher rate of morbidity and even mortality than those associated with Methicillin sensitive Staphylococcus aureus (MSSA). The role of pre-operative screening for the individual patient is to identify those at risk and implement a strategy for decolonisation. This is designed to either eradicate the MRSA prior to surgery or, at least reduce the burden of carriage and therefore potentially reduce the post-operative risk of significant infection. From a public health perspective, pre-operative screening with a view to peri-operative isolation, has been shown to reduce the total
burden of MRSA carriage and infections. Where possible, screening should occur for all high risk patients undergoing surgery and being admitted to health care facilities.

Given that most surgical site infections arise from pathogens found on the patient’s skin surface, there is a valid argument, not just for intraoperative skin preparation, but for pre-operative cleansing, to reduce the overall skin bacterial count. This is a practice that has been widely used based on data indicating antibacterial washes result in a reduction of bacterial flora on the skin. Despite the reduction in bacterial count, there is minimal science to suggest pre-operative antibacterial washes result in a reduction in surgical site infections. The Cochrane Collaboration have performed a meta-analysis on pre-operative bathing or showering with skin antiseptics and concluded that, while there is evidence that pre-operative washing with plain soap is efficacious at reducing surgical site infection, the addition of chlorhexidine antiseptics provide no additional advantage. Showering or washing with soap or detergent prior to surgery appears to be a simple intervention to recommend as a routine.

INTRA-OPERATIVE PREVENTATIVE STRATEGIES

Intra-operative warming has been discussed previously but its importance with respect to minimising surgical site infection should be re-emphasised. Maintaining normothermia should begin in the anaesthetic bay prior to commencement of surgery, and the aim should be to maintain body temperature above 36.0°C throughout surgery. This can be achieved by performing surgery laparoscopically, where possible, increasing operating ambient room temperature, pre- and intra-operative warming with forced air body heaters, fluid warming devices and minimising exposure and fluid lavage.

It almost goes without saying in this ‘post-Semmelweis’, ‘post-Lister’ era, that antiseptic hand washing occur prior to the use of sterile equipment for all forms of surgery. Nonetheless, it should be reiterated. Multiple forms of antiseptic solutions are used for hand washing, both alcohol and aqueous based, including chlorhexidine, povidine-iodine and triclosan agents. While all are effective agents in decreasing
bacterial skin counts, there is limited clinical evidence to suggest any agent is superior to the other. Despite the lack of clinical evidence, there is evidence that chlorhexidine agents appear to be superior to povidine-iodine agents with respect to decreasing the amount of skin bacteria.\textsuperscript{327} Alcohol based agents with humectants to prevent skin drying, are becoming more popular due to their rapid effect on skin organisms, as well as their property of causing less irritation and dermatitis. It has to be born in mind, however, that alcohol is not as effective on spores, so it is recommended that the ‘initial’ hand wash of the day be one containing other agents.\textsuperscript{328}

Antimicrobial prophylaxis with intravenous antibiotics given at the time of surgery, has already been discussed with respect to reducing surgical site infection. This is a very well established strategy with level 1 evidence existing for a number of decades, indicating the proven effect of pre-operative antimicrobial prophylaxis.\textsuperscript{139-140} Recent evidence suggests that post-operative dosing is not routinely required,\textsuperscript{139} and that the combination of intravenous and oral antibiotics appears to be superior to either one used alone.\textsuperscript{139} Data also suggests that timing the antibiotic dose to result in peak concentrations at the time of dissection, is critical.\textsuperscript{142} It would be considered appropriate to adhere to the Australian Therapeutic Guidelines’ recommendations with respect to prophylactic antibiotic administration, and to time intravenous administration in the 60 minutes prior to incision time.\textsuperscript{141}

The appropriate solution for skin cleansing at the time of surgery has caused debate and been discussed in the previous chapter. The NICE guidelines recommend that: “the site is prepared immediately prior to incision using a suitable antiseptic, such as chlorhexidine or povidine iodine”.\textsuperscript{329} Many think that this is inadequate, with recent evidence showing the superiority of chlorhexidine over povidine iodine,\textsuperscript{146} and believe also that alcohol should be combined with either of the above for maximum efficacy. The author believes that, given the current evidence,\textsuperscript{330} skin preparation for colorectal surgery prior to incision, should be a combination of chlorhexidine and isopropyl alcohol.

The use of incision drapes after skin prep should be avoided in colorectal surgery. These were developed with the intention of providing a barrier and minimising the risk
of contamination. In actual fact, they probably do the opposite by encouraging proliferation of skin pathogens under the plastic ‘skin’. In order to avoid this, impregnated drapes were developed, with povidine iodine impregnated into the adhesive surface. A Cochrane Review has identified an increased risk of surgical site infections when adhesive non-impregnated drapes are used, and no improvement in infection rates when impregnated drapes are used.\textsuperscript{331}

Ensuring that glucose levels remain controlled during surgery has been mentioned as a pre-operative strategy, but is particularly important during the operative period. Although being part of the domain of the anaesthetist, the surgeon should be aware, as part of the peri-operative team, that the metabolic response to surgery can include insulin-resistant hyperglycaemia, and strict intra-operative control can assist in avoiding this.\textsuperscript{318-319} In view of the current science surrounding this, the Department of Health in Scotland, as part of their quality improvement strategy (DH High Impact Intervention care bundle to reduce surgical site infection), suggests that a diabetic patient’s blood glucose level be kept under 11 mmol/l throughout the operation,\textsuperscript{332} which seems a reasonable recommendation.

Tissues heal better when provided with the ideal conditions of perfusion and, ultimately, oxygenation. When the opposite occurs and a state of shock exists, there are higher risks of non-healing and subsequent infection. Maintaining normothermia, minimising blood loss and exposure, maintaining good blood glucose control and minimising tissue oedema from fluid overload, are all means to achieve ideal perfusion. Keeping haemoglobin levels stable and ensuring adequate haemoglobin saturation are means to maintain adequate tissue oxygenation, provided perfusion is good. Increasing tissue oxygenation by increasing inspired oxygen has been studied to determine whether this results in less surgical site infections. The results of trials looking at ‘hyperoxaemia’ in surgery have shown mixed results, as discussed in chapter 1. The reason for the differences seen in outcomes may reflect a combination of heterogeneity in operations, with potentially different pathogens, and in patient case mix. Rather than re-analysing these trials, a quote from the NICE guidelines seems a sensible way to approach the topic: “optimal oxygenation should be maintained during and post-surgery to ensure maintenance of greater than 95% oxygen saturation of
The author is of the belief that hyperoxygenation (FiO₂ 80%) during surgery, has been proven to be a safe intervention and could be considered routine to achieve the NICE guidelines. Hyperoxygenation may prove to be more effective in certain groups of patients (high anaerobic load from spillage, obesity with decreased perfusion of subcutaneous tissue), once studied in greater detail, and considering the safety and ease of intervention, seems reasonable.

After fascial closure, wound or incision lavage, is commonly practiced by abdominal surgeons. A number of agents have been used for this, but probably the most widely studied is povidine-iodine as a form of antiseptic wash prior to skin closure. A meta-analysis on this technique (24 RCTs, n=5004) has revealed it to be effective for all forms of surgery (RR 0.58, 95% CI: 0.4 to 0.83; p=0.003). This significant effect does not persist when abdominal surgery alone is assessed (16 RCTs, n=1768). Although a reduction in surgical site infections from 16.7% to 12.4% was observed if povidine-iodine was used, this was not significant (RR 0.74, 95% CI: 0.54 to 1.01; p=0.058). It is possible that this finding in abdominal surgery represents ‘under powering’ given the overall finding of the meta-analysis, and certainly deserves more research. Given the safety, simplicity, and low cost of a povidine-iodine lavage it appears to be a reasonable intervention following colectomy, prior to skin closure.

In addition to antimicrobial irrigation, surgeons over the years have employed antibiotics applied topically in wounds in order to reduce SSIs. Of these, the most popular has been gentamicin. A meta-analysis on the use of gentamicin to reduce SSIs in wounds has been undertaken. Many of the trials in this meta-analysis concentrated on the use of gentamicin in clean/contaminated wounds, which would be considered applicable for colorectal surgery. Only two trials in the meta-analysis studied the use of gentamicin in laparotomy wounds, however, with conflicting results. The largest of these revealed a higher incidence of SSI associated with the implants, highlighting the need for further research in this group of patients. The overall data appears promising though, with a reduction of approximately 50% in SSI rates. The meta-analysis includes 15 RCTs (n=6979), indicating a significant reduction in SSI (OR 0.51, 95% CI 0.33 to 0.77; p=0.001), with a greater reduction seen when trials performed on clean/contaminated wounds only were analysed (OR 0.43, 95% CI 0.20 to 0.93;
p=0.003). Numbers needed to treat in order to prevent one SSI were also low (NNT=9) for clean/contaminated surgery. While further research is required in laparotomy patients, this technique seems to be an applicable one for clean/contaminated wounds, pilonidal sinus surgery being a prime example.

The mechanism of skin closure is a controversial subject with respect to reducing surgical site infections. Proponents of continuous subcuticular skin closure argue that it provides a superior cosmetic outcome, while proponents of interrupted forms of skin closure (particularly surgical clips), lay claim to the benefit of simplicity and speed of closure with this technique. The colorectal surgical community, in particular, has traditionally favoured the latter form of closure given the high rate of surgical site infection seen following colorectal surgery. The theory behind this choice is that when superficial infection with a localised collection is seen within the wound, individual clips can be removed simply in order to drain the infection without compromising the entire length of the wound. Other surgical specialties (orthopaedic and obstetric, in particular) have suggested, however, that in the presence of a clean wound, ‘waterproof’ closure by means of a continuous subcuticular technique, results in less infection when compared with interrupted closure. The mechanism proposed, by which increased infection occurs with interrupted closure, is either via bacterial migration down the closure material that pierces the skin, or through the wound ‘gaps’ left in between the interrupted clips or sutures. A Cochrane systematic review on all trials comparing continuous versus interrupted skin closure techniques for non-obstetric surgery (five RCTs n=827), has revealed no difference in surgical site infection between the two methods (continuous v interrupted: SSI RR 0.73, 95% CI 0.40 to 1.33; p=0.30). It did, however, reveal a significant reduction in superficial wound dehiscence among the group receiving continuous closure techniques (RR 0.08, 95% CI 0.02 to 0.35; p=0.00086). Although only one large RCT (n=1080) out of Japan has been performed in gastrointestinal surgery to compare the two techniques with respect to SSI, a very similar trend in favour of continuous closure was identified (SSI 8.4% v 11.5%, RR 0.709, 95% CI 0.474 to 1.062; p=0.12). Quite clearly, a large trial needs to be conducted in colorectal surgical patients comparing the two techniques, with
enough power to detect a difference in SSI of between 2-3%. Until then, the body of evidence suggests a small advantage lies with continuous skin closure techniques.

Recently, it has been proposed that certain suture materials are more prone to bacterial contamination and subsequent infection, than others. In order to counteract this quality, coating of suture materials with antimicrobial agents has become popular. In particular, triclosan has been used, and shown in vitro, to be effective. Clinical results appear mixed, however. A meta-analysis of all RCTs analysing triclosan coated sutures, revealed a reduction in SSIs favouring the use of coated sutures (RR 0.70, 95% CI 0.57 to 0.85; p<0.001). Most of the trials in this meta-analysis assessed polyglactin, a synthetic braided material that has been shown to be more prone to contamination and inflammation than non-braided alternatives. It is also absorbed fairly rapidly, making it a poor choice for fascial closure. Most colorectal surgeons do not use it routinely for abdominal closure after colectomy, favouring less reactive and slower absorptive monofilament materials, such as polydioxanone, that have a potentially lower rate of bacterial contamination. Studies assessing the use of triclosan coating on polydioxanone sutures when used for colorectal surgery, have shown no advantage with the coated sutures. A Hungarian multicentre study (RCT, n=485) compared SSI rates between polydiaxanone with and without triclosan coating following colorectal surgery, and found no difference (12.2% vs 12.2%). Following on from this, a larger German study (multicentre RCT, n=1224) identified a similar outcome with respect to SSI following colorectal surgery (triclosan coating 14.8% vs non-coated 16.1%, RR 0.91, 95% CI 0.66 to 1.25; p=0.64). In addition, there is the concern regarding allergy to triclosan, which has been documented. Given these findings, and the increased cost associated with antimicrobial coating, it would seem logical to suggest it not become routine practice, provided non-braided, monofilament materials are employed for closure.
POST-OPERATIVE PREVENTATIVE STRATEGIES

Whereas intra-operative strategies to minimise post-operative SSIs tend to focus on the confines of the operating room, it is the surrounds that play a large part in ensuring SSI rates remain low.

The importance of hand hygiene and minimising cross contamination between patients cannot be underestimated, particularly with regard to minimising virulence and resistance of organisms to treatment within the hospital environment. The WHO, in particular, have been instrumental in emphasising the need for hand hygiene, not just in post-operative patients, but for all patient contact episodes.328 There is adequate evidence to highlight the need for alcohol based agents when performing hand hygiene,342 as recommended in the WHO Guidelines on Hand Hygiene in Health Care.328 This hand hygiene needs to be enforced when inspecting post-operative wounds and changing dressings.

There is less evidence to support the use of wound dressings post-operatively, although it would be considered standard of care.329 There is even less consensus when assessing which type (amongst the myriad available) of dressings to use post-operatively, and virtually no reasonable consensus as to how long to leave dressings on. It is the authors opinion, given the absence of evidence, that dressings are probably only useful to prevent soiling of clothes from wound exudate, although this may depend on whether the wound is closed in an interrupted fashion (allowing potential defects) or continuously.

The final aspect of post-operative care with respect to minimising SSIs, is that of length of hospital stay. While it is well established that an SSI is associated with increased length of hospital stay,343 it also appears that an increased length of stay is inversely responsible for a proportion of HAIs,344 a significant number of which are SSIs. Although it is difficult to assess accurately what impact increasing length of stay has on rates and impact of SSIs, improving early discharge, where possible, can only be a good thing for the post-operative patient.
2.3  Wound Protection in Colorectal Surgery

The concept of wound protection in surgery is not a new one. Since the days of Lister, attempts have been made to prevent the surgical wound being exposed to organisms. The relationship of surgical site infections to organism exposure was further explored by Altemeier. He described a relationship, between both the degree of exposure of the wound to organisms and the virulence of those organisms, to surgical site infection.\textsuperscript{345} This concept has been expanded on by the CDC. They have described a classification based on the degree of wound contamination that forms the basis of assessing the pre-operative risk of developing a post-operative surgical site infection. This classification describes four ‘tiers’ of contamination: clean, clean/contaminated, contaminated and dirty.\textsuperscript{298-299} Each of these have been described earlier in the chapter, and elective colorectal surgery generally tends to fall into the second category of clean/contaminated, although if excessive intra-operative spillage or contamination occurs, then this classification changes to a contaminated one, and infection rates increase.

In view of this, colorectal surgery has been traditionally associated with increased rates of surgical site infections when compared to other surgeries, as a result of potential increased exposure of the wound to a higher variety of organisms. It makes logical sense, therefore, to attempt to minimise exposure to these organisms. Wound protectors were designed to achieve this and first began to emerge in the 1960s.\textsuperscript{346} Initial trials looking at their ability to reduce surgical site infection provided mixed results\textsuperscript{347,348} and it would be fair to say that, at least in Australia, most colorectal surgeons, due to the cumbersome nature of the early protectors, had given the practice of using wound protectors away by the turn of the century.

The earliest wound protectors were simply sterile sponges or other similar materials that were sutured or fixed to the wound edges. These were subsequently replaced by a plastic wound protector with a single inner ring that sat loosely within the peritoneal cavity, while a large square of plastic attached to the inner ring was fixed, with either clips or a sterile adhesive, to the outer drapes or abdominal skin. This resulted in an occlusive plastic barrier, which potentially prevented contamination from the
operative field, but not from the skin. It was an improvement from sponges that were permeable; however, the non-permeable nature of the plastic allowed a build up of fluid underneath the plastic, from the skin and wound, that collected in the wound during the course of the operation. Removal of the plastic single ring protector was somewhat cumbersome and often resulted in spillage of the fluid on the outer side of the plastic and into the wound as well. In addition, the loose nature of the plastic meant that it retarded surgical progress by obstructing vision, and getting in the way of instrumentation. Following on from initial research that was promising in terms of its capacity to reduce surgical site infection when subsequent studies were not so positive, use of this form of protection was not considered routine.

The dual ring wound protector overcame a number of the practical deficiencies present with the single ring protector, however. Chief among these was its ability to retract the wound edges. By providing two semi-rigid rings with a non-permeable layer of plastic between the rings, the protector could be ‘wound out’ within the wound.

The way the dual ring wound protector works is that one ring is placed in the peritoneal cavity while the other is placed on the skin, and by winding the outer ‘skin’ ring, the plastic retracts the wound edges. With the dual ring protector, when compared with its single ring counterpart, there is no excess plastic, fluid does not tend to accumulate, retraction is also provided, it does not interfere with vision and instrumentation, and it can be removed easily without spillage. The other potential advantages of this form of protection and retraction are that it minimises excess traumatic retraction from external retractors, and possibly even results in wound haemostasis, as a result of the even circumferential pressure applied to the wound throughout the surgery.

All of these advantages were theoretical, and despite the development and application of this form of technology, it was not put to the practical test until after its development and distribution to the surgical market. Horiuchi and his team in Japan were the first to put the dual ring protector to the research test by conducting two studies: one assessing whether the protector decreased bacterial numbers in the wound, and the other an RCT assessing whether the protector resulted in decreased
surgical site infection following abdominal surgery.\textsuperscript{350} Their research identified that the dual ring wound protector was an effective agent in decreasing the rate of bacterial cultures from the wound edge, and it was also effective at reducing surgical site infections following abdominal surgery.\textsuperscript{349-350}

Prior to the publication of these two trials, the dual ring wound protector was trialled by this author and his colleague, Dr Brian Draganic, and both felt the protector to be a useful retractor with the potential to decrease surgical site infection. With this in mind, an RCT was constructed assessing the effectiveness of the dual ring wound protector with respect to reducing surgical site infection following open colorectal surgery.

The following is the transcript of this trial, which was presented by Kate Reid, a Bachelor of Medical Science student, under the dual supervision of Dr Stephen Smith and Dr Brian Draganic (both of the Colorectal Department, John Hunter Hospital, The University of Newcastel, NSW, Australia) at the Royal Australasian College of Surgeons Annual Scientific Congress in Brisbane in 2009. It was later accepted for publication by the Diseases of the Colon and Rectum, and published in October 2010.
Authorship Confirmation Page

This is to confirm, from the following fellow authors, that Stephen Smith was the Architect, Chief Investigator and Corresponding Author of the trial:

Barrier wound protection decreases surgical site infection in open elective colorectal surgery: a randomized clinical trial

Kate Reid

Peter Pockney

Brian Draganic
2.4 Barrier wound protection decreases surgical site infection in open elective colorectal surgery: a randomized clinical trial.

Abstract

Purpose: Surgical Site Infection following colorectal surgery is a frequent and costly problem. Barrier protection at the time of this form of surgery has been used with varying results. The aim of this randomized study was to examine the efficacy of barrier retractional wound protection in the prevention of surgical site infections in open, elective colorectal surgery.

Methods: One Hundred and Thirty consecutive patients undergoing open elective colorectal resectional surgery were randomly assigned to have either barrier retractional wound protection or standard wound retraction. Patients were then followed up for a minimum of 30 days postoperatively. The primary endpoint was surgical site infection as defined by the Centres for Disease Control and Prevention. The secondary endpoint was performance of the wound protector as assessed by operating surgeons.

Results: There was a significant reduction in the incidence of incisional surgical site infections when the wound protector was used: 3/64(4.7%) versus 15/66(22.7%); p=0.004. Most surgical site infections were diagnosed after discharge from hospital (78%), and there was no difference in the rates of reoperation, readmission or formal wound drainage between the two groups. Surgeons found the wound protector to be helpful with retraction during surgery, with 88% (7/8) adopting it as part of their standard setup.

Conclusions: In this study the use of barrier wound protection in elective open colorectal resectional surgery resulted in a clinically significant reduction in incisional surgical site infections. Barrier wound protection of this nature should be considered routine in this type of surgery.

Introduction
Surgical Site Infection (SSI) is a common and costly complication of colorectal surgery. The incidence of SSI in colorectal surgery is reported to be between 11% and 27%. This figure increases when an independent surgeon-trained observer is used, and where outpatient follow up is conducted, with as many as 32% - 72% of SSIs being diagnosed after discharge from hospital. The cost of SSI can be quantified either in terms of increased morbidity and mortality, or as a monetary cost to the health care system. Patients who develop an SSI are likely to spend additional days in hospital and are more likely to be readmitted to hospital within 30 days of discharge. The additional cost to the hospital system of an ‘incisional superficial’ SSI following colorectal surgery is approximately UK£2267. There are also further additional costs to the patient and the community, in terms of loss of productivity, the cost of care and lost income. These costs are much more difficult to quantify.

The development of an SSI depends on a number of factors best summarised by Altemeier who proposed the equation that the risk of infection can be expressed as:

\[
\text{Risk of Infection} = \text{Dose of bacterial contamination} \times \text{Virulence} \times \text{Resistance of Host}
\]

Virulence and host defences are factors that are difficult to control for and the “dose of bacterial contamination” is the factor over which surgeons have the most control.

The concept of using a physical barrier between surgical work and the wound edges (wound protector) in order to decrease potential exposure to bacterial contaminants has existed for some time. The results of studies on early “wound protectors” were contradictory, with regards to their ability to decrease the rate of SSI, as well as their ‘ease of use’.

The Alexis® (Applied Medical, Rancho Santa Margarita, CA, USA) wound protector was developed in 2000, with a design that acted as a form of barrier protection, while also retracting wound edges. This wound protector is made up of two stiff
rings with a cylinder of impervious plastic between the two rings. The inner ring is placed in the peritoneal cavity, while the outer ring is placed outside of the abdomen. The outer ring is then rolled over the cylinder of impervious plastic until the plastic becomes taught circumferentially around the wound. The key differences between this protector and previous wound protectors is the ability of it to reliably provide protection to the whole wound, as well as its ability to be removed easily without spillage into the wound.

At the time of design of this study there had been no clinical trial to our knowledge to assess the efficacy of this form of retraction in open colorectal surgery. The primary objective of this study was to determine if this form of barrier protection resulted in a decrease in SSI when used at the time of open colorectal surgery. The secondary objective was to determine the wound protectors’ ability to assist with retraction.

**Methods**

All eight gastrointestinal surgeons with an appointment at the John Hunter Hospital (JHH) participated in the study. Consecutive patients were recruited from four hospital sites where the participating surgeons worked. All patients over 18 scheduled for an elective colorectal resection were eligible to participate in the study. Patients who were cognitively impaired or otherwise unable to give informed consent were excluded from the study. Patients undergoing a laparoscopic colorectal resection were also excluded due to the concern about possible extraction site metastases in the absence of wound protection. The study was conducted over 18 months from January 2007 until June 2008.

The study protocol was approved by the local ethics committee (Hunter New England Human Research Ethics Committee: 06/11/22/5.04) in November 2006. The trial was registered with the Australian New Zealand Clinical Trials Registry: ACTRN12609000020280. The trial was performed by the Division of Surgery, John Hunter Hospital, Newcastle, NSW, Australia.

**Randomization**
Randomization was performed after consent had been obtained and after the patient was anaesthetised. Allocation was performed in blocks of 20 by computer generated sequence allocation and concealment was achieved by using opaque envelopes opened at surgery by a third party.

**Interventions**

Participants demographic details were collected, and information on co-morbidities recorded. Mechanical bowel preparation was used at the discretion of the treating surgeon and its use was recorded.

All patients received a single dose of intravenous prophylactic antibiotics according to Australian Therapeutic Guidelines\(^\text{14}\) (Cephazolin 2g and Metronidazole 500mgs) after being anaesthetised and prior to skin incision. A repeat dose of Cephazolin was given to patients at 3 hours if their procedure had not been completed. All patients had skin preparation with Betadine, which was left to dry prior to skin incision.

Ventilation was maintained intraoperatively with 80% oxygen and no nitrous oxide was used. Oxygen was also continually administered for 24 hours postoperatively by nasal prongs. Patient warming devices were used intraoperatively and in the recovery ward (Bair Hugger\(^\text{®}\), Arizant, MN).

In the control group wound retraction was achieved by retractors routinely used by the treating surgeon. Patients in the intervention group had the wound protector placed once the peritoneum was opened and adhesions to the anterior abdominal wall were cleared. Treating surgeons then used extra retraction where required by the retractors of their choice. All patients underwent colorectal resection and anastomoses as per the technique of the treating surgeon.

Wound closure was standardised with mass fascial closure using 1 PDS\(^\text{®}\) (Ethicon) followed by a wound washout using warm normal saline and subcuticular skin closure with 3/0 Caprosyn\(^\text{®}\) (Covidien). Wounds were dressed with a transparent hydrocolloid dressing (COM feel\(^\text{®}\)) that remained in place for 5 days.
All patients were mobilised and given a full fluid diet on day 1 with progression to a selective diet once this was tolerated. They were discharged from hospital when mobile, independent in activities of daily living and medically fit.

The principal outcome measure was the incidence of superficial or deep SSI occurring within 30 days of surgery, as defined by the Centres for Disease Control (CDC). Definition of a surgical site infection as defined by the CDC is;

“Any infection of the superficial or deep tissues or the organ/space affected by surgery, and which occurs within 30 days of surgery when no prosthesis has been implanted.”

An infection is defined by the CDC as being the presence of at least one of the following:

1. Purulent drainage, with or without laboratory conformation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

All post operative assessment was performed by one trained observer (KR) who was blind to the allocation and was not a practicing clinician at the institution involved. Wounds were reviewed on day three, day five, the day of discharge and at post surgery out patient follow up by the observer. In addition to this antibiotic usage was assessed in hospital and at out patient follow up. Antibiotics were prescribed for SSI’s only if there was evidence of systemic sepsis or surrounding cellulitis and the wound was adequately drained or draining. All patients General Practitioners were also notified to determine if any antibiotics had been prescribed within 30 days of surgery.
Operating surgeons were surveyed about their experiences with the devices at the completion of the study. Specifically surgeons were asked whether they would use the wound protector routinely in the absence of any proven reduction in SSI. They were also asked to clarify the ability of the protector to assist with retraction using a five point score as: very unhelpful, unhelpful, no change, helpful, very helpful. A Visual Analogue Scale was also filled out by participating surgeons assessing general assistance in retraction that the wound protector provided (0-10 with 0 representing no assistance and 10 representing best possible assistance).

**Statistical Analysis**

Prior to commencement of recruitment in this trial Horiuchi et. al published a randomized clinical trial examining the use of the Alexis® wound protector in general surgical patients. A subgroup analysis of colorectal operations within this trial identified a reduction in SSI from 13.4% to 0% when the wound protector was used. Based on this data a power calculation was performed and in order to identify a reduction from 13% to 0% (80 per cent test power and alpha level of 0.05) 56 patients were required in each arm. Allowing for loss to follow up of approximately 15% a total sample size of 132 patients was chosen.

Patients were analysed according to intention to treat principles. Fishers exact test was used for categorical baseline data, while comparison between non categorical baseline data was with students t- test. Comparison was made between SSI using Fisher’s exact test. Statistical analysis was performed using Minitab 14® Statistical software and the analyst was blinded as to which group was control or intervention (groups were designated A or B by a third party for analysis).

**Results**

At the conclusion date 135 patients were enrolled out of a total of 137 eligible patients. Two patients refused consent and five were excluded from analysis (2 deaths and 3 protocol violations). The protocol violations consisted of two patients who had their wounds closed with surgical skin staples rather than the prescribed subcuticular suture and one patient who was too obese for the extra large wound protector which fell out of the wound.
The study population therefore comprised of 130 patients randomized to either the control group (66) or the wound protection group (64). No patient in this group of 130 was lost to follow up (see consort diagram).

The cohort of 130 consisted of 76 men and 54 women with a mean age of 63 (range 21-95) years and a mean BMI of 28. The two groups were well matched with regards to demographic data and characteristics (table 1). There were no differences between the two groups with regards to the procedures performed. Both groups were equally represented in the four hospitals involved in the study. One out of eight surgeons had an unequal distribution of groups (7 wound protector vs 1 control), while the remaining 7 had equivalent distributions. There was no difference between the two groups with regards to the other operative details outlined in table 2.

No adverse events occurred as a result of use of the wound protector.

Eighteen wound related SSI’s were diagnosed in the entire cohort. The majority of infections (78%) were diagnosed after discharge from hospital. Seventeen of these infections were superficial SSI’s, while one deep SSI occurred in the control group, necessitating operative drainage. One organ space infection developed in each group, both requiring percutaneous drainage, while two postoperative anastomotic leaks occurred in the wound protector group requiring reoperations.

Incisional related surgical site infection occurred in 15/66 (22.73%) patients in the control group compared with 3/64 (4.69%) in the wound protector group (15/66 vs 3/64; p=0.004): see results table 3.

This represented an absolute risk reduction of 18.04% reduction in SSI when the Alexis wound protector was used, and a Numbers Needed to Treat (NNT) in order to prevent one SSI of 6 (95% CI 3.4-15.0).

There was no difference in the rate of surgical interventions or readmissions for SSI between the two groups (table 3).

Surgeons participating in the trial found the wound protector to be useful as a retractor, with 7/8 (88%) rating it as helpful or very helpful and adopting it as
standard for their laparotomy setup. The mean VAS for its value as a retractor as rated by surgeons involved was 7 (range 5-10).

Discussion

This randomized clinical trial comparing the use of the wound protector to standard retraction in elective colorectal resectional surgery revealed a significant reduction in SSI in patients in the intervention arm. The reduction in SSI in the patients randomized to the wound protector group was not only highly significant but clinically relevant.

To our knowledge this is the first trial to assess the ability of this form of wound protection to decrease SSI in resectional colorectal surgery. It mirrors the findings of the subgroup analysis of colorectal patients in Hiriuchis’ study,16 and reinforces the value of impervious wound protection for this group of patients.

Maxwell et al.11 describes the theory behind wound protection with impervious plastic as an attempt to protect the sides of the wound from inevitable contamination from skin and enteric bacteria as well as protecting it from trauma during the operation. Prior studies assessing this form of protection have produced conflicting results,12,13 possibly as a result of the ‘cumbersome’ properties of older styles of wound protectors.

The wound protector employed in this study differs from earlier styles of wound protectors in its ability to afford full wound protection as a result of the firm and retractable nature of the inner and outer rings. The design of this protector enables the impervious cylinder of plastic between the two rings to lie firmly in contact with the wound once the outer ring has been ‘wound’, regardless of the wound depth. In contrast to previous designs it provides consistent protection of the entire wound for the duration of the procedure and can also be removed without spillage of fluid onto the wound prior to closure. Our trial sought to determine if this property resulted in a more effective form of protection and retraction. It stands to reason that surgery with a potentially higher rate of wound contamination would benefit more from this form of wound protection and it is with this in mind that we chose to test its properties on colorectal resectional surgery. Horiuchi et al.16 performed a study on a wide range of general surgical
procedures and found that the wound protector appeared most effective for colorectal operations, with a reduction in SSI from 13.4% to 0%. Our study designed purely for colorectal surgery revealed a similar rate of reduction, albeit from a higher baseline with the similar proportional reduction validating this wound protector's ability.

While both groups in this study were well matched, representation of the groups was unequally matched for one surgeon. It is difficult to see how this chance occurrence could be prevented, with stratification for 8 surgeons being impractical. It is also difficult to see how this occurrence could have affected outcome: this surgeon had 7 wound protector vs one control patients and no postoperative SSI's.

The potential weakness of this study is the high SSI rate in the control group. It is unlikely that this represented any form of bias with observer, patients and analyst being blinded as to the form of intervention. Interventions such as antibiotic prophylaxis, peri-operative hyper-oxygenation, and maintenance of normothermia were all employed in order to minimise the baseline SSI. Possibly the main factor accounting for the high SSI in the control arm of this study is the high mean BMI of the cohort (28 compared with 22 in Horiuchi's cohort). Tanner et al identified high BMI as being the most significant risk factor for the development of SSI, with rates as high as 27% in their study when strict CDC criteria were used with 30 day follow up by experienced observers. This finding compares favourably with the results in this trial and further validates the comparative findings with Horiuchi's trial.

In this study we also utilised a follow up method that involved a blinded, unbiased, surgeon-trained observer. This method has been shown to increase the detected infection rate, indeed sometimes doubling the detected rate. The use of a 30-day post-surgical follow up, also used in this study, ensures that out-of-hospital or post-discharge SSIs are also picked up, and this has also been shown in other studies to at least double the detected infection rate. Indeed 78% of SSIs in this study were diagnosed after discharge from hospital. The overall SSI incidence in this study was 13.85% while the in hospital SSI rate was 3.18%. The exclusion of post discharge infections gives surgeons a false impression about the risk of SSI. As
the length of hospital stays reduces, the impact of SSI may appear to those working in the hospital system to have been substantially reduced but in reality the problem has not been solved, but merely shifted into the community. Our study highlights this previously described phenomenon.

The ability of this wound protector to assist with retraction is a result of the stiff nature of the two rings, that when rolled with the inner ring in the peritoneal cavity and the outer ring on the skin provides circumferential wound retraction. Further directed wound retraction is usually required, however the wide view afforded is why surgeons in our study felt that the protector was useful purely on the basis of its retractional ability.

This randomised clinical trial of the use of retractional wound protection in open colorectal resectional surgery has demonstrated a statistically significant decrease in the rate of SSI. The large and clinically relevant reduction in SSI between the two study groups along with the retraction afforded by this form of wound protector suggests that barrier protection of this nature should be considered standard practice in open colorectal surgery.

References

Example of Alexis Wound Protector prior to insertion at laparotomy

Alexis Wound Protector after placement in laparotomy wound
Consort diagram barrier wound protection study

Elective Colorectal Resections
N=240

Laparoscopic Resection
N = 101

Open Resection
N= 139

Exclusions
N=2 (<18 yo)

Eligible Patients
N=137

Control
N =68

Active
N=67

Refused consent
N=2

Recruited
N = 135

Protocol violation
N=1

Death prior to completion of follow up
N =1

Control
N =67

Active
N =65

Control
Follow up complete
N = 66

Active
Follow up complete
N = 64

Protocol violation
N=2

Death prior to completion of follow up
N = 1
### Patient demographic data: table 1

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<td>Alcohol abuse (&gt;14SD/wk)</td>
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### Operative details: table 2

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<td>Colostomy takedown procedures</td>
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<td>173.4(76.5)</td>
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<td>Blood loss: mean mls (SD)</td>
<td>162(306)</td>
<td>128(206)</td>
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<td>Public vs. private hospital</td>
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<td>NS</td>
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<td>Surgeon distribution 1/2/3/4/5/6/7/8</td>
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<td>Incision midline vs. transverse</td>
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<tr>
<td>---------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>SSI: as per CDC guidelines (%)</td>
<td>15 (22.73%)</td>
<td>3 (4.69%)</td>
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<tr>
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<td>Readmissions for SSI</td>
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<td>Formal wound drainage for SSI</td>
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<td>Purulent wound drainage</td>
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<td>Intravenous antibiotic (no. of courses used to treat SSI)</td>
<td>10</td>
<td>3</td>
<td>0.077</td>
</tr>
<tr>
<td>Oral antibiotics (no. of courses used to treat SSI)</td>
<td>10</td>
<td>3</td>
<td>0.077</td>
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<tr>
<td>Total length of stay: mean days(SD)</td>
<td>12.3(6.2)</td>
<td>13.7(14.1)</td>
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</tbody>
</table>
2.5 Wound Closure Techniques in Colorectal Surgery

In order to minimise surgical site infection, a number of wound closure techniques have been applied in the field of colorectal surgery.

It became apparent in the late 19th century that certain suture materials were more prone to infection than others, and modern research has shown that monofilament sutures are less prone to infection than their braided counterparts. Presumably, this relates to the interstices present in braided sutures, where bacteria can lodge and be protected from phagocytosis, by leukocytes. In much the same way, minimising knot formation and suture bulk, can minimise infection. This has led to the widespread adoption of continuous, rather than interrupted suture techniques, to close wounds. It has also resulted in surgeons abandoning the technique of subcutaneous sutures, which used to add unnecessary suture material, while not providing increased wound strength.\(^\text{351}\)

In clean surgery, it appears that avoiding skin closure with interrupted sutures or clips results in less surgical site infection.\(^\text{335-336}\) It is less clear if this is the case in clean/contaminated surgery\(^\text{338}\) although as discussed in the previous chapter, continuous skin closure results in less superficial dehiscence rates for this form of surgery.\(^\text{337}\) For heavily contaminated or dirty wounds, the practice has generally been to avoid a ‘water-tight’ closure and adopt either the practice of interrupted closure, or leaving the superficial wound open for a variable amount of time. The former has the advantage of providing closure while still allowing for suture removal and relief of infection in the case of subcutaneous collections, while the latter tends to prevent ‘containment’ of any collection and potential prevention of septic episodes.

Delayed primary closure is a technique that has been employed with success for closure of contaminated wounds.\(^\text{352}\) It is the technique of leaving a heavily contaminated wound ‘open’, with the view to closure at a later time period once contamination is minimised and the patient is in a potentially better physiological state. This minimises infection rates, but has the drawback of repeated procedures.
Finally, avoiding skin closure by means of secondary closure is a successful way to minimise infection in heavily contaminated wounds. Most often, this is achieved in the current surgical era by vacuum dressings, and is a very useful surgical adjunct for the traumatic or heavily contaminated wound, in the already physiologically unstable patient. The prime example of a colorectal patient requiring a wound vacuum dressing, would be the patient requiring a ‘take back’ for anastomotic leakage.

One form of secondary closure that has been popularised for contaminated wounds is the ‘purse string’ suture closure. Mostly utilised for appendicectomy wounds, historically, the name is quite obviously derived from the string used to close the apex of older style purses, hence the origin of the terms: “tightening the pursestring”, or “controlling the pursestring”. The original purse strings were a single thread placed in a circular fashion around the apex or open end of the purse, that when pulled, would close the purse.

Figure 6: Picture of an older style purse, with a purse string

The concept of the purse string suture is that it provides the advantage of minimising infection (as with other forms of secondary closure) by still maintaining an open wound, but has the advantage over other forms of secondary closure of minimising wound size. Minimising wound size potentially results in more rapid healing, and less ‘scar’ area.
Although descriptions of delayed primary and secondary closure are common in the literature, comparative studies are rare. After the technique of purse string skin suture was described for ileostomy closure, the author and his colleague, Dr Brian Draganic, felt that this was an ideal way to close an ileostomy. Given the high contamination rates associated with ileostomy closure and the fact that the aperture is a circular one, it makes logical sense to perform a circular incision around the stoma and close this in a purse string fashion in order to maintain a small opening for infected fluid and material to ‘escape’, and to minimise scar tissue by ‘drawing in’ the edges of the incision. Despite this logic, at the time of the creation of the following randomised clinical trial, no comparative trials on the subject existed. The author and his colleague designed the following trial in order to determine if pursestring skin suture closure, performed at the time of ileostomy reversal, resulted in less surgical site infection, and improved cosmesis.

The following is the transcript of this trial, which was presented by Kate Reid, a Bachelor of Medical Science student, under the dual supervision of Dr Stephen Smith and Dr Brian Draganic (both Department of Colorectal Surgery, John Hunter Hospital, The University of Newcastle, NSW, Australia) at the Royal Australasian College of Surgeons Annual Scientific Congress in Brisbane in 2009. It was also presented by Dr Peter Pockney, the Colorectal Fellow working under the supervision of Dr Stephen Smith and Dr Brian Draganic at the Annual Scientific Convention of Surgeons of Great Britain and Ireland (ASGBI) in Glasgow in 2009. It was later accepted for publication by the British Journal of Surgery and published in October 2010.
Authorship Confirmation Page

This is to confirm, from the following fellow authors, that Stephen Smith was the Architect, Chief Investigator and Corresponding Author of the trial:

Pursestring closure of ileostomy wounds is superior to conventional closure for short term outcomes: a randomised controlled trial

Kate Reid

Peter Pockney

Tim Poliitt

Brian Draganic
2.6 Pursestring closure of ileostomy wounds is superior to conventional closure for short term outcomes – a randomized controlled trial

Abstract

Background: Ileostomy closure is an operation with an underappreciated morbidity, including surgical site infection, small bowel obstruction and anastomotic leaks. Surgical Site Infections (SSI) in particular are a frequent occurrence following closure of contaminated wounds. We report a randomized controlled trial comparing a pursestring closure technique with the current conventional linear closure technique.

Methods: Sixty one patients were randomized to conventional or pursestring closure of ileostomy wounds. The primary endpoint was the incidence of surgical site infection, including those requiring hospital or community treatment.

Results: Pursestring closure resulted in fewer surgical site infections than conventional closure: 2/30 (6.6%) vs 12/31 (38.7%) (p=0.005).

Conclusion: The pursestring method results in a clinically relevant reduction in SSI after ileostomy closure.

Introduction:

Surgical site infection (SSI) after ileostomy closure is a common problem, with reported incidence varying from 0% to 41% in the literature. This confers morbidity on individual patients and leads to slower returns to normal activity. It can cause significant increases in costs for health care providers, including extra days in hospital, increased use of medication and other consumables, and increased nursing costs in the community. There have been trials to investigate different ways of reducing SSI, including antibiotic implants, and delayed against primary closure. These have not produced clear benefits for patients, and so the optimal method of closure has hitherto not been defined.

The traditional way of closing an ileostomy has been to incise the skin with an elliptical cut, skirting the muco-cutaneous junction above and below the stoma,
extending the wound to apices sufficiently medial and lateral to the stoma to allow closure without tension. Once the stoma has been mobilised and closed, and returned to the abdomen, the sheath is closed and the elliptical skin incision is closed in a linear fashion with traditional sutures, either continuous or interrupted, or skin clips, or with glue.

Banerjee 5 reported a method of wound closure after reversal that appeared to have a lower SSI rate than conventional linear closure. Sutton et al 6 refined this report and described a short series of successful, infection free reversals using this method.

Banerjee’s method, termed the “pursestring” closure, involves mobilising the stoma by incising the muco-cutaneous junction around its whole circumference. The stoma is then freed from the subcutaneous fat and fascia layers, closed and returned to the abdomen. The fascia is closed and a purse-string suture placed within the hole in the subcutaneous layer and drawn in. The resulting small skin defect is left open; it can be loosely packed with either gauze or an absorbent wick. If used, a non-absorbable suture needs to be removed at approximately 2 weeks post procedure, which usually coincides with a routine post operative review where appropriate.

The pursestring technique therefore combines the concept of leaving the wound open to provide drainage and minimise SSI, while still providing some degree of wound apposition to minimise healing time.

The concern however with any form of closure by secondary intention is the potential effect on time to healing, cosmesis and patient satisfaction. Despite the description of the pursestring technique in the literature there is no comparative data to guide clinicians as to whether the routine application of this form of closure is appropriate.

This paper describes a prospective, randomised controlled trial which compares traditional linear closure with the pursestring closure with SSI as the primary outcome measure. It also seeks to determine whether cosmesis and surgical satisfaction is affected by pursestring closure as secondary outcomes.
Methods

This trial was performed by the Department of Colorectal Surgery, John Hunter Hospital, Newcastle, NSW, Australia. Recruitment took place between November 2006 and December 2007. Surgery was performed by two surgeons (BD, SRS) at four institutions.

All patients listed for elective closure of ileostomy at these institutions were approached to take part in the study. Informed consent was obtained prior to randomization. All participants were at least 18 years old and were excluded from the trial if they had language difficulties or an impaired mental state.

Ethical approval was granted by local research ethics (Hunter New England Human Research Ethics Committee: 06/06/28/5.04). The trial was registered with the Australian New Zealand Clinical Trials Registry, reference ACTRN12609000021279.

Randomization

Randomization was performed after the patient was anaesthetised. Allocation was performed in blocks of 20 by computer generated sequence allocation and concealment was by opaque sealed envelopes that were opened at the time of incision by a third party.

Interventions

The standard operative technique for traditional closure consisted of an elliptical incision around the stoma, with dissection into the peritoneal cavity and a formal resection of the ileostomy. The small bowel was joined with a side to side stapled anastomosis (GIA 80®; Autosuture), while the resulting entero-enterotomy was overstapled with a staple reload (GIA 80®; Autosuture) allowing resection of the Ileostomy peripheral to the staple line. Fascial closure was achieved en masse using 0 PDS® (Ethicon) and skin closure achieved with vertical mattress interrupted 3/0 Caprosyn® (Autosuture). Pursestring closure consisted of a circular incision around the Ileostomy utilising the same dissection and resection techniques for the small bowel. Fascial closure was identical to traditional closure,
while the circular skin incision was drawn in using a pursestring subcuticular suture (0 Prolene®; Ethicon).

A single dose of intravenous antibiotics was given at induction for all patients in the trial (Cephazolin 1g if <80kg, 2g if >80kg and Metronidazole 500mg). Anaesthesia was standardised and ventilation was maintained intraoperatively with 80% oxygen. Patient warming devices were used (Bair Hugger®, Arizant, MN) intraoperatively and a wound washout was performed using warm sterile saline after fascial closure and prior to skin closure. All patients were mobilised and given a full fluid diet on day 1. They were discharged from hospital when mobile, independent in activities of daily living, and medically fit.

**Outcome measures**

The primary outcome measure was SSI. The Center for Disease Control (CDC, Ga) definition of SSI was used. This is “Any infection of the superficial or deep tissues or the organ/space affected by surgery, and which occurs within 30 days of surgery when no prosthesis has been implanted.”\(^8\) An infection is defined by the CDC as being the presence of at least one of the following:

1. Purulent drainage, with or without laboratory conformation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.\(^9\)

All follow up both in and out of hospital was performed by a single trained observer (KR). The observer was not a practicing clinician involved with the trial and had undergone previous training in another trial at our institution examining SSI’s following laparotomies for colorectal resections. Due to the inherent nature of the trial it was not possible to blind the observer.
The secondary outcome measures recorded were time taken to complete healing, patient satisfaction with the surgical outcome and the patients’ perspective of the final cosmetic result of the operation. Cosmetic outcome was assessed by Visual Analogue Scale (VAS) from 0-10 with 0 representing worst possible outcome and 10 representing best possible outcome. Surgical outcome satisfaction was assessed using a 5 point Likert scale with patients choosing one of five options: very dissatisfied, dissatisfied, nonplussed, satisfied and very satisfied. 

Follow up was performed for all patients on postoperative days 1, 2 and 3 in hospital as well as at point of discharge. A further follow up was performed at 30 days postoperative. Wound inspection was performed by the observer at all points of follow up and in addition patients were questioned regarding signs of SSI, antibiotic use, community nurse visits and visits to General Practitioners (GP’s) at the 30 day visit. Patient satisfaction and cosmetic outcome was assessed by a telephone interview at a minimum of 12 months from operation.

**Statistical analysis**

The initial trial design used an estimate of the incidence of SSI with conventional closure of being 20% (published range 0% – 41%)\(^1\)\(^-\)\(^4\). In order to detect a clinically relevant reduction in SSI from 20% to 5%, with 80 per cent test power and an \(\alpha\) level of 0.05 a sample size of 59 was required for each group (total sample size of 120 allowing for dropouts and randomization).

Following this initial plan a study performed on all ileostomies created within our institution over a 5 year period revealed an unexpectedly high rate of complications \(^1\)\(^1\). As a result of this study it was decided that the authors’ standard clinical practice would be to defunction high risk anastomoses with colostomies rather than ileostomies. As a result of the potential loss of recruitment a decision was made to perform a planned interim analysis at the halfway mark of recruitment. Recruitment was stopped at this point due to the results obtained from this analysis.

Patients were analysed according to intention to treat principles. Categorical data was assessed using the \(\chi^2\) test except where cell frequencies were less than 5, when Fisher's exact test was used. Comparison of means was performed using
Students \( t \) test. Comparison was made between SSI using Fisher’s exact test. Statistical analysis was performed using Minitab 14® Statistical software and the analyst was blinded as to which group was control or intervention (groups were designated A or B by a third party for analysis)

**Results**

Between November 2006 and December 2007 sixty one patients underwent elective ileostomy reversal. All sixty one were approached and consented to take part in the study. There were no exclusions and no loss to follow up. The consort diagram for the progress of the recruited patients is shown in figure one.

The demographic characteristics, reasons for stoma formation and patient comorbidities are presented in table 1.

There were no intraoperative complications in either group, and both groups had a similar mean length of stay with no difference in overall complications. (table 2)

The overall SSI rate for the trial was 22.9% (14/61). Four SSI’s were diagnosed in hospital (3 in control group) resulting in 71% of SSI’s being diagnosed after discharge and an overall ‘inhospital’ SSI rate of 6.6%.

There was a marked difference between the SSI rates in the two arms of the study, 2/30 (6.6%) in the pursestring arm vs 12/31 (38.7%) in the control arm (p=0.005). There were no readmissions specifically for SSI and no reoperations in either group. There were five cases of superficial wound dehiscence (1 in pursestring arm, 4 in control arm) while four wounds required drainage (all control). A total of four courses of intravenous antibiotics were used (1 pursestring / 3 control) while thirteen courses of oral antibiotics were prescribed (5 pursestring / 8 control). Community nurse visits were required for five patients (2 pursestring / 3 control).

The Numbers Needed to Treat (NNT) by pursestring technique in order to prevent one SSI in this study equates to 3.1.

There was no difference between the two groups with regards time to healing (20.6 days pursestring v 24.6 days control).
There was similarly no difference between the two groups with regards to satisfaction with surgical outcome: 24/30 very satisfied, 6/30 satisfied in pursestring group compared to 22/31 very satisfied, 9/31 satisfied in control group.

Finally there was no difference with regards to the secondary outcome of cosmesis: mean VAS pursestring 7.8 vs 7.38 control.

**Discussion**

This randomized controlled clinical trial comparing pursestring closure with conventional closure for ileostomy wounds demonstrates a lower incidence of SSI when ileostomy wounds are closed using the pursestring method. The reduction of SSI shown in this trial is not only statistically significant but clinically relevant (32 per cent reduction in SSI with pursestring closure).

The patient populations in the two arms of the trial were well matched in most regards, with the exception of gender and original indication for surgery. We cannot explain the disparity between male and female allocations generated by the randomisation process, but are aware of no gender factors which significantly affect wound healing. Similarly, we cannot account for the difference in original disease that led to primary surgery. The number of non cancer patients (13) is small in this trial, and a skewed distribution between the two arms is more likely to occur with small numbers being randomised than with large.

True ‘blinding’ in this trial was not possible. The patients and the observer were not told which of the methods had been used. The trial arm allocation is, however, clear on simple inspection of the wound for an observer who is aware of the differences between the techniques, so this cannot be considered a true blinded trial. This is an inevitable and insoluble problem in this type of study. In an attempt to overcome the potential bias that lack of blinding may have brought to this study we used an independent trained observer as the outcome assessor. The observer was trained at using the CDC guidelines for SSI, and these were strictly adhered to.
The control arm has a similar rate of infection to the primarily closed wounds in some of the previously published studies of ileostomy closure that are in the literature. We are comfortable that this is a true reflection of the actual SSI rate that occurs after this procedure. SSI rates are higher if the patients are observed both in hospital and after discharge in the community, and this is reflected in this study with 71% of SSI's clinically occurring after discharge from hospital. Follow up in this trial was for a minimum of 30 days in order to capture all SSIs that occurred.

Other surgeons have discussed that it is easy to control and treat the minor infections that usually result from closure wounds. However, that doesn’t diminish either the harm to individuals that result from slow healing or the potential for catastrophe that any superficial SSI has should it develop into systemic sepsis.

The longer term implications of SSIs in this type of wound such as the development of incisional hernias also need to be considered. If pursestring closure results in a significant reduction of SSIs such as expressed in this small trial this might result in similar ratios of reductions in incisional hernias with longer term follow up. It must be pointed out that this trial is not designed to determine whether this is the case and a trial involving much larger numbers would be required.

It must be pointed out however that in the individual with a thick abdominal wall fascial closure can be quite difficult with the pursestring technique due to limited access. While the traditional incision can easily be extended at either end, the pursestring incision cannot and this access may hamper adequate closure, also with the potential to increase incisional hernias.

Different surgical techniques have been used in the past in order to diminish SSI following ileostomy closure. Leaving the wound entirely open without a pursestring is a potential way to avoid SSI’s, however the secondary intention that results is a much slower process than primary closure, with a large unsightly scar resulting. Leaving a drain (either placed subcutaneously or of the Penrose variety in one end of the wound) is another alternative, but increases the nursing input in the post-operative period and is not reliable at preventing the infections that
become apparent after discharge from hospital (the majority of SSIs). The pursestring closure ‘marries’ the principles of both these techniques (drainage and secondary intention) while also providing rapid healing.

We attribute the difference in infection rates in our study to the morphology of the wounds that result from the techniques. The linear closure is indeed a closure of the skin layer, whether by clips, glue, interrupted or continuous sutures, subcuticular or mattress in pattern. The superficial dermal layers will heal quickly, with the potential to close bacterial contamination in the superficial wound space, promoting symptomatic infection in the post operative period. The pursestring closure is in fact not a closure of the wound at all; there is a small opening left in the centre of the wound, where skin is not in apposition to skin. This small opening closes by secondary intention in the weeks following the operation, but in the early post surgical period allows free drainage of serous fluid and contaminants from the wound, preventing symptomatic infection from developing.

We have shown in the context of this trial that pursestring closure may enhance the speed of the secondary intention process, while also maintaining a comparable cosmetic outcome.

In conclusion the results of this randomized clinical trial reveal that pursestring closure of ileostomy wounds result in reduced Surgical Site Infection rates without compromising other clinical outcomes.

Reference List

5 Banerjee A. Pursestring skin closure after stoma reversal. Dis Colon Rectum 1997; 40(8) 993-4
10 www.dssresearch.com/toolkit/sscalc/size.asp
Ileostomy closure suture placed around circular incision
Example of incision closure after tying purse string suture
Example of long term cosmesis following conventional linear closure ileostomy

Example of long term cosmesis following pursestring closure ileostomy
**Consort diagram:**

- **Assessed for eligibility**: N=61
- **Excluded**: N=0
- **Randomised**: N=61
- **Conventional Closure**: N=30
  - **Lost to Follow up**: N=0
  - **Analysed**: N=30
- **Purse String Closure**: N=31
  - **Lost to Follow up**: N=0
  - **Analysed**: N=31
Table 1: Patient Characteristics

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<th>Linear closure (n=31)</th>
<th>Purse-string closure (n=30)</th>
<th>P</th>
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<td>Age (years)*</td>
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<td>Sex ratio (M : F)</td>
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</tr>
<tr>
<td>ASA status*(1/2/3)</td>
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<td>9/16/5</td>
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</tr>
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<td>Original indication for surgery</td>
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<tr>
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<tr>
<td>No</td>
<td>9</td>
<td>15</td>
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<tr>
<td>Body mass index (kg/m²)*</td>
<td>26.3(4.9)</td>
<td>24.9(5.0)</td>
<td>0.274†</td>
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<tr>
<td>Time from primary surgery to closure (days)*</td>
<td>144.8(78.0)</td>
<td>111.4(44.5)</td>
<td>0.045†</td>
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</tbody>
</table>

*Values are mean(s.d.). ASA, American Society of Anesthesiologists. †Student’s t test; ‡Fisher’s exact test; §Chi-square test.
Table 2: Comparison of outcomes in the two groups

<table>
<thead>
<tr>
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<th>Purse-string closure (n=30)</th>
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<td>Operating time (min)*</td>
<td>48.2(22.0)</td>
<td>48.4(19.0)</td>
<td>0.970†</td>
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<td>Length of hospital stay (days)*</td>
<td>6.1(3.5)</td>
<td>5.5(3.9)</td>
<td>0.529†</td>
</tr>
<tr>
<td>Postop. pain (VAS 1–10)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3.1(2.3)</td>
<td>3.4(1.8)</td>
<td>0.574†</td>
</tr>
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<td>Day 2</td>
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<td>1.9(1.9)</td>
<td>2.1(2.1)</td>
<td>0.698†</td>
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<tr>
<td>SSI</td>
<td>12</td>
<td>2</td>
<td>0.005‡</td>
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<tr>
<td>Healing time (days)*</td>
<td>24.6(10.4)</td>
<td>20.6(11.9)</td>
<td>0.167†</td>
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<td>Cosmesis at 12 months (VAS 1–10)*</td>
<td>7.4(0.9)</td>
<td>7.8(1.5)</td>
<td>0.208†</td>
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<tr>
<td>Cosmesis in patients without SSI (VAS 1–10)*</td>
<td>7.3(1.0)   (n=19)</td>
<td>7.8(1.6)  (n=28)</td>
<td>0.243†</td>
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</table>

*Values are mean(s.d.). VAS, visual analogue scale; SSI, surgical site infection. †Student’s t test; ‡Fishers exact test.
Chapter 3.

3.1 The Importance of Adequate Post-operative Analgesia

Adequate post-operative analgesia is essential for recovery following all forms of abdominal surgery. Apart from the fact that unnecessary suffering as a result of pain, is inhumane, studies have shown that adequate analgesia has the potential to decrease the rate of post-operative complications, such as pneumonia, prolonged ventilation, reintubation, cardiac complications, immobility and thrombo-embolic phenomena, and the rates and duration of post-operative ileus, following abdominal surgery.\textsuperscript{356,357} In addition, adequate analgesia has the potential to minimise longer-term complications by blocking immune-suppression that major surgery causes, as well as potentially decreasing long term chronic pain, which has a higher association with increased acute post-operative pain.\textsuperscript{358}

Before considering management of post-operative pain, one needs to determine how and to what severity, pain is affecting the post-operative patient. To this extent, assessment systems have been devised, to determine how much analgesic assistance is required in the post-operative environment, as well as to determine if escalation is required in certain patients. Assessment systems have been mainly subjective and not entirely reliable due to the influence that experience, anxiety, fear and cultural background have on the interpretation of pain. The most internationally accepted assessment tool is the 10 point pain assessment scale, most commonly referred to as the Visual Analogue Score or Numeric Rating Scale, where 1 is no pain, and 10 is the worst pain imaginable.\textsuperscript{359} It could be argued that more objective forms of pain assessment should also be considered in order to guide analgesic management. These include: measurements of analgesic consumption, respiratory function tests, mobility scores and sedation scores.

Ideal post-operative analgesia is management whereby pain is minimised, side effects are minimal, and recovery is hastened with minimal complications. All forms of analgesic intervention have their problems, however. The mainstay of pain therapy
following abdominal surgery, for years, has been opiates, but the advent of ERAS programs has led to an increased awareness of the problems associated with these medications, particularly following colorectal surgery. The side effects of opiates are many, but include: sedation, respiratory depression, nausea, vomiting, delayed gastrointestinal transit and delayed bowel function. All these side effects are undesirable following colorectal surgery, and with this in mind, many attempts have been made, to minimise opiate intake. Opiate sparing strategies include: neuro-axial blockade (with local anaesthetic and/or opiates), locoregional blockade, local anaesthetic infiltration techniques and other non-opiate medications. The use of different types of pharmacological agents to facilitate adequate post-operative analgesia, while minimising the side effect profile of opiates, is known as multimodal analgesia, and this concept has been around for about 15-20 years now. The most commonly used agents in a multimodal approach include: opiates in their different forms, paracetamol, non-steroidal anti-inflammatory agents and COX-2 inhibitors. Other less commonly used medications include: ketamine, gabapentin and pregabalin, magnesium and clonidine. Some of these are still in the experimental phase with respect to clinical efficacy in the post-operative setting.

Given the significant side effect profile of medical therapy (particularly opiate therapy), the thoracic epidural using local anaesthesia has become the gold standard of care for recovery following colorectal surgery. A well placed thoracic epidural managed in an environment with experienced nursing supervision, not only has the ability to abolish somatic pain following abdominal surgery, but to diminish the sympathetic stress response that follows major surgery, and block the visceral sympathetic response that is responsible for post-operative ileus. In addition, trials have shown that epidural analgesia may have the added potential benefit of decreasing intra-operative blood loss, improving post-operative respiratory function and decreasing post-operative catabolism. Given all these potential benefits, it is not surprising that many ERAS units around the world routinely use this form of analgesia for recovery following colorectal resectional surgery, even in its laparoscopic form. There are potential drawbacks, however. The previously mentioned MASTER trial showed benefit only in respiratory morbidity associated with epidural placement, and the latest
Cochrane Review on the topic draws the same conclusion. The common side effects of epidurals include hypotension and muscle weakness, which may slow mobilisation. Epidural analgesia may also mask important abdominal signs and require frequent review, given the propensity for hypotension, ‘masking’ and ‘top-ups’ for incomplete blockade. Given this need for frequent review, it is imperative that thoracic epidurals are managed in an experienced nursing environment, with either a high nurse to patient ratio, or ready access to staff experienced with epidural management. In addition, there are the two most feared complications of epidurals, haematoma and abscess, both of which are catastrophic and can lead to permanent neurological defects if not recognised and dealt with early. Although these complications are rare, given the significance associated with them, and the fact that many patients are on anticoagulants, their routine use in highly litigious countries, such as the United States and Australia tends to be lower than in European countries.

With the above in mind, there is the need to explore alternative forms of ‘neural blockade’. Spinal techniques, most commonly in the form of a ‘one-off’ morphine lumbar spinal injection, have been described with success for colorectal surgery. The advantage of this over an epidural, is its simplicity and safety, but it does not confer the same benefits in terms of longevity of blockade, nor does it diminish the sympathetic stress response to the same degree as an epidural block does. Paravertebral blockade is very effective for unilateral somatic blockade, and is used most commonly for unilateral operations such as nephrectomy or thoracotomy. Travelling further distally along the neural pathway, blockade can be performed at the more regional level for abdominal surgery. Techniques such as transversus abdominis plane (TAP) blocks or rectus sheath (RS) blocks have recently been described with some success and a high degree of safety. TAP blocks are placed in the plane between the transversus and internal oblique muscles, while RS blocks are placed just anterior or ‘on’ the posterior rectus sheath. Even further ‘distal’ towards the incision, is the technique of wound infusion, that can be achieved either into the ‘neural plane’ within the wound, or simply into the muscular and subcutaneous tissues.
3.2 Post-Operative Local Anaesthetic Wound Infusions in Colorectal Surgery

The first descriptions of local anaesthetic wound infusions to assist recovery following colorectal surgery, began to emerge in the late 1980s, but randomised clinical trials assessing their efficacy were not performed until into the 21st century. Ideal for their simplicity, in terms of insertion and maintenance, and potential relative safety, local anaesthetic infusions appear, on face value, to be enticing. Providing afferent blockade at the source of the post-operative pain is also logical, and it is somewhat surprising that this development has been a relatively new arrival, in terms of the management of post-operative pain.

Complete afferent blockade at the site of incision, of course, is not possible in colorectal surgery. Muscular pain from the incision is not that well controlled by this method, as the neuronal supply to the muscles is often in a more proximal location to the source of blockade at the incision. Visceral ‘pain’ is also poorly affected by infusion into the wound, although there are methods to counteract this, either by direct peritoneal infusion or infusion into the pre-peritoneal space.

In terms of assessing the relative efficacy of local anaesthetic wound infusions, heterogeneity of the trials also make for difficult interpretation. The variety of incisions and methods of placement, not to mention rates, duration and formula of local anaesthetics, make any surgeon’s assessment, as to the applicability of each type of infusion to their surgical practice, a very tough one. Despite this, there does appear to be merit in performing wound infusions. A meta-analysis of all randomised clinical trials analysing post-operative wound infusions in colorectal surgery, revealed that wound infusions significantly reduce opioid consumption as well as pain on movement for the first three hospital days. Both these outcomes would certainly be considered clinically relevant ones. Mean opioid consumption was 40 MeQ less in the wound infusion group overall, based on data from five RCT’s involving 542 patients (WMD -40.13, 95% CI: -76.74 to -3.53; p=0.03). Reduction in movement related pain appears...
most effective on the first post-operative day (WMD -1.14, 95% CI: -2.24 to -0.041; p=0.04), but remains significant over day 2 (WMD -0.97, 95% CI: -1.91 to -0.029; p=0.04) and day 3 (WMD -0.61, 95% CI-1.01 to -0.2; p=0.0038). Despite these outcomes, there was no improvement in length of hospital stay or return of bowel function associated with local anaesthetic infusions in the context of this meta-analysis.

All the trials in this meta-analysis consisted of patients undergoing open colorectal surgery. Given the significant reduction in pain seen with laparoscopic colorectal surgery when compared to its open counterpart, wound infusions did not seem to play a part in the early evolution of laparoscopic colorectal resections. In view of the increasing amount of colorectal resections performed laparoscopically, it was the author’s opinion that wound infusions should be examined in detail for this form of surgery. Prior to the design of the following randomised clinical trial, there had been no published RCT on this topic, so an RCT was designed to examine the efficacy of wound infusions placed in the neural plane in the major extraction wound at the time of surgery.

The following is the transcript of this trial, which was presented by Dr Sarah Moore, a research registrar, under the supervision of Dr Stephen Smith (Department of Colorectal Surgery, John Hunter Hospital, The University of Newcastle, NSW, Australia) at the Royal Australasian College of Surgeons Annual Scientific Congress in Perth, 2010. It was later accepted for publication by Techniques in ColoProctology and published in 2012.
Authorship Confirmation Page

This is to confirm, from the following fellow authors, that Stephen Smith was the Architect, Chief Investigator and Corresponding Author of the trial:

Randomized clinical trial of ropivacaine wound infusion following laparoscopic colorectal surgery

Sarah Moore

Kate Reid

Brian Draganic
3.3 Randomized clinical trial of ropivacaine wound infusion following laparoscopic colorectal surgery

Abstract

Background: Wound infusions with local anaesthesia have been used with varying success following laparotomy for colonic resections. This trial sought to determine the efficacy of ropivacaine wound infusion following laparoscopic colorectal surgery.

Methods: 48 consecutive patients undergoing elective laparoscopic resectional surgery were randomized to receive either a local anaesthetic wound infusion (ropivacaine 0.5%) or normal saline for a period of 72 hours. The primary endpoint was postoperative pain as assessed by analgesic consumption, while secondary endpoints assessed were visual analogue pain scores, respiratory function, gastrointestinal function, length of stay and postoperative complications.

Results: There was no difference in mean postoperative analgesic consumption between the two groups over 72 hours (143mEq morphine control vs 94mEq intervention; p=0.108). Likewise there was no difference in daily postoperative analgesic consumption or visual analogue pain scores between the two groups. Patients in the ropivacaine group experienced less reduction in their postoperative Forced Expiratory Volume at 1 second on day 1 (mean difference FEV1 0.4 Litres; p=0.015). There was no difference between the two groups with respect to return to gut function and postoperative complications.

Conclusions: In this study, local anaesthetic wound infusion with ropivacaine following elective laparoscopic colorectal surgery improves early respiratory function, but does not appear to provide an improvement in postoperative analgesia or other clinically relevant postoperative outcomes.

Introduction

With the advent of Enhanced Recovery After Surgery (ERAS) programmes an increased emphasis has been placed on recovery after colorectal surgery with
neuroaxial blockade.¹,² The potential benefits to this form of blockade include a reduction in postoperative opiate use for analgesia, as well as an improvement in respiratory and gut function.³-⁶ There are, however, potential risks associated with neuroaxial blockade such as haematoma, infection and paralysis.⁷ Postoperative care of patients with continuous neuroaxial blockade is also a highly intensive activity requiring experienced nursing support.⁸

The alternative to neuroaxial blockade, is via a locoregional approach, which can be administered either as a depot injection⁹ or via an infusion,¹⁰ and can be delivered peripherally at the site of surgical incision, or anywhere along the ‘neural’ path between the exit of the nerves from epidural space to the surgical site. Peripheral wound infusions can be easily achieved by placing a catheter directly in the wound, but this logically should not alter ‘muscular’ pain caused by surgical trauma and it is this type of pain that theoretically affects the ability of the patient to take deep breaths, thereby potentially compromising their respiratory function.¹¹ Alternatively catheters can be placed in the ‘neural’ plane, where the somatic nerve fibres travel between muscle layers.¹² This can be achieved laterally in the abdomen by ultrasound guidance,¹³ or more simply at incision closure by running the catheter laterally in the correct plane between the posterior rectus sheath and the rectus muscle, or more laterally between the internal oblique and transverses musculature.¹⁴

Multiple studies have been performed to assess the efficacy of local anaesthetic wound infusions for laparotomy wounds.¹⁵-²⁰ These have produced conflicting results, and there are no trials to our knowledge, assessing the efficacy of this approach for laparoscopic colectomy.

The aim of this trial was to assess the role of wound infusions with local anaesthesia for postoperative analgesia following laparoscopic colonic resection. In particular this trial was designed to assess if infusion both into the wound as well as the ‘neural’ plane resulted in less postoperative pain, a reduction in opiate use and an improvement in respiratory function.

Methods
This prospective randomized clinical trial was performed by the Department of Colorectal Surgery, John Hunter Hospital, Newcastle, NSW, Australia. The study protocol was approved by local ethics (Hunter New England Human Research Ethics Committee: 06/12/13/5.03). The trial was registered with the Australia and New Zealand Clinical Trials Registry: ACTRN12609000745246.

All patients over 18 scheduled for an elective laparoscopic colonic resection were invited to participate in the study. Patients on preoperative opiate analgesics, with existing pain syndromes, renal failure, or who were cognitively impaired or otherwise unable to give informed consent were excluded. Patients with rectal resections or resections involving stomas were also excluded.

Surgical technique involved tunnelling an epidural catheter laterally from the extraction wound such that the fenestrated tip of the catheter lay in the most lateral aspect of the wound with fenestrations in both the ‘neural’ and the subcutaneous planes. Skin closure was then performed using a subcuticular 3/0 Caprosyn® (Covidien) continuous suture.

Postoperatively an infusion was commenced through this catheter using a 50ml syringe driver. Patients were randomized to receive either saline 0.9% (control) or ropivacaine 0.5% (intervention) at 8ml per hour for 72 hours.

Randomization was performed after consent had been obtained and following completion of the operating procedure. Allocation was in blocks of 10 by computer generated sequence allocation. Both patients and treating surgeons were blinded as to allocation, and all data collection was performed by a third party with no knowledge as to group allocation.

Postoperative analgesia was standardised by use of a Patient Controlled Analgesic (PCA) device, with fentanyl being the analgesic of choice (morphine was used if fentanyl was deemed unsuitable by the anaesthetist). All patients received regular paracetamol 4g daily. Patients were commenced on a full fluid diet the day after surgery, with progression to a selective diet once they passed flatus. Discharge occurred once patients were tolerating a selective diet, had evidence of full return of gastrointestinal function, were fully mobile, were not requiring regular opiate
analgesia and were considered able to return to fully independent activities of daily living.

Data collection involved baseline demographics and spirometry. Postoperatively overall in-hospital opiate consumption as well as daily opiate consumption was recorded. Spirometry was performed daily postoperatively as well as at follow-up appointment. Visual Analogue Scores (VAS) for pain were recorded daily (0 for no pain, with 10 representing worst possible pain). Tolerance of diet, nausea and vomiting was recorded daily in a categorical fashion. Time to flatus and bowel motion was also recorded by the patient. Length Of Stay (LOS) and postoperative overall, as well as wound-related complications were recorded.

**Statistics**

A pilot study of 20 consecutive patients following laparoscopic colonic resectional surgery at John Hunter Hospital revealed a mean 72 hour postoperative opiate requirement of 60 meq (±18 meq) of morphine. Based on a perceived clinically relevant analgesic reduction of 25% (80% test power and alpha level of 0.05), 50 patients were required (25 in each arm).

**Results**

51 consecutive patients undergoing laparoscopic colonic resections were recruited between March and September 2007. 3 cases were cancelled, resulting in 48 patients being operated and randomized. A further 3 protocol breaches occurred (one spinal, one epidural and one intraoperative ‘unblinding’) resulting in 45 eligible patients. 24 patients were randomized to receive normal saline (control), while 21 received ropivacaine (intervention). Follow-up was complete on all 45 of these patients (see figure 1. consort diagram).

Baseline demographics revealed a higher rate of respiratory disease in the intervention group (5/21 vs 0/24; p=0.017), as well as a lower FEV1 in the intervention group (2.1 L vs 2.5 L; p=0.029). All other demographics were similar (see table 1).

There was no difference between the two groups with respect to operations performed or intraoperative data (see table 2). No conversions to open procedures
occurred in either group and there was no difference in incision types or lengths between groups.

Postoperative mortality was zero, and postoperative morbidity was low, with 4 patients returning to theatre: 1 in the control group for a pelvic collection, 1 in the intervention group for a pelvic collection and 2 in the intervention group for postoperative haemorrhage (1 from the anastomosis, 1 from colonic mesentery). There were no anastomotic leaks in either group, and no difference in wound related complications between the two groups (table 3).

There was no difference in total postoperative analgesic use between the two groups over 72 hours (143 mEq morphine control, 94 mEq morphine intervention; p=0.1078), and likewise no daily difference in analgesic use between groups (figure 2). There was also no difference in VAS for pain between the two groups (figure 3).

There was a difference in postoperative respiratory function between the two groups (figure 4). Patients in the intervention group had less reduction in their FEV1 on day1 (mean difference 400ml; p=0.0153, 95% CI 0.089-0.784). There was no difference in respiratory function between the two groups over the second and third postoperative days.

There was no difference between the two groups with respect to time taken to pass flatus, time taken for first bowel motion or length of hospital stay (table 4).

**Discussion**

This randomized clinical trial comparing ropivacaine and saline wound infusions following laparoscopic colorectal resectional surgery revealed no difference in postoperative pain between the two groups. Patients in the ropivacaine group experienced less reduction in their postoperative respiratory function on day 1.

A number of randomized clinical trials have been published assessing the use of continuous local anaesthetic agents following open colorectal surgery but little data is available surrounding the same technique for the laparoscopic approach. A systematic review of five randomized trials in open colorectal surgery revealed that patients who received local anaesthetic wound infusions required...
less opiates postoperatively, but there was no difference in other more clinically relevant parameters associated with improved analgesia such as return of gut function and length of stay.20

Respiratory morbidity following abdominal surgery is a frequent and clinically relevant complication.7 The association between postoperative abdominal muscular pain, with poorer respiratory excursion, and subsequent respiratory morbidity is well established.11 This study revealed that patients in the intervention group suffered less reduction in their postoperative lung function on the first day following surgery, possibly as a result of less postoperative ‘muscular’ pain around the incision site, and therefore less impairment in respiratory excursion and FEV1. The intervention group had a higher rate of patients with pre-existing respiratory disease, which may have had an impact on the outcome of respiratory function, so difference from preoperative baseline was chosen as the outcome measurement of choice to assess recovery.

An important aspect of recovery following colorectal surgery is the return of gastrointestinal function. One of the potential advantages of more central neuroaxial blockade is the ability to block the sympathetic splanchnic response, thereby minimising postoperative ileus.3,4,6 Wound infusions lack the ability to achieve this, so rely on minimising pain and reducing opiate requirements in order to hasten return of gut function. This theoretical benefit was put to the test in this trial and a number of aspects of gastrointestinal function were assessed including time to flatus, first bowel motion as well as diet tolerance. No direct benefit in terms of gut function was observed as a result of the intervention in this trial.

Catheter location may play a crucial role in postoperative analgesia with wound infusion techniques. Polglase et al19 found no difference in postoperative pain when the catheter was placed subcutaneously in the wound following laparotomy for colectomy, while Wang et al23 that the reason for diminished postoperative opiate consumption in the intervention arm of their study, involving similar intervention, was the placement of the catheter at the muscular edge. Placement of the catheter in the subfascial plane following inguinal hernia surgery has been shown to decrease postoperative pain and result in the ability to perform this procedure in an ambulatory setting.24 More peripheral catheter placement in the ‘transversus
abdominus' plane, between the transverses and internal oblique musculature, has been described, with success in reducing pain following open nephrectomy, while further posterolateral placement in the same plane using ultrasound guidance has also been described. Placement in the pre-peritoneal plane appears to result in reduction in postoperative pain as well as hastening postoperative gut function. Differences in placement techniques make meaningful comparisons difficult across trials of this nature, but also suggest that the ideal anatomical location for infusional analgesia is yet to be determined.

Morbidity was low in this study, and in particular no complications occurred as a direct result of local anaesthetic infiltration. There was no difference in wound related complications seen between the two groups in this study. It should be noted that follow up was in hospital only, and as such surgical site infection could well be underestimated in both groups. Laboratory studies and a recent literature review have shown that local anaesthetics possess inherent antimicrobial properties, although there is no relevant data to our knowledge, to suggest this translates into improved clinical outcomes. The meta-analysis by Karthikesalingam et al indicates that wound infusions with local anaesthetics appear to be safe, and our study lends support to this.

Mobility following surgery is an important factor in improving outcomes. Syringe driver infusion pumps were used for the purpose of the trial, and are quite cumbersome to carry around. Other similar studies have used smaller (and more costly) infusion devices, and the authors suggest that future trials involving comparisons of analgesic regimes, also include some form of mobility assessment as an outcome.

Further research is required to determine the optimal form of postoperative analgesia for laparoscopic colorectal surgery and in particular attention needs to be placed on comparison between site of delivery as well as modes and timing of delivery. The optimal mode of delivery should be safe, effective at reducing pain and opiate requirements, result in improving important clinical recovery parameters such as respiratory and gut function, require minimal support and not be a barrier to mobility.
This trial reveals that the infusion of post operative local anaesthetic into the wound following elective laparoscopic colorectal resection is a safe manoeuvre that doesn’t appear to reduce postoperative analgesic consumption. Based on the results of this trial the routine use of this type of infusion is not recommended, however consideration should be given to its use in patients with significant respiratory disease, particularly in the first 24 hours after surgery.

References

Figure 1: Consort Diagram

Potential participants
n=53

Refusal n=1
Allergy to local anaesthetic n=1

Recruited participants
n=51

Cancelled operation n=3

Randomized participants
n=48

Protocol breaches n=3

Control participants
n=24

Follow up data
n=24

Intervention participants
n=21

Follow up data
n=21
### Table 1: Patient Demographics

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### Table 2: Operative Data

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Table 3: Postoperative Morbidity

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Table 4: Postoperative Outcomes

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Figure 2: Analgesic Consumption (morphine mEq)

Figure 3: Daily Postoperative Visual Analogue Pain Scores
Figure 4: Postoperative Respiratory Function: Reduction in FEV1 compared to baseline

![Graph showing FEV1 reduction](image)

MD day 1 = 400 ml; p=0.0153
## Supplementary:

**DATA SHEET – ROPIVOCAINE WOUND INFUSION RCT**

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### DAY 1:

**VISUAL ANALOGUE PAIN SCORE**

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<table>
<thead>
<tr>
<th>FEV1</th>
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DAY 2:

**VISUAL ANALOGUE PAIN SCORE**

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</table>

FEV1..............................FVC........................................
NAUSEA..............................................................
VOMITING.............................................................
DIET.................................................................
PCA / NARCOTIC USE .................................
ORAL ANALGESIA............................................
F LATUS YES/NO TIME: BOWEL MOTION YES/NO TIME:

DAY 3:

**VISUAL ANALOGUE PAIN SCORE**

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</table>

FEV1........................................FVC.................................
NAUSEA..............................................................
VOMITING.............................................................
DIET.................................................................
PCA / NARCOTIC USE ..........................................................

ORAL ANALGESIA ..........................................................

FLATUS  YES/NO  TIME:  BOWEL MOTION  YES/NO  TIME

ONE MONTH FOLLOW UP:

VISUAL ANALOGUE PAIN SCORE

0 2 4 6 8 10

HOSPITAL DISCHARGE OUTCOMES

TIME ON PCA ..........................................................

TIME TO DISCHARGE ..................................................

TIME TO FIRST STOOL ..................................................

TIME TO FIRST FLATUS .............................................

POST-OP COMPLICATIONS ...........................................
3.4 Abdominal Wall Neuromuscular Blockade

The logical next step, with respect to post-operative analgesia following abdominal colorectal surgery, is to provide a more directed approach to afferent neural blockade. There is not one single nerve that provides somatic supply to the abdominal wall, hence, one cannot perform a straightforward nerve block to assist with post-operative afferent blockade. The somatic nerves of the abdominal wall do, however, travel within planes that lend themselves to ‘field blockade’ where depots of local anaesthetic can be placed.

After passing laterally to the paravertebral muscles, the thoraco-abdominal nerves (dermatomal distribution T7-T11), the subcostal nerve (T12) and the ilio-hypogastric nerve (T12-L1) all course around the abdominal wall in the same plane, running just superficially to the transversus abdominis muscle. They all run on this muscle for a variable distance, with the upper thoraco-abdominal nerves freeing themselves of the costal margin somewhat more antero-medially to the more inferior nerves. The densest distribution of these nerve fibres occurs between the anterior superior iliac spine and the costal margin. It is at this point that most TAP blocks are administered, mostly using ultrasound guidance.

As the nerves travel more medially towards the midline, they travel in close proximity, just anterior to the posterior rectus sheath, and given the nature of this sheath, this provides an enclosed area suitable for injectate of local anaesthesia, between the sheath and the rectus abdominis muscle. This rectus sheath block can be placed using ultrasound guidance or under direct vision at the time of surgery.

The potential advantage of abdominal wall blocks over wound infusions is that they provide a more proximal block and require less overall volume. This may in turn potentiate better ‘muscular’ analgesia, so important in the recovery process after surgery, by assisting respiratory recovery and mobility.

The most commonly described abdominal wall block for abdominal surgery is the TAP block, which surprisingly, was only recently described. Rafi is the first person credited with describing the TAP block in 2001, outlining a technique of injecting local
anaesthetic into the region of the lumbar triangle of Petit. He described a ‘blind’
technique relying on a ‘double pop’ to identify the neural plane; the first ‘pop’
signifying penetration of the external oblique fascia, while the second ‘pop’ indicated
the needle piercing the internal oblique, and lying in the correct plane between the
transversus abdominis and internal oblique. Hebbard went on to describe the
technique using ultrasonography, which has gained widespread popularity. This
involves an approach more distal in the course of the nerves as they traverse the
abdominal wall in the same plane, between the anterior superior iliac spine and the
costal margin. Hebbard then went on to describe an extension of the technique to
block the upper abdomen more effectively, utilising a subcostal approach in addition,
further supero-medially. McDonnell has performed a number of early studies
looking at the clinical efficacy of TAP blocks from cadaveric dissection studies assessing the distribution of the field blockade, all the way through to randomised clinical trials on abdominal surgery. Since his publications, the amount of clinical trials assessing TAP blockade has exploded.

The most up to date Cochrane meta-analysis on the role of TAP blockade was
published in 2010. This review identified five RCTs involving 236 participants, and
found that TAP blockade, when compared to standard care, resulted in less post-
operative requirement for opiates at 24 hours (MD morphine -21.95 mg, 95% CI -37.91 to -5.96), and 48 hours post-operatively (MD -28.50 mg, 95% CI -38.92 to -18.08). In the context of this meta-analysis, pain at rest was also decreased in two out of the three trials that analysed pain scores.

Four years later, a meta-analysis on the role of TAP blockade following laparoscopic surgery has been performed, identifying 10 RCTs involving 633 patients, highlighting the rapid uptake of this form of post-operative analgesia. This meta-analysis revealed that TAP blockade was associated with a fairly minimal reduction of approximately 6mg in morphine equivalent usage following laparoscopic surgery. It also appears, on the basis of this study, that pain at rest (VAS) is less in the first 24 hours following surgery in patients receiving TAP blocks, when compared to standard care (WMD -1.33, 95% CI -2.19 to -0.48).
The following trial is an RCT performed on TAP blockade following laparoscopic colorectal surgery. Prior to the commencement of this trial, there was no RCT assessing the efficacy of TAP blocks following laparoscopic colorectal surgery. Given the popularity of this form of post-operative analgesia, as well as its proven efficacy in other forms of abdominal surgery, the author believed a new trial of this nature was warranted. The previously presented trial on wound infusions had highlighted improvement in respiratory function with this modality of analgesia following laparoscopic colorectal surgery, and this was also a major factor in the decision to set up a trial. It would appear logical that if a wound infusion provided objective improvement in muscular excursion, resulting in earlier recovery of respiratory function, that a more proximal form of neural blockade within the muscle plane, would result in an even greater benefit. Another factor in the decision to perform a trial on TAP blockade was the ‘bulky’ apparatus involved with a wound infusion. Although mobility was not assessed in the previous trial, it became apparent to the authors of the trial that the wound infusion devices appeared to hinder mobility and, potentially recovery, as a result. In view of this, it was felt that one of the potential advantages of an intra-operative abdominal wall block was the removal of these devices from the equation. Based on results from the previous trial on wound infusions in laparoscopic colorectal surgery, there was a large cohort from which to draw a sample size, and an existing platform of experience to design and perform a trial assessing TAP blockade in laparoscopic colorectal surgery.

The following is the transcript of this trial, which was presented by Dr Stephen Smith (Colorectal Department, John Hunter Hospital, The University of Newcastle, NSW, Australia), at the international Triennial Tripartite Colorectal Conference in Birmingham, 2014. It was one of six finalists chosen for the British Journal of Surgery prize session for best presentation of the conference. It has been published in the International Journal of Colorectal Disease in 2015.
Authorship Confirmation Page

This is to confirm, from the following fellow authors, that Stephen Smith was the Architect, Chief Investigator and Corresponding Author of the trial:

Transversus abdominis plane blockade in laparoscopic colorectal surgery: a double blinded randomized clinical trial

Brian Draganic

Peter Pockney

Phillip Holz

Ryan Holmes

Brendan McManus

Rosemary Carroll
3.5 Transversus abdominis plane blocks in laparoscopic colorectal surgery: A randomized clinical trial

ABSTRACT

Background: Adequate postoperative analgesia is essential for recovery following colorectal surgery. Transversus abdominis plane (TAP) blocks have been found to be beneficial in improving pain following a variety of abdominal operations. The objective of this study was to determine if TAP blocks are useful in improving postoperative recovery following laparoscopic colorectal surgery.

Methods: A prospective double blind randomized clinical trial, involving 158 consecutive patients having laparoscopic colorectal surgery, was performed by a university colorectal surgical department. Patients were randomized to either TAP blockade using ultrasound guidance, or control, with the primary outcome being postoperative pain, as measured by analgesic consumption. Secondary outcomes assessed were pain visual analogue score (VAS), respiratory function, time to return of gut function, length of hospital stay, postoperative complications and patient satisfaction.

Results: A total of 142 patients were followed up to trial completion (74 control, 68 intervention). Patients were well matched with regards to demographics. No complications occurred as a result of the intervention of TAP blockade. There was no difference between groups with regards to analgesic consumption (161 MEq morphine control v 175 MEq morphine TAP; p=0.596). There was no difference between the two groups with regards to the secondary outcomes of daily VAS, respiratory outcome, time to return of gut function, length of hospital stay, postoperative complications and patient satisfaction.

Conclusion: TAP blockade appears to be a safe intervention, but confers no specific advantage following laparoscopic colorectal surgery.

INTRODUCTION
Recovery following colorectal resectional surgery is dependent on a number of factors, one of the most important of which is postoperative pain and analgesia.\(^1\) There is considerable evidence that the laparoscopic approach to this form of surgery results in less postoperative pain,\(^2\) and stress response.\(^3\) As a result, less invasive forms of regional, or neuroaxial anaesthesia tend to be employed, to assist in the postoperative setting, than with traditional open surgery.\(^4\) Despite this, evidence exists that techniques employing locoregional anaesthesia can assist patients in their recovery following laparoscopic surgery.\(^5\) One of these techniques is the Transversus Abdominis Plane (TAP) block, which has been trialled with a degree of success in a number of abdominal surgeries.\(^6\)

The TAP block is a form of locoregional anaesthesia that can best be described as a ‘neural field’ block.\(^7\) This block relies on identifying the plane laterally in the abdominal wall, between the internal oblique and transversus muscles, and infiltrating this space to separate the muscles, so as to ‘bathe’ the nerves as they travel through the plane.\(^8\) This can be achieved by a blind ‘double pop’ technique more posteriorly,\(^7,8\) or preferably by using ultrasound guidance.\(^9\) The point of maximal convergence of the nerves is between the anterior superior iliac spine and the costal margin, and most descriptions of the TAP block refer to infiltration in this region.\(^10\)

The concept of using the TAP block to assist recovery following laparoscopic colorectal resectional surgery seems, in theory, to be a sound one. TAP blocks have been studied cadaverically, and in patients, to cover dermatomal territory from T10-L1,\(^11,12\) and the extraction wound for this surgery is usually a unilateral, lower abdominal incision that covers a small dermatomal territory, therefore lending itself to this form of blockade.

It is well established that reducing postoperative pain results in a reduction in cardio-respiratory complications, as a result of improved respiratory excursion and a lower stress response.\(^13\) It is also established that reducing pain results in a reduction in rates of ileus\(^13\) and also a reduction in the amount of opiates required, thus further enhancing return of gut function.\(^14\)
We hypothesized that TAP blockade decreases the amount of postoperative pain following laparoscopic colorectal resectional surgery. The aim, therefore, of this prospective randomized clinical trial was to determine if TAP blockade results in less use of narcotics, less subjective pain, improved respiratory function, and enhanced recovery following this form of surgery.

METHODS

Selection Criteria

From March 2008 to December 2012, patients over the age of 18 undergoing laparoscopic colorectal resectional surgery for any indication, at the John Hunter Hospital (JHH) or Newcastle Private Hospital (NPH), Newcastle, New South Wales, Australia, were screened for trial eligibility. Exclusion criteria were emergency surgery, abdomino-perineal resection, age under 18, inability to provide written informed consent, coagulopathy, severe renal impairment, dependence on opiates, requirement of central neuroaxial blockade, postoperative ventilation or allergy to opiates or local anaesthesia (including documented arrhythmia or long QT syndrome associated with local anaesthetics).

Surgery

All operations were performed at the JHH or NPH (both on the same campus). Surgery was performed by one of three surgeons (BD, PP, SS), either as the primary surgeon, or as the 'scrubbed in' direct supervisor. All technical aspects of the surgery were left to the discretion of the individual consultant surgeon. All port sites were infiltrated with Bupivacaine 0.25% with Adrenaline. Operative duration was taken as time from skin preparation until dressing placement.

Anaesthesia

Anaesthesia was standardised. No premedication was used. Intravenous antibiotics were given prior to induction as per Australian antibiotic guidelines: Cepahazolin 2g, Metronidazole 500mg. A repeat dose of Cephazolin 1g was given for cases lasting longer than 3 hours. Patients were 'prewarmed' in the anaesthetic bay and subsequently during surgery using a Bair Hugger® (Augustine Medical, Eden Prairie, MN, USA). Propofol (Fresofol®, Fresenius Kabi, Australia) was used
for induction, while either Atracurium (Tracrium®, GlaxoSmithKline, Australia) or Rocuronium (Esmeron®, Merck Sharp and Dohme, Australia) was used as a muscle relaxant, and Desflurane (Suprano®, Baxter, Australia) or Sevoflurane (Sevorane®, Abbott, Australia) were used for maintenance. Intraoperative analgesia was achieved using intravenous Fentanyl (DBL® Fentanyl Citrate, Hospira, Australia). Ventilation was achieved using a minimum of 70% oxygen, while Nitrous Oxide was avoided for all cases. All intravenous fluids were warmed, with a maximum of 2 litres of crystalloid intraoperatively.

**Perioperative Care**

All patients were placed on an established ERAS program, used in previous trials at the same institutions. This consisted of a prehabilitation program, referral to a smoking cessation program for smokers, referral for alcohol minimisation (for >30 g daily intake), preoperative immunonutrition (Impact®, Nestlé, Australia), and the avoidance of Mechanical Bowel Preparation (MBP). Nasogastric tubes were not used intraoperatively. Urinary catheters were avoided where possible, and if required, were removed in the first 24 hours. Drains were not used routinely and high flow oxygen was given for at least 6 hours postoperatively.

Patients were placed on a selective diet on the first postoperative day, and were mobilised and encouraged to sit out of bed from the first postoperative day.

Patient Controlled Analgesic (PCA) devices were used postoperatively for analgesia, using Fentanyl (DBL® Fentanyl Citrate, Hospira, Australia) in 20 microgram boluses, 5 minute lockout intervals, and with no background infusion. Regular Paracetamol was given to all patients (1g every 6 hours), and no oral opiates were given while the PCA was in use. The PCA was taken down at the discretion of the treating surgeon, and replaced with intermittent Oxycodone (Endone®, Aspen, Australia) 5mg every 3 hours as required only.

Patients were discharged after day 2, provided they were tolerating a selective diet with evidence of gut function, fully ambulant with adequate analgesia, and able to perform activities of daily living, with no evidence of complications.

**Intervention**
After induction of anaesthesia, patients were randomized. Those in the control arm received standard intra and postoperative care. Patients in the intervention arm underwent bilateral TAP block, performed under sterile conditions, with ultrasound guidance (linear 10 mHz probe). The blocks were placed lateral to the umbilicus, with infiltrate commencing in the midaxillary line, and extending medially from point of commencement, once injectate was visualised in the correct plane. The injectate consisted of Ropivacaine 3mg/kg of body weight, made up to 40mls, with 20mls injected on either side.

**Primary Outcome**

The primary outcome was postoperative pain, as measured by analgesic consumption (mEq morphine).

**Secondary Outcomes**

Secondary outcomes were pain Visual Analogue Scores (VAS), Difference in Respiratory Function (from preoperative baseline), as measured by Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Forced Expiratory Volume in 1 second (FEV1), Time to return of Flatus, Time to first Bowel Motion, Episodes of postoperative Nausea and Vomiting, Length of Hospital Stay (LOS), Postoperative Complications, and Patient Satisfaction.

**Sample Size**

Based on a recently completed trial, looking at the effect of wound infusion on postoperative pain, performed in our institution after laparoscopic colectomies (mean morphine consumption 143 mEq, SD 28 in control group), 15 128 patients are required (64 in each group), in order to demonstrate a 10% reduction in postoperative narcotic use with an alpha error of 0.05 and power of 80%. Allowing for a 10% dropout rate 140 has been chosen as total sample size.

**Data Collection**

Data was collected by two independent analysts (RH and RC), who were not involved with the clinical care. Routine baseline demographic data, along with Respiratory Function Tests (RFT’s), were recorded and daily visits were
performed for the first three postoperative days. These visits were timed, to be as close as possible to the time of day that the surgery was performed. The following data was recorded on days 1-3: Visual Analogue Scores (0 to 10, with 0 being equivalent to no pain, and 10 being equal to the worst pain imaginable) at rest, on deep breathing and coughing, RFT’s (FVC, FEV1 and PEF), Categorical data (Yes or No) on Nausea, Vomiting, Flatus or Bowel Motion, and a record of what type of diet was tolerated. Further data was obtained from the notes, after discharge, about length of stay, complications, and analgesic consumption. The PCA device computer records were analysed following discharge for records of analgesic consumption, in 24 hour blocks, for the first 3 days as well as total usage. A 30 day follow up visit was also performed to identify any post discharge complications, as well as to ensure RFT’s had returned to normal, and to record patient satisfaction with analgesia (a five point score: 1=very satisfied, 2=satisfied, 3=neither satisfied, nor unsatisfied, 4=unsatisfied and 5=very unsatisfied).

**Randomization**

At the time of the operative procedure, allocation was performed. The treating anaesthetist rang a central location for allocation. Randomization to Intervention (TAP block), or Control (standard care) was performed using computer generated random numbers, without stratification. Concealment was performed by using numbered opaque envelopes, kept at a central location, and opened sequentially at the time of the anaesthetists phone call. A third party not involved with clinical care or follow up performed all randomization, opening of envelopes and allocation. Blockade was performed after the surgical team left the operating theatre.

**Blinding**

Patients were blinded as to their allocation, and all treating clinicians, with the exception of the anaesthetist, were also blinded. Anaesthetists were not involved in any aspect of postoperative care. Documentation as to allocation was performed by the anaesthetist, and concealed in the opaque envelope so as to allow access only in the event of an emergency. All follow up data collection was performed by an independent clinician, both blinded to the allocation, and not involved in the
clinical care of the patient. Statistical analysis was performed by a blinded analyst, with groups known only as A or B until analysis was complete.

Statistics

Patients were analysed according to intention to treat principles. Statistical analysis was performed using StatsDirect. The analyst was blinded as to which group was control or intervention (groups were designated A or B by a third party for analysis). Comparison between means was performed using student’s $t$-test, while Fisher’s Exact test was used for categorical data.

RESULTS

Between March 2008 and December 2012, 226 patients were screened for trial inclusion. Of eligible patients, a total of 142 were randomized (74 Control, 68 Intervention), followed up and analysed, with no loss to follow up in either arm (Figure 1 - CONSORT diagram).

Patient demographics

Both patient groups were equally matched at baseline, with regards to demographic data, with no significant difference in age, sex, ASA grade, comorbidities and indication for surgery (table 1). There were significant differences between groups with respect to baseline respiratory function, favouring the control group (table 2).

Intraoperative Parameters

There was no difference between the two groups with respect to intraoperative factors (table 3).

Perioperative Complications

There was no difference between the two groups, with respect to intra and postoperative complications. There was one death in the control group (postoperative small intestinal ischaemia), which occurred on day 5 after surgery. There were five anastomotic leaks requiring surgical intervention (3 in the control arm, 2 in the intervention), and two reoperations for other causes (one for small
bowel obstruction in the intervention group and one for haematoma in the control group). Table 4 outlines in more detail perioperative complications.

**Analgesic Outcomes**

There was no difference in overall inpatient analgesic consumption between the control (161.1 +/-, Mean Morphine mEq +/- SEM) and intervention (174.7 +/- ) groups, p=0.596. Breakdown into time frames, likewise, revealed no difference between groups, with respect to analgesic consumption at 24, 48 and 72 hours (table 5).

There was no difference between the two groups, with respect to postoperative Visual Analogue Scores (VAS) at rest, with a deep breath or a cough, recorded at 24, 48 and 72 hours (table 6).

**Respiratory Outcomes**

There was no difference in respiratory function between the two groups, with respect to the difference from preoperative baseline, measured at 24, 48 and 72 hours (table 7).

**Gastrointestinal Function Outcomes**

There was no difference between groups with respect to; time to return of flatus and bowel motion, or proportion of patients with delayed return of GI function (more than 72 hours). Likewise, there was no difference in episodes of nausea, vomiting and postoperative ileus between the two groups (table 8).

**Length of Stay**

Length of stay (LOS) was similar in both groups, with no difference in mean (6.3 days control v 7.5 days TAP; p=0.217) or median LOS (4 days control v 4 days TAP).

**Complications and Patient Satisfaction**

There was no difference in rates of complications between the two groups (table 4), and likewise no difference in patient satisfaction scales between the two groups (table 9).
Adverse Events

There were no adverse events related to TAP blockade, either as a result of the procedure, or anaesthetic related toxic.

DISCUSSION

This prospective randomized clinical trial appears to indicate that a ‘single shot’ TAP block, at the time of laparoscopic colorectal resectional surgery, with ropivacaine, confers no clear postoperative advantage.

Over the last 6 years clinical trials have emerged, providing evidence for the efficacy of TAP blockade following abdominal surgeries.\textsuperscript{16,17,18} A Cochrane meta-analysis of TAP blocks for abdominal surgery,\textsuperscript{19} reveals that TAP blocks appear to reduce postoperative opioid consumption and pain scores, following abdominal surgery. This meta-analysis revealed that there was no reduction in postoperative nausea, vomiting or sedation, associated with TAP blockade. There are only 5 trials in this review, all with fairly small numbers, and associated with a moderate risk of bias overall, according to the Cochrane reviewers.\textsuperscript{19} None of the trials assessed this form of blockade for laparoscopic colorectal surgery, and none of the trials addressed objective postoperative functional outcomes, such as respiratory function, return of GI function and mobility.\textsuperscript{16-18,20,21}

One of the potential strengths of this study is the relatively large numbers involved. Given the fact that no measured outcome revealed any hint of a trend in favour of the intervention, combined with the large numbers involved, it is unlikely, even in the event of a type 2 error, that there will be any clinical benefit from a single shot TAP block for this group of patients. Another potential strength of the study is the inclusion of objective and functional outcomes. Measuring respiratory function and return of GI function enables an objective assessment of clinical relevance. While subjective assessment of postoperative analgesia remains important, we believe there should be more emphasis placed on functional outcomes that are clinically relevant, in studies such as this.

One potential weakness of the study is the lack of assessment of functional physical capacity of the participants. While length of stay provides some form of assessment
of the return to preoperative physical capacity, it remains open to external influence from social, cultural, financial and age related factors, not to mention factors associated with the institution and treating team. A more objective way of measuring return to functional physical capacity, such as a mobility score, would have been an ideal way to assess the effect of local anaesthetic neuromuscular blocks on postoperative recovery.

Another potential weakness of the study is the duration of blockade afforded by a ‘single shot block’. Although a relatively long acting local anaesthetic, the duration of Ropivacaine blockade (approximately 4-8 hours for TAP blocks) does not, in principal, lend itself to improved analgesic outcomes beyond 24 hours. Liposomal local anaesthetics were not approved for deep tissue infiltration in Australia at the time of commencement (or indeed completion) of this trial, but would appear to be a logical choice for further study. Postoperative infusions into the same plane, are also an area for further study, and a previous trial looking at this revealed an improvement in postoperative lung function after laparoscopic colectomy.

Other studies have shown TAP blockade to be effective following abdominal surgery. It is possible that, as a result of minimal somatic pain experienced by this group of patients (mean VAS in control group 3.3/10, 24 hours postoperatively), that TAP blockade is less useful for laparoscopic colectomy, than for other forms of abdominal surgery.

TAP blocks appear to be a relatively safe intervention, based on results from previous trials on ultrasound guided TAP blockade and this is further validated by the results of this study, with no adverse outcome associated with TAP blockade. The use of ultrasound to guide insertion provides good visualisation of the layers of the abdominal wall, and allows the needle to be safely visualised, along with the injection ‘bleb’ in the correct plane. There were 68 patients randomized to TAP blockade, and all 68 consecutive patients underwent ultrasound scanning with identification of the perceived correct plane, injectate in this plane, with no identified complication associated with either the procedure for injectate, or complications related to the local anaesthetic.
Whenever a procedural intervention is trialled, one naturally questions the expertise of the persons performing the intervention. Despite the assistance afforded by ultrasound scanning, there would obviously still be some form of learning curve associated with TAP blocks. A separate analysis of high versus low volume proceduralists was also performed on completion of the trial. Although this was not a pre-stated outcome, no improvement was identified in the primary outcome, when experience (more than 12 TAP blocks performed prior to the trial) was taken into account (table 10).

Despite the safety, and ease of application of this technique, it is our belief that this is not a useful procedure to perform for laparoscopic colectomy. Given the large numbers involved in this study, along with the variety of outcomes evaluated, with no hint of any advantage related to a single shot TAP block, it is unlikely that a significantly large clinical benefit may exist, even if this intervention is studied in greater detail for laparoscopic colectomy.

There remain questions for further research, however, mostly in the form of either longer acting blocks, or infusions. Further research should be conducted in this direction, with the aim being to ultimately provide somatic and even visceral blockade, such that opiates are ultimately not required for postoperative pain following laparoscopic colectomy. Studies investigating the effect of any form of neural blockade on postoperative recovery should include assessment of recovery of objective outcomes, in the form of respiratory, gastrointestinal and physical function.

REFERENCES


CONSORT Flow Diagram

Assessed for eligibility n=226

Excluded n= 84
  - Open procedure (n=49)
  - Abdomino-perineal resection (n=4)
  - Declined to participate (n= 7)
  - Neuroaxial blockade (n=6)
  - Postoperative ventilation (n=2)
  - Opiate dependence (n=2)
  - Study personnel unavailable (n=14)

Enrollment

Randomized n= 142

Allocation

Allocated to Control n= 74
Allocated to Intervention n= 68

Follow-Up

Lost to follow-up = 0
Lost to follow up = 0

Analysis

Analysed n=74
Analysed n= 68
### Table 1: Baseline Patient Demographics

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<tr>
<th>Characteristic</th>
<th>Control Group B (n=74)</th>
<th>TAP Group A (n=68)</th>
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<tr>
<td>Age (Mean years)</td>
<td>63.156757 ± 14.486</td>
<td>64.814706 ± 14.185</td>
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</tr>
<tr>
<td>Male : Female</td>
<td>45(61):29(39)</td>
<td>32(47):36(53)</td>
<td>0.1049</td>
</tr>
<tr>
<td>BMI (Mean)</td>
<td>27.118 ± 5.233</td>
<td>27.462 ± 5.602</td>
<td>0.708</td>
</tr>
<tr>
<td>Indication for surgery</td>
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<tr>
<td>Malignant : Benign</td>
<td>60(81):14(19)</td>
<td>50(75):17(25)</td>
<td>0.2916</td>
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<tr>
<td>Comorbidities</td>
<td>56 (76)</td>
<td>59 (87)</td>
<td>0.0982</td>
</tr>
<tr>
<td>ASA (1:2:3:4)***</td>
<td>16:34:20:1</td>
<td>4:48:14:1</td>
<td>0.035</td>
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ASA (1:2:3:4)*** was compared using Fishers exact test, P = 0.035.

### Table 2: Pre-Operative Spirometry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group B (n=74)</th>
<th>TAP Group A (n=68)</th>
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<tbody>
<tr>
<td>FVC (L)</td>
<td>3.53 ± 1.5</td>
<td>2.99 ± 1.03</td>
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<tr>
<td>FEV₁ (L)</td>
<td>2.87 ± 1.32</td>
<td>2.35 ± 1.35</td>
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<tr>
<td>PEF (L/min)</td>
<td>411.32 ±189.08</td>
<td>347.89 ± 148.36</td>
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</tr>
</tbody>
</table>

TAP, Transversus abdominis plane. FVC, Forced vital capacity. FEV₁, Forced expiratory volume in 1s. PEF, Peak expiratory flow.

Data are expressed as mean +/- standard deviation.
Table 3: Operative Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group B (n=74)</th>
<th>TAP Group A (n=68)</th>
<th>A</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation Time (min)</td>
<td>128.1 ± 39.3</td>
<td>145.7 ± 45.6</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Conversion to laparotomy</td>
<td>1 (1.4%)</td>
<td>3 (4.4%)</td>
<td>0.329</td>
<td></td>
</tr>
<tr>
<td>Right Colectomy</td>
<td>34 (46)</td>
<td>29 (43)</td>
<td></td>
<td>0.737</td>
</tr>
<tr>
<td>Left Colectomy</td>
<td>5 (7)</td>
<td>3 (4)</td>
<td></td>
<td>0.721</td>
</tr>
<tr>
<td>Rectal Resection</td>
<td>35 (47)</td>
<td>33 (49)</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Subtotal Colectomy</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td></td>
<td>0.107</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Control Group B (n=74)</td>
<td>Group TAP (n=68)</td>
<td>A</td>
<td>P</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------</td>
<td>------------------</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>Morbidity</td>
<td>24 (32%)</td>
<td>23 (34%)</td>
<td></td>
<td>0.862</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative bowel ischemia</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Operation</td>
<td>1 (Haematoma)</td>
<td>1 (SBO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBO</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PONV</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant Pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSI</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative haemorrhage</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deconditioning</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Analgesic consumption (morphine milliequivalents)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=74)</th>
<th>TAP Group A (n=68)</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr mEq</td>
<td>87.50</td>
<td>79.58</td>
<td>0.474</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>SD±68.48</td>
<td>SD±62.32</td>
<td></td>
<td>-13.87 to 29.70</td>
</tr>
<tr>
<td></td>
<td>SEM 7.96</td>
<td>SEM 7.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hr mEq</td>
<td>126.12</td>
<td>110.70</td>
<td>0.386</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>SD±111.69</td>
<td>SD±98.48</td>
<td></td>
<td>-19.64 to 50.48</td>
</tr>
<tr>
<td></td>
<td>SEM 12.98</td>
<td>SEM 11.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hr mEq</td>
<td>137.82</td>
<td>123.45</td>
<td>0.510</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>SD±128.34</td>
<td>SD±131.00</td>
<td></td>
<td>-28.67 to 57.42</td>
</tr>
<tr>
<td></td>
<td>SEM 14.92</td>
<td>SEM 15.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mEq</td>
<td>174.68</td>
<td>161.11</td>
<td>0.596</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>SD±147.05</td>
<td>SD±157.36</td>
<td></td>
<td>-36.93 to 64.08</td>
</tr>
<tr>
<td></td>
<td>SEM 17.09</td>
<td>SEM 19.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analgesic consumption**

![Graph showing morphine use over time (24hr, 48hr, 72hr, Total) for Control and TAP groups. The graph indicates a similar trend with a p-value of 0.596.](image)
Table 6: Visual Analogue Scores (VAS) at A: rest, B: deep breath and C: cough

A

\[ p = 0.434 \quad p = 0.236 \quad p = 0.321 \]

B

\[ p = 0.894 \quad p = 0.397 \quad p = 0.930 \]
### Table 7: Respiratory Function: mean difference from preoperative baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=74)</th>
<th>TAP Group A (n=68)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC at 24 hrs</td>
<td>1.21</td>
<td>1.14</td>
<td>0.653</td>
</tr>
<tr>
<td>FVC at 48 hrs</td>
<td>1.23</td>
<td>0.94</td>
<td>0.106</td>
</tr>
<tr>
<td>FVC at 72 hrs</td>
<td>0.90</td>
<td>0.67</td>
<td>0.203</td>
</tr>
<tr>
<td>FEV1 at 24 hrs</td>
<td>0.99</td>
<td>0.90</td>
<td>0.536</td>
</tr>
<tr>
<td>FEV1 at 48 hrs</td>
<td>1.00</td>
<td>0.71</td>
<td>0.056</td>
</tr>
<tr>
<td>FEV1 at 72 hrs</td>
<td>0.70</td>
<td>0.53</td>
<td>0.263</td>
</tr>
<tr>
<td>PEF at 24 hrs</td>
<td>130.17</td>
<td>129.29</td>
<td>0.971</td>
</tr>
<tr>
<td>PEF at 48 hrs</td>
<td>129.46</td>
<td>111.27</td>
<td>0.468</td>
</tr>
<tr>
<td>PEF at 72 hrs</td>
<td>105.54</td>
<td>86.80</td>
<td>0.435</td>
</tr>
</tbody>
</table>

TAP, Transversus abdominis plane. CI, Confidence intervals. FVC, Forced vital capacity (L). FEV₁, Forced expiratory volume in 1s (L). PEF, Peak expiratory flow (L/min)

Data is expressed as mean with 95% CI
FVC: Mean difference from baseline

FEV1: Mean difference from baseline
PEF: Mean difference from baseline

Control = Blue, Intervention = Red
Table 8: Postoperative return of gastro-intestinal function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group B (n=74)</th>
<th>TAP Group A (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Flatus &lt;24hrs</td>
<td>n=27</td>
<td>n=16</td>
<td>0.421</td>
</tr>
<tr>
<td>Time to Flatus 24-48hrs</td>
<td>33</td>
<td>34</td>
<td>0.390</td>
</tr>
<tr>
<td>Time to Flatus &gt;48hrs</td>
<td>13</td>
<td>18</td>
<td>0.227</td>
</tr>
<tr>
<td>Time to Bowel Motion &lt;24hrs</td>
<td>7</td>
<td>3</td>
<td>0.570</td>
</tr>
<tr>
<td>Time to Bowel Motion 24-48hrs</td>
<td>11</td>
<td>10</td>
<td>0.543</td>
</tr>
<tr>
<td>Time to Bowel Motion 48-72hrs</td>
<td>21</td>
<td>17</td>
<td>0.707</td>
</tr>
<tr>
<td>Time to Bowel Motion &gt;72hrs</td>
<td>28</td>
<td>32</td>
<td>0.309</td>
</tr>
<tr>
<td>Nausea day 1</td>
<td>42</td>
<td>41</td>
<td>0.674</td>
</tr>
<tr>
<td>Vomiting day 1</td>
<td>15</td>
<td>21</td>
<td>0.154</td>
</tr>
<tr>
<td>Nausea day 2</td>
<td>27</td>
<td>31</td>
<td>0.277</td>
</tr>
<tr>
<td>Vomiting day 2</td>
<td>12</td>
<td>15</td>
<td>0.386</td>
</tr>
<tr>
<td>Nausea day 3</td>
<td>22</td>
<td>18</td>
<td>0.673</td>
</tr>
<tr>
<td>Vomiting day 3</td>
<td>4</td>
<td>5</td>
<td>0.653</td>
</tr>
</tbody>
</table>

Table 9: Patient Satisfaction with Analgesia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group B (n=74)</th>
<th>TAP Group A (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfied (1-2)</td>
<td>65 (88%)</td>
<td>61 (90%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Unsatisfied (3-5)</td>
<td>9 (12%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Comparison of anaesthetist’ experience and TAP block efficacy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experienced (n=36)</th>
<th>Others (n=32)</th>
<th>P</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEq: first 24 hrs</td>
<td>87.13</td>
<td>71.09</td>
<td>0.293</td>
<td>-14.16  to 46.24</td>
</tr>
<tr>
<td>MEq: first 48 hrs</td>
<td>127.17</td>
<td>92.17</td>
<td>0.145</td>
<td>-12.36  to 82.36</td>
</tr>
<tr>
<td>MEq: first 72 hrs</td>
<td>148.63</td>
<td>95.12</td>
<td>0.084</td>
<td>-7.25   to 114.26</td>
</tr>
<tr>
<td>MEq: Total</td>
<td>197.24</td>
<td>120.47</td>
<td>0.038</td>
<td>4.46 to 149.08</td>
</tr>
</tbody>
</table>
Chapter 4: Post-operative Gastrointestinal Motility

4.1 The Importance of Gastrointestinal Motility following Colorectal Surgery

The normal control of gastrointestinal motility is elaborate and relies upon a complex interaction between neural and hormonal factors. A gross simplification of the factors that control normal gastrointestinal motility arbitrarily divides the process into an extrinsic and intrinsic network.\(^{373}\)

The extrinsic network consists of the visceral afferent and efferent nerves that are autonomic and consist of the parasympathetics (the vagus and sacral plexus) and sympathetics (the thoracolumbar outflow). In general, the parasympathetic afferents are believed to be important with regard to relaying information and coordinating motility, secretion and absorption, while the efferent parasympathetic activity generally causes propulsion and motility by mostly stimulating smooth muscle activity. This can be through either an excitatory or inhibitory mechanism. The sympathetic afferents tend to relay noxious stimuli from the gut, while the efferent activity is inhibitory to gut function and motility.\(^{373,374}\)

The intrinsic network is often referred to as the enteric nervous system, and this system has the ability to perform independently, relying on local neural ‘circuitry’ and signals from neurohumoral peptides. These peptides include, but are not limited to, nitric oxide, substance P and vasoactive intestinal peptide.\(^{373-374}\)

It is clear that the coordinated peristaltic activity that needs to occur within the gastrointestinal tract relies on closed circuits, peptides, and the extrinsic network, such that while an upstream segment of intestine is causing propulsion of contents downstream, the next segment of intestine is able to relax first to accommodate the propulsion, then initiate propulsion itself, transferring intraluminal contents downstream. Any disturbance in this complex chain results in a ‘holdup’, or gastrointestinal dysmotility, and when this occurs for a given time frame after surgery, it is referred to as post-operative or paralytic ileus.
There is general consensus that a degree of gastrointestinal dysmotility uniformly occurs following abdominal and, particularly, colorectal surgery. Consensus about what degree is considered abnormal and thus constitutes the label of ileus, is not consistent, however. A variety of definitions of post-operative ileus have been proposed that include: absence of flatus or stool by post-operative day 6, prolonged hospitalisation as a result of lack of bowel function by day 6, lack of bowel activity more than five days post-operatively, and nausea or vomiting requiring cessation of oral intake on or after day 4 post-operatively. Recently a systematic review and global survey by Vather et al, suggested that after reviewing the literature and obtaining opinions from published experts, that perhaps there is a need for three definitions. One definition for post-operative ileus could simply be: ‘the time taken for passage of flatus or stool and tolerance of oral diet’. There could be a separate definition for prolonged post-operative ileus: ‘two or more of nausea/vomiting, inability to tolerate oral diet for over 24 hrs, absence of flatus over 24 hrs, distension, or radiological confirmation occurring after day 4 post-operatively’. Finally, there could be a definition for recurrent post-operative ileus: ‘two or more days of nausea/vomiting, inability to tolerate oral diet over 24 hrs, absence of flatus for over 24 hrs, distension, or radiological confirmation, occurring after apparent resolution of post-operative ileus’.

It is quite clear in this day and age of ERAS and laparoscopic surgery, that many centres aim for a median length of stay, of a time frame less than that of the definition, in most studies of an ileus. The return of gastrointestinal function prior to discharge, and prevention of ileus, is therefore becoming an inherently more important aspect of recovery following colorectal surgery. It was thought that the ‘normal’ recovery of gastrointestinal function following colorectal surgery was somewhere between 0-24 hours for the small intestine, 24-48 hours for the stomach and 48-72 hours for the colon. This may be an overestimation, however, with newer research suggesting time frames of less than half this in some cases, perhaps mostly due to more minimally invasive surgery.

While precise times for normal return of gastrointestinal activity vary and exact definitions of ileus are unclear, there is no doubt that the delayed return of motility is
less than ideal. It results in increased patient discomfort, dissatisfaction, increased complications and, of course, prolonged hospital stay with subsequent increased costs. Estimates vary with regard to this cost, in the same vein that definitions of ileus vary, but most recent data from coding activity within the USA reveals a significant increase in cost for colectomy patients who suffer post-operative ileus, of approximately US$8,000 (US$16,612 with ileus vs US$8,316 without). This equates to, across the country an annual estimate of US$1.46 billion for ileus costs following all forms of abdominal surgery! With this in mind, it becomes paramount that surgeons consider all forms of therapy, and intervention to prevent and manage post-operative ileus.
4.2 Evidence Base for Prevention of Ileus

The most obvious way to prevent ileus is to avoid surgery, but there are a number of other more realistic preventative and treatment strategies to minimise the impact of ileus and hasten the return of normal gastrointestinal motility.

While patient factors have been less studied with respect to postoperative ileus than with other surgical complications, such as surgical site infection, there are some indications that male sex, obesity, diabetes, prior abdominal surgery and peripheral vascular disease may increase the risk of post-operative ileus.\(^{379,380}\) To a large extent, it is difficult to control for these factors pre-operatively, although in individuals, it may add weight to the decision to place a thoracic epidural.

Interestingly, it appears that even simply having a general anaesthetic, excluding the surgical insult, has an impact on normal gastrointestinal motility, with the inhalational agents halothane and nitrous oxide being implicated.\(^{381}\) Without doubt though, the impact of the surgical insult cannot be underestimated. The surgical location appears vitally important, with direct manipulation of the gastrointestinal tract being the key.\(^{382}\) Colorectal, pelvic and other gastrointestinal operations, where manipulation of the intestines are required, remain the surgeries with the highest rates of post-operative dysmotility.\(^{382,383}\) The concept of bowel manipulation in relationship to ileus, is highlighted by studies showing that the retroperitoneal approach to abdominal aortic aneurysm repair has lower rates of ileus than the trans-abdominal approach,\(^{384}\) and by the fact that surgery such as cholecystectomy has low rates of ileus when compared to gynaecological surgery, both of which do not require resection of bowel, but one of which requires more manipulation to exclude bowel from the operative field. In addition to manipulation, the degree of exposure of the bowel plays a part in dysmotility. The longer the operation and subsequent exposure of the bowel, the higher the risk of ileus and this, coupled with the factor of manipulation, makes the art and skill of surgery a vitally important factor in minimising ileus. Minimising the incision size, avoiding unnecessary bowel handling and excessive retraction, and minimising operative duration, are all skills essential to good surgery and to maximising gastro-intestinal recovery.\(^{385}\)
On the topic of surgical skill, intra-operative (and post-operative) bleeding and intra-abdominal contamination also increase the risk of ileus. Following on from intra-operative contamination, post-operative sepsis and peritonitis are both risk factors, minimised by good surgery for post-operative ileus. It goes without saying that it is desirable to avoid these complications in terms of minimising morbidity.

Open abdominal surgery increases the risk of post-operative gastrointestinal dysmotility, or conversely, laparoscopic surgery improves gut function recovery. There are a number of potential explanations for the superiority of laparoscopic surgery with respect to gastrointestinal recovery. There is less incision size with laparoscopic surgery, potentially resulting in lower sympathetic tone. There is more rapid functional recovery, translating to earlier mobility, thus helping to enhance gut recovery. There is less pain and therefore less of a need for opiates with laparoscopic surgery, further enhancing recovery. Possibly the most important aspects of laparoscopic surgery, however, are the lack of exposure, with bowel remaining in a warm environment, and the lack of manipulation of bowel. Regardless of the weight afforded to each of the above potential factors, there is an advantage of approximately 24 hours, in terms of time to gastrointestinal recovery associated with laparoscopic colon resection over its open counterpart, and this should certainly sway the decision to perform colectomy laparoscopically, where possible.

Avoiding routine nasogastric tube placement has been shown to decrease the rates of respiratory complications, but emptying the stomach and avoiding feeding also has the effect of delaying gastrointestinal function as a result of the absence of feedback from a distended stomach. Avoiding routine nasogastric tube placement, therefore, is advantageous in minimising rates of ileus.

Correcting abnormalities in electrolytes is important in preventing ileus. Potassium and magnesium, in particular, are implicated, and states of hypokalaemia and hypomagnesaemia may occur following surgery, both as a result of sympathetic stimulation and gastrointestinal losses. Hypokalaemia results in muscle weakness, and intestinal paralysis and potassium is therefore a vital serum electrolyte to keep within normal range following surgery. Magnesium is also responsible for muscular
contraction, via parathyroid hormone and calcium, as well as its action on the Na/K ATPase pump, and both high and low levels have been implicated in ileus.\textsuperscript{386} It is essential that both electrolytes are monitored closely after colorectal surgery.

The role of thoracic epidural blockade has been discussed previously, particularly with respect to its analgesic efficacy, but there is no doubt that a good functioning thoracic epidural has the ability to enhance early gastrointestinal functional recovery by blocking the thoraco-lumbar sympathetic outflow and sympathetic stimuli to the gastrointestinal tract. In addition to sympathetic blockade, its analgesic efficacy both inhibits sympathetic drive and minimises the need for opiates. It appears that local anaesthetic is the important factor in thoracic epidurals with regards to gastrointestinal function, reducing time to return of gut function by 37 hours when compared with systemic opiate-based therapies, and 24 hours when compared with epidural opioid therapies, although the combination of local anaesthetic and opiates in an epidural may provide superior pain relief when compared to one therapy only.\textsuperscript{161} The dramatic improvement seen in the return of gut function is the major reason thoracic epidurals are still used routinely in many ERAS centres, even when laparoscopic surgery is performed.

Mu opioid receptor antagonists are a relatively new development and have attracted widespread interest in the colorectal community. Alvimopan is the newest and most promising of the selective mu opioid antagonists, and has been designed in such a fashion, with a large molecular size, to prevent it crossing the blood-brain barrier. As a result, it has the ability to block the peripheral gastrointestinal effects of opiates, without interfering with the central analgesic effects. There have been a number of promising trials on alvimopan since 2001 highlighting the ability of this drug to improve outcomes following abdominal surgery. It should be noted that most of these studies have been sponsored in some form or another, but despite this, the results seem promising. A meta-analysis performed on five trials using alvimopan following abdominal surgery revealed a reduction in length of stay, improvements in return of gastrointestinal function, and more rapid times to tolerate the introduction of diet in patients receiving alvimopan.\textsuperscript{387} Further research has suggested a cost benefit, with the drug saving an estimated US$100 per patient.\textsuperscript{388} There is some data on the use of
alvimopan in colorectal surgery, but no trials have been performed on laparoscopic colorectal surgery, highlighting the need for further research, particularly in the form of unsponsored trials.

Although mu opioid receptor antagonists are an exciting development, it makes logical sense to try and decrease opiate intake in the first instance. The concept of multi-modal analgesia is to use other forms of analgesia, in addition to opiates, to reduce opiate intake and the negative effects opiates have on gastrointestinal recovery. The most common forms of analgesia, used as part of a multi-modal regime, are paracetamol and NSAIDs, as described in the first chapter, although more recently, tramadol, a synthetic opiate with fewer gastrointestinal side effects, has been used with a view to minimising post-operative gastrointestinal dysmotility.

There have been many attempts to find a pharmacological cure for prolonged post-operative ileus, with minimal success. Medical therapies including the pro-motility agents metoclopramide, cisapride, domperidone and erythromycin have been tried and found to be unsuccessful, perhaps with the exception of cisapride. The problem with cisapride lies in its potential for cardiac toxicity, and reports of arrhythmia and sudden death have led the Australian Prescriber to suggest it should be avoided where possible. Given the evidence that increased sympathetic activity is partly responsible for ileus, and thoracic epidurals have the ability to cancel out this effect, it makes good sense that beta-blockers would be of benefit in preventing post-operative ileus. Unfortunately, animal trials on beta-blockers have been unsuccessful, as it appears that the alpha-2 adrenoreceptor is responsible for the sympathetic response. Guanethidine and yohimbine, rather than propranolol, appear effective in the rat model in minimising the effect of gastrointestinal dysmotility caused by laparotomy, and offer promise. Preventing acetyl-choline breakdown at the neuromuscular junction is a practice used for colonic pseudo-obstruction but has not been routinely applied for post-operative ileus, mostly due to concerns about arrhythmias as well. Finding drugs to inhibit the gastrointestinal peptides; substance P and vasoactive inhibitory peptide (VIP), has led to the use of octreotide in ileus. Although experimental, octreotide has been shown in animal models to ameliorate ileus, however the exact mechanism is unclear, as levels of substance P and VIP in
experimental models do not appear predictable with octreotide dosing. Further research, on finding ways to dampen substance P and VIP release is required, but possibly the most important peptide requiring ongoing research is nitric oxide. It appears that this inhibitory neurotransmitter is central to the process of post-operative ileus, being released by leucocytes and parenchymal cells of the gastrointestinal tract. When release is prevented, ileus in experimental animals resolves dramatically. In addition, nitric oxide and prostaglandin release are closely linked, with nitric oxide driving most of the release process. NSAIDs and COX inhibitors are vital, therefore, and have been shown to have benefit, not just in minimising the requirement for opiates, but in attacking inflammatory release at the source. Laparotomy incision appears to stimulate COX-2 activity, while gut manipulation leads to increased COX-1 and nitric oxide activity.

Another potential method to enhance post-operative gastrointestinal function is to address the luminal contents. A number of ERAS programs suggest the routine use of laxatives or osmotic agents. Despite these agents being used regularly, there is little available data to guide treatment. To the author’s knowledge, there is only one RCT on this topic assessing the use of bisacodyl following elective colorectal surgery. A modest benefit in time to first post-operative bowel motion was found, associated with the use of bisacodyl, although no difference was found in terms of time to first flatus or time to tolerate diet. Given the paucity of data, despite the minimal morbidity associated with the use of laxatives and osmotic agents, it would appear judicious to limit their use until further research is conducted on the topic.

Peri- and post-operative intravenous infusional delivery of local anaesthetics has been performed now for over 50 years, but it still remains far from routine practice. This is quite an interesting phenomenon, given the available evidence. As discussed in chapter 1, there is a large volume of evidence on this topic highlighting the benefit of this practice. There are at least 29 RCTs on the topic and a meta analysis involving 1754 subjects reveals improvements in post-operative pain, length of hospital stay and gastrointestinal function, in patients receiving infusional local anaesthetics following surgery. In particular, three RCTs performed on patients undergoing colorectal surgery revealed a benefit in terms of gastrointestinal function associated with
intravenous lidocaine infusions following laparoscopic, open and hand-assisted laparoscopic colectomy. Despite these findings, the practice of infusional local anaesthetic following colorectal surgery is rarely performed, presumably based on concern over toxicity, although this too seems rare in the reported literature.

While wound infusions have been discussed in detail in the previous chapter, with respect to their analgesic efficacy, the concept of peritoneal infusion was raised only briefly. Local anaesthesia infused into the peritoneal cavity has been poorly researched following colorectal surgery, presumably based on the fact that, in other forms of surgery, it has been shown not to be all that beneficial. To the author’s knowledge, there is only one RCT on this topic assessing intraperitoneal ropivacaine in the form of a three day infusion following open colorectal surgery. This placebo-controlled study revealed that patients in the infusion arm showed signs of improved recovery, with less pain and opioid use, improved surgical recovery scores and diminished systemic cytokine and cortisol response. Quite clearly, a similar study, perhaps on a larger scale, needs to be replicated in laparoscopic colorectal surgery.

As outlined in chapter 1, early routine post-operative feeding is not only safe, but it appears to confer significant benefits in terms of reducing post-operative complications and length of hospital stay. There may even be a beneficial effect of early feeding on gastrointestinal recovery, due to stimulation of the visceral motor efferents of the extrinsic network in response to visual, oral and nasal stimuli, and activation of the enteric network in response to distension in the stomach and upper gastrointestinal tract. Regardless of whether it hastens the return of gastrointestinal function, given the other benefits associated with early feeding it should be considered routine practice.

In synergy with the concept of early post-operative feeding, comes the concept of ‘sham feeding’ with chewing gum. Sham feeding was first proposed to assist with post-operative gastrointestinal recovery around the turn of the century, and the first RCT on sham feeding for colorectal surgery was performed in 2002. Although a very small trial (n=19), the results were very encouraging in favour of sham feeding. The fact that sham feeding improved gastrointestinal function made good physiological sense:
Mastication results in vagal stimulation, which in turn releases salivary and gastric juices, and stimulates motility in the gastrointestinal tract. When this concept first emerged, early post-operative feeding was certainly not the routine in most colorectal surgical centres, so the concept had great appeal: chewing, without swallowing food seemed to make sense to surgeons at the time. The concept of sham feeding spread rather rapidly, due to dramatic improvements seen in post-operative gastrointestinal function, and even in some trials, improvements in length of stay and post-operative complications. Sham feeding with gum also seemed an ideal intervention: cheap, simple and safe, with perhaps even a ‘distractional’ component to assist with recovery. Meta-analyses soon cropped up, highlighting the fact that sham feeding was safe and extremely effective. Chan’s meta-analysis on trials assessing the use of sham feeding in colorectal surgery, revealed significant improvements associated with sham feeding. They identified a reduction in time to flatus after surgery of 20.8 hours (p=0.0006), a reduction in time to first bowel motion of 33.3 hours (p=0.0002), an improvement in time to discharge of 2.4 days, and a reduction in complications by 55% (p=0.05), all in favour of sham feeding. Although this concept seemed exciting, there were two factors that made further research on the topic essential. The first was that numbers were still small; there were only 158 patients in 5 RCTs in the entire cohort of this meta-analysis. The second factor that made interpretation of the impact of sham feeding difficult, was the fact that none of the five trials incorporated rapid post-operative feeding. It was around the time of this analysis that many units were starting to incorporate rapid feeding into their ERAS programs. If sham feeding resulted in rapid return of gastrointestinal function and reduced complications, did it do so on the basis of the gum or the mastication process and, if the latter, was it actually required if patients were allowed to eat at the same time? Given these two factors, the author felt it was appropriate to design and perform an RCT that addressed these issues. It was also felt that it may be useful to address whether sham feeding was more or less effective in laparoscopic or open colorectal surgery. A two-armed RCT involving 168 patients (84 laparoscopic, 84 open) undergoing colorectal resection was therefore undertaken.
The following is the transcript of this trial, which was presented by Patrick Lim, a Bachelor of Medical Science student, under the dual supervision of Dr Stephen Smith and Dr Brian Draganic (both Colorectal Department, John Hunter Hospital, The University of Newcastle, NSW, Australia) at the Royal Australasian College of Surgeons Annual Scientific Congress in Perth in 2010, and subsequently at the triennial international Tripartite Colorectal Conference in Cairns by Dr Gregory Nolan, the colorectal registrar for Dr Stephen Smith and Dr Brian Draganic. It was later accepted for publication by Annals of Surgery, and published in September 2013.
Authorship Confirmation Page

This is to confirm, from the following fellow authors, that Stephen Smith was the Architect, Chief Investigator and Corresponding Author of the trial:

Sham feeding with chewing gum following elective colorectal resectional surgery: a randomized clinical trial

Patrick Lim

Owen Morris

Greg Nolan

Sarah Moore

Brian Draganic
4.3 Sham feeding with chewing gum following elective colorectal resectional surgery: a randomized clinical trial

Abstract

Objective: To determine if sham feeding with chewing gum improved gastrointestinal recovery following colorectal resection surgery, in the presence of routine postoperative feeding.

Background: Sham feeding with chewing gum has been shown to accelerate the return of gut function following colorectal surgery. This study sought to determine whether sham feeding with gum, following colorectal resection, accelerates return of gastrointestinal function in patients on a rapid feeding enhanced recovery program.

Methods: A randomized “two armed” controlled clinical trial was performed. Equal groups of open and laparoscopic colorectal resection surgical patients were recruited. Patients in the intervention arm received chewing gum four times a day postoperatively. All patients in the trial were placed on an established, standardised enhanced recovery after surgery (ERAS) program. The primary outcome was time to return of gut function, assessed by time to flatus and first bowel motion. Secondary outcomes were time to tolerate diet, symptomatology of ileus in the form of nausea, vomiting and distension, pain as assessed by analgesic consumption and visual analogue scales, complications, and length of hospital stay.

Results: One hundred and sixty one patients were recruited. Postoperative morbidity was equivalent between groups, with no complications related to gum chewing. There was no difference between groups with respect to the primary outcomes of time to flatus and bowel motion. There was less perception of pain in the intervention group on days 4 and 5, and no difference with respect to all other secondary outcomes.

Conclusion: Sham feeding with gum, after open and laparoscopic colorectal resectional surgery is safe, but does not hasten the return of gastrointestinal function in patients who receive accelerated postoperative feeding.
INTRODUCTION

Postoperative ileus is a common sequela of colorectal surgery. It is responsible for delayed recovery, and can be responsible for considerable postoperative morbidity. In the absence of prolonged postoperative ileus, there is still a delay in return of normal gut function following colorectal surgery that contributes to length of hospital stay (1).

The cause of ileus is believed to be multifactorial(1). Contributing factors of ileus include: stress response to surgery and use of perioperative interventions. The severity of ileus is influenced by the extent of surgical trauma and bowel manipulation. The effect of trauma is mediated through activation of sympathetic activity, which is known to cause a decrease in bowel motility. Associated with the stress response is release of inflammatory mediators including vasoactive intestinal peptide, substance P and nitric oxide, which appear to contribute to postoperative ileus(2-5). Opioids, used as analgesics perioperatively, have a marked effect on time to return of normal gut function; some studies even suggest a dose related response to amount of morphine given and time to return to normal gut function(6).

Many techniques have been used in order to reduce postoperative ileus and to hasten recovery of gut function following surgery. These include simple therapies such as early mobilisation and avoidance of opiates (7, 8). Strategies to minimise surgical stress such as laparoscopic surgery, minimising incision size, adopting transverse incisions where appropriate, minimising bowel handling and maintaining intraoperative normothermia are also utilised in order to minimise ileus (9-12). Therapies to block the sympathetic response include thoracic epidurals, intraperitoneal local anaesthetic and finally, prokinetics such as metoclopramide, erythromycin and cisapride have been used to hasten gut function (13-17).

Chewing gum has recently been used as a form of sham feeding to stimulate acceleration of gut function following abdominal surgery (18-32). The principle behind this concept is activation of the complex autonomic cephalic-vagal
response. This response occurs following chewing, in order to prepare the gut for food (33). The response leads to both humoral and nervous stimulation of bowel motility. Following colorectal resection there is autonomic dysregulation, and in the last 10 years there is a growing body of evidence showing improvement of gut function postoperatively, following colorectal surgery, with the use of chewing gum (18-32).

In recent times there has been a move towards early feeding regimes postoperatively, as part of ERAS programs (34, 35). With these early feeding regimes, the role of sham feeding becomes less clear. It may be that simply feeding postoperatively is enough to stimulate the cephalic-vagal response, or it may be that ‘super-stimulation’ with additional sham feeding further enhances the response.

We hypothesized that the addition of sham feeding with chewing gum accelerated return of gut function following colorectal surgery in patients on ERAS programs. In a prospective randomised “two armed” clinical trial, we investigated the effects of sham feeding with chewing gum on gut function and overall recovery in such patients, who were fed early following colorectal resectional surgery.

METHODS

Selection criteria

From June 2008 to March 2011 all patients over the age of 18 undergoing colorectal resectional surgery for any indication at either John Hunter Hospital or Newcastle Private Hospital, Newcastle, New South Wales, Australia, were screened for trial eligibility. Exclusion criteria were emergency surgery, age under 18, inability to provide written informed consent or an inability to chew gum.

Surgery

All surgery was performed in two hospitals on the one campus. Surgery was performed by eight surgeons. All surgery was performed or directly supervised by consultant surgeons, and technical aspects of the surgery were left to the discretion of the individual consultant surgeons. Allocation to laparoscopic or open surgery was performed at the time of operative consent, with intention to treat
principle. Laparoscopic conversion to open surgery was defined as laparotomy incision for any purpose other than specimen extraction. Operative duration was time from skin prep until dressing placement.

**Anaesthesia**

Anaesthesia was standardised, with no premedication, Propofol (Fresofol®, Fresenius Kabi, Australia) for induction, Atracurium (Tracrium®, GlaxoSmithKline, Australia) or Rocuronium (Esmeron®, Merck Sharp and Dohme, Australia) as muscle relaxant and Desflurane (Suprane®, Baxter, Australia) or Sevoflurane (Sevorane®, Abbott, Australia) for maintenance. Ventilation was maintained with minimum 60% oxygen and Nitrous Oxide was avoided for all cases. All intravenous fluids were warmed, with a maximum of 2 litres crystalloids intraoperatively.

**Perioperative care**

An established ERAS program was utilised for all patients on the trial. Most elements of the traditional ERAS were incorporated. This included avoidance of Mechanical Bowel Preparation (MBP) for all resections not involving defunctioning stomas, preoperative immunonutrition (Impact®, Nestlé, Australia), no nasogastric tubes, avoidance of urinary catheters for most colectomies, with early removal for anterior resection, avoidance of drains, preoperative and intraoperative warming (Bair Hugger®, Augustine Medical, Eden Prairie, MN, USA), high flow oxygen for at least 6 hours postoperatively, early mobilisation, and early commencement of diet.

Standardised diet consisted of high energy fluids immediately postoperatively, with progression to selective diet once patients felt they could tolerate it. No motility agents or opioid antagonists were used postoperatively.

Patients were discharged after day 2, provided they were tolerating a selective diet with evidence of gut function, fully ambulant with adequate analgesia, and able to perform activities of daily living, with no evidence of complications.

**Intervention**

Patients in the chewing gum group were instructed to chew sorbitol free gum for 15 min four times a day at 8am, 12pm, 4pm and 8pm; while patients in the control
group did not receive and were instructed not to chew any gum. The administration of the therapy was implemented by ward nursing staff and recorded on a separate ‘masked’ record in the patients file.

**Primary outcome**

The primary outcome was return of gastrointestinal function, as measured by time to first flatus and time to first bowel motion.

**Secondary outcomes**

Secondary outcomes were time to tolerate diet, symptoms of nausea, vomiting and distension, postoperative pain as measured by analgesic consumption and Visual Analogue Pain (VAS) scales, complications including readmissions, and length of hospital stay.

**Data collection**

Prospective demographic data collection included age, sex, comorbidities, ASA, previous surgery, surgical indication, and BMI.

Perioperative data collected included procedure, surgeon, hospital, operative duration, total narcotic requirements, operative approach including conversion rates, incision location and size, and intraoperative complications.

Data collection was by an independent investigator, not involved with clinical management, during the postoperative period, on a daily basis. The primary outcomes of time to first flatus and time to first bowel motion were recorded by the patient on a questionnaire (figure 1), which was collected daily by the investigator, and the outcomes of ileus symptoms, gum tolerance, VAS pain scores, and analgesic consumption were recorded daily at this appointment. The symptoms of nausea, vomiting and distension were collected individually and recorded categorically (Yes or No), with separate analyses for overall 5 day rates as well as daily rates. Comparison for VAS (0-10, with 0 equivalent to no pain, and 10 equivalent to worst possible pain) was performed daily, while analgesic consumption was recorded as morphine milliequivalents, with both daily and overall rates analysed and compared.
Data regarding complications, pathological outcomes and length of stay was collected at discharge time. The local health network clinical applications portal was also used to check for coded complications, and readmissions. A further phone call was made at 30 days to patient and treating surgeon to ensure no data was missed.

Randomization

Allocation to open or laparoscopic arms of the trial was performed at the time of consent. Randomization was performed using computer generated random numbers, in blocks of 10, without stratification. Concealment was performed by using numbered opaque envelopes, kept at a central location, and opened sequentially, at the commencement of surgery. Randomization, opening of envelopes and allocation were all performed by a third party not involved with clinical care or follow up.

Blinding

Sham feeding, by its nature does not lend itself to a suitable placebo controlled trial. The patients, ward nurses and the research assistant were therefore not able to be blinded. All other clinicians and investigators were blinded. This was achieved by providing a concealed universal trial chart in the patients bed notes, allowing ward nurses to know which patients to administer gum to, while preventing access to treating surgeons and other clinicians. Patients filled in their own questionnaires (figure 1) in order to prevent bias and subjectivity. Patients were also educated by the research assistant to conceal their allocation by avoiding chewing gum when their treating clinicians were present, and all patients were given containers to dispose of their gum when required.

Sample size

Based on a pilot sample, a power calculation was performed: in order to determine a clinically relevant reduction of 24 hours in time to bowel motion (90% test power and α level of 0.05) 80 patients were required (40 in each arm). To allow for dropouts, two additional patients were recruited for each arm (84 patients overall).
The initial trial design involved 3 groups (each with 84 patients): open colorectal resections, laparoscopic colorectal resections and upper gastrointestinal resections. Recruitment and problems with surgical equipoise necessitated cancellation of the upper gastrointestinal arm of the study. The initial basis for power calculation meant that this arm could be cancelled without concern regarding sample size. This resulted in a trial of 168 colorectal resectional patients.

No interim analysis was planned or performed.

**Statistics**

Patients were analysed according to intention to treat principles. Statistical analysis was performed using SPSS® version 15.0 software (SPSS, Chicago, IL, USA). The analyst was blinded as to which group was control or intervention (groups were designated A or B by a third party for analysis). Comparison between means was performed using students *t*-test, while Fisher’s Exact test was used for categorical data. Analysis was performed for the overall group, followed by subgroup analysis for the open and laparoscopic arms.

**Ethics approval and trial registration**

Ethical approval was given by local ethics regional board: Hunter New England Human Research Ethics Committee, New South Wales Health Department, NSW, Australia (07/06/20/5.01). Registration with approved clinical trials registry, Australian New Zealand Clinical Trials Register was undertaken (ACTRN12607000538448). Ethics approval and registration were performed prior to trial commencement (October 2007).

**RESULTS**

Between June 2008 and March 2011, 175 patients were screened for trial inclusion. Of eligible patients, two patients refused consent, resulting in 168 patients being enrolled, consented and allocated. Seven patients (3 in control and 4 in intervention) required postoperative ventilation for greater than 24 hours, while four patients withdrew their consent following allocation (1 in control and 3 in intervention), resulting in final analysis being available on 157 patients (see figure 2, Consort diagram).
**Patient demographics**

Both patient groups were equally matched at baseline, with regards to demographic data, with no significant difference in age, sex, ASA grade, comorbidities and indication for surgery (see table 1). The same finding was present in both laparoscopic and open arms of the study.

**Intraoperative parameters**

There was no difference between the two groups with regards to operative data, as shown in table 2, with no difference also between groups in both arms of the study.

**Perioperative complications**

There was no difference in complication rates between the two groups. One patient in each group had an intraoperative haemorrhage (defined as transfusion requiring), one patient in the control group had a ureteric injury, and one patient in the control group suffered an intraoperative myocardial event requiring intervention and ICU placement. There was one death in the control group, which occurred as a result of intestinal ischaemia, diagnosed at reoperation on the 7th postoperative day. There were 2 postoperative anastomotic leaks in each group, which required reoperation (see table 3). All patients in the intervention group were compliant with chewing gum four times a day, with no complications related to the intervention.

**Gut function outcomes**

There was no difference in mean time to flatus between the control (50.97 +/- 3.79): (mean hrs +/-SEM), and intervention (42.75 +/-3.92) groups of the study; p=0.134.

The same outcome persisted when both laparoscopic and open arms were analysed separately.

There was no difference in mean time to bowel motion between the control (98.61 +/-7.06): (mean hrs +/-SEM), and intervention (89.64 +/-5.94) groups of the study; p=0.333.
The same outcome persisted when both laparoscopic and open arms were analysed separately (see figures 3 and 4).

There was no difference in time to tolerate diet, or in symptoms of ileus (table 4).

**Analgesic outcomes**

Both groups had similar analgesic consumption rates (figure 5), with the same finding present in both laparoscopic and open arms. Patients who received chewing gum had less perception of pain than their control counterparts, with significantly lower VAS scores on days 2-5 postoperatively (figure 6). Patients who received chewing gum in the laparoscopic arm of the study, also had less perception of pain than their control counterparts, with significantly lower VAS scores on days 2-5 (figure 7). This finding was not present in the open arm of the study.

**Length of stay**

Length of stay (LOS) was similar in both groups, with no difference in mean or median LOS in laparoscopic or open groups, as well as in overall data (figure 8).

**Adverse events**

All patients in the intervention arm were compliant with, and tolerated the chewing gum, and there were no adverse events or complications related to the chewing gum. No unplanned analyses were performed.

**DISCUSSION**

Postoperative ileus is a major contributing factor in prolonged hospital stay following colorectal surgery (1). The aetiology of postoperative ileus is considered multifactorial, with contributions from both humoral and nervous system reactions to surgery (1). There are theories suggesting that the efferent cephalic-vagal response to sham feeding promotes gastrointestinal motility, and previous studies suggest that sham feeding with chewing gum is effective in encouraging gastrointestinal recovery following abdominal surgery (18-32).
A meta analysis performed by Chan et al. (18), on trials assessing the use of chewing gum in patients undergoing colorectal surgery, revealed a clinically significant reduction in time to flatus (20.8 hrs), bowel motion (33.3 hrs), and length of stay (2.4 days), in patients who received gum postoperatively. The authors of this study felt it was important to establish whether these outcomes were reproducible, particularly in patients who were fed early postoperatively. The findings of this study did not appear to reflect the outcomes seen in Chan’s meta analysis.

One of the potential reasons for the different outcome seen in this study and previous ones may relate to adequate numbers and power. This study was powered in order to determine what was perceived as a clinically relevant outcome (24 hour reduction in time to first bowel motion). The power calculation was performed in order to enable analysis for each group (open and laparoscopic colonic resections), but also to provide further ‘strength’ with a pooled analysis for both. To the authors knowledge this is the largest trial of its kind to address sham feeding in colorectal patients, and contains more patients than the systematic review performed by Chan et al (18). Earlier trials had sample sizes between 19 and 43, and may potentially have been underpowered, as well as resulting in the potential for publication bias.

Another potential reason for the difference in outcome could be the difference in feeding regimes. Presumably sham feeding would be no more efficient in promoting the efferent cephalic-vagal response than routine feeding. Patients in this trial were allowed to progress to diet with no specific restrictions, while previous trials had differing regimes. Of the five trials included in Chan’s meta analysis, none included patients on an established ERAS program. Three trials had a clear description of the postoperative feeding protocol, with one trial leaving nasogastric tubes in postoperatively (19), while the other two commenced sips of water on the first postoperative day, only escalating diet after passage of flatus (25, 29). Postoperative regimes of restricting dietary intake may result in sham feeding being more effective in this group of patients, and potentially explain the differing outcomes seen between the meta analysis of Chan et al and this study. The mean time to flatus in the control arm of this study (50.97 hrs), was less than that seen in
both the control (77.05 hrs), and intervention (58.27 hrs) groups of Chans’ meta
analysis, further validating this argument.

It is possible, following on from this argument that this trial was underpowered to
reflect the potential improvement sham feeding may have had, in addition to
normal feeding. In both open and laparoscopic groups of this study a trend
appeared towards improved function with the addition of gum. It is possible, in the
context of previous results that this trend is real and represents a type II error,
with the true result being less effective (but still real) in the presence of
accelerated feeding.

Open colorectal surgery potentially results in additional trauma and stress
response when compared with laparoscopic colorectal surgery, resulting in
increased rates of ileus and slower return of gastrointestinal function (9-12). If the
addition of sham feeding were to provide a small proportional benefit, it may
therefore be potentially more beneficial in the open colorectal surgical patients.
This trial was specifically designed in order to obtain robust data regarding both
groups of patients. In order to obtain this a ‘two armed’ trial was created, rather
than simply stratifying patients. This resulted in a trial of longer duration than was
initially anticipated, as a result of an increased trend in our institutions of
laparoscopic surgery. The fact that both arms of the trial had similar outcomes
further adds validity to the findings.

A combination of lack of equipoise and poor recruitment necessitated cancellation
of the upper gastrointestinal arm of this study. There was concern amongst the
upper gastrointestinal surgeons in our institution, particularly regarding the
heterogeneity of surgery and duration of surgery, with its impact on
gastrointestinal recovery, as well as debate about the postoperative feeding
protocol. When it became clear, following a 12 month review of recruitment, that
numbers in this arm were well below expected recruitment, and below
recruitment in the other 2 arms of the study, a decision was made to abandon this
study arm. Given the trial design and power calculation based on each arm rather
than overall numbers, it was felt this was possible without compromising the rest
of the trial.
Perception of pain was less in the chewing gum or intervention group of the study, particularly in the laparoscopic arm of this trial. While an argument could be made that sham feeding may have decreased pain perception as a result of less symptoms of ileus such as bloating and distension, this did not appear to be the case. There was no difference in overall symptoms of ileus between the two groups of this arm, and no difference in analgesic consumption between them. Another argument could be that chewing gum acted as a distraction from pain, however this finding was not replicated in the open arm of the trial. Perhaps the strongest reason for the finding was the higher conversion to open cases seen in the control group, which although not statistically significant (8 v 3, p=0.088), may have resulted in a greater perception of pain.

Given the current emphasis on ERAS programs, with the ‘push’ towards earlier gastrointestinal recovery and discharge, we hypothesized that the addition of gum chewing would lead to improved gut and functional recovery, in patients already receiving oral intake. However, this was not the case as demonstrated by our clinical trial. Our results show that there is no added benefit of sham feeding to the patient who is already on diet postoperatively.

The potential advantage of sham feeding over other forms of medical intervention to accelerate gastrointestinal function lies in its safety profile. In this study there were no side effects, adverse events or complications arising directly from chewing gum in the intervention groups. Prior studies have revealed similar outcomes, highlighting the safety of sham feeding (18-27). The potential for sham feeding, therefore, may exist in the group of patients, who are for any reason unable to tolerate, or unsafe to commence, a diet postoperatively.

In summary, this study reveals that sham feeding, with chewing gum, does not enhance gastrointestinal recovery following laparoscopic or open elective colorectal resectional surgery, in the presence of an accelerated feeding program. Chewing gum is a safe intervention following this form of surgery, however, and more research is required to determine its role in patients with established ileus, where oral intake is limited.

References


34. COCHRANE DATABASE SYSTEMATIC REVIEWS. Andersen H, Lewis S, S T. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. 2006;CD004080. Review.(4).

**Figure 1: Patient Questionnaire**

**Patient Questionnaire**

*Effect of Chewing Gum on Postoperative Recovery*

*A Randomised Control Trial*

Patient Questionnaire

Patient ID:
Date of Operation:
Today’s Date: Time:

Please rate your pain (on a scale from 0-10)

0____________________________________________________________10

0 = No pain at all
10 = Worst pain imaginable

Over the last 24 hours have you (please circle appropriate response)

A) Felt Nauseated Y / N
B) Felt Bloated Y / N
C) Felt Hungry Y / N
D) Vomited Y / N

What time and date did you first pass wind? Time:_________ Date:_________

What time and date did your bowel first work? Time:_________ Date:_________

Regarding your last 3 meals, were you able to eat and keep down your:

A) Breakfast? Y / N If no why not? __________ e.g. meal not provided, felt too sick to eat, vomited back up, away etc.
B) Lunch? Y / N If no why not? __________
C) Dinner? Y / N If no why not? __________

Were you able to chew gum for at least 15 minutes on each occasion? Y / N or N/A

If No, how long did you chew the gum for during the

First occasion: _____ min
Second occasion: _____ min
Third occasion: _____ min
Fourth occasion: _____ min

Was there any difficulty chewing the gum? Y / N

If Yes why?
Consort Diagram:

Assessed for eligibility  
N=175

Exclusions N=5

Eligible patients  
N=170

Refused consent N=2

Enrolled  
N=168

Randomized  
Control  
N=42

Intervention  
N=41

N=41

Control  
N=43

Intervention  
N=41

N=40

Allocated  
N=40

N=40

Analysed  
N=39

N=38

N=39

Laparoscopic  
N=84

Open  
N=84
## Table 1: Baseline Demographic Data

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<th>Chewing Gum Group (n=77)</th>
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<td>Operation Time (mean minutes)</td>
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<td>169</td>
<td>0.870</td>
</tr>
<tr>
<td>Laparoscopic/Open</td>
<td>39/41</td>
<td>39/38</td>
<td>0.874</td>
</tr>
<tr>
<td>Laparoscopic conversions</td>
<td>8/39</td>
<td>3/38</td>
<td>0.192</td>
</tr>
<tr>
<td>Right Hemicolecetomy</td>
<td>24</td>
<td>21</td>
<td>0.727</td>
</tr>
<tr>
<td>Left Colectomy</td>
<td>29</td>
<td>29</td>
<td>0.870</td>
</tr>
<tr>
<td>Subtotal Colectomy</td>
<td>5</td>
<td>5</td>
<td>1.000</td>
</tr>
<tr>
<td>Low Anterior Resection with loop stoma</td>
<td>18</td>
<td>15</td>
<td>0.698</td>
</tr>
<tr>
<td>Rectal Resection with permanent stoma</td>
<td>4</td>
<td>7</td>
<td>0.363</td>
</tr>
<tr>
<td>Complications</td>
<td>Control Group (n=80)</td>
<td>Chewing Gum Group (n=77)</td>
<td>P</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Complication rate</td>
<td>27 (34%)</td>
<td>26 (37%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Intraoperative Complications</td>
<td>3</td>
<td>1</td>
<td>0.620</td>
</tr>
<tr>
<td>Total Complications*</td>
<td>35</td>
<td>34</td>
<td>1.000</td>
</tr>
<tr>
<td>Anastomotic Leak</td>
<td>2</td>
<td>2</td>
<td>0.620</td>
</tr>
<tr>
<td>Readmissions</td>
<td>6</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>30 day Mortality</td>
<td>1</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Complication grades†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>15</td>
<td>0.868‡</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>11</td>
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<tr>
<td>3</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Includes readmissions, †Clavien-Dindo classification (36), ‡Chi-square test
Figure 3: Time to pass Flatus

Data are in mean values as central lines, box as +/- SEM and whiskers as 95% CI

Figure 4: Time to first Bowel Motion

Data are in mean values as central lines, box as +/- SEM and whiskers as 95% CI
Figure 5: Total In-Hospital Analgesic Consumption

Data are in mean values as central lines, box as +/- SEM and whiskers as 95% CI.

Figure 6: Overall Visual Analogue Pain Scores (0-10)

Data are in mean values +/- SEM.
Figure 7: Laparoscopic Visual Analogue Pain Scores (0-10)

Data are in mean values +/- SEM.

Figure 8: Length of Stay (Days)

Data are in mean values as central lines, box as +/- SEM and whiskers as 95% CI.
Summation

Over the past eight years that these trials have been performed and published, there has been significant change in the way colorectal surgery is practised. There is also, of course, much more literature published on the topics. The following is an attempt to summarise the influence that these trials have had on the way ERAS in colorectal surgery is practised, as well as summarising how the information from the trials is put into the author’s practice.

The trial on wound protection has been at the forefront of attempts to reduce surgical site infection in colorectal surgery. Many trials on wound protectors have been performed since this paper, most reproducing similar results, with one exception. The one paper finding no difference in SSI between wound protectors and controls, utilised the older form of single ring wound protectors. The authors of the paper presented in this PhD on wound protectors believed, based on previous trials and anecdotal use of the single ring wound protector, that it was unlikely to result in less SSIs for a number of reasons. The single ring wound protector is ‘clumsy’ to insert and results in wound spillage at the time of removal. It doesn’t have the ability to prevent fluid from the skin edges entering the incision, and doesn’t possess the ability to retract and, therefore, cannot result in wound haemostasis or minimise traumatic retraction from other instruments. In view of this, it was not assessed in our paper. All other published trials on the dual ring wound protector since our study inception have produced similar findings to our paper, and a recent meta-analysis on the topic, published in 2015 (5 RCTs n=755), has found an overwhelming and clinically relevant reduction in SSIs (RR 0.29, 95% CI 0.15-0.55) when dual ring wound protectors are used in abdominal surgery. Given the current available level of evidence, the use of dual ring wound protectors in colorectal surgery should be considered routine, and is routine practice at the author’s institution.

Purse string wound closure following stoma reversal has been less closely studied, and only one other RCT on the topic has emerged since the publication of our paper. This study was very similar in many ways to the paper presented here and also emerged with nearly identical findings, with a substantial reduction in SSI rate: 11/30: 36.6% control vs 0/31: 0% purse string (p<0.0001), highlighting the advantage of purse
string closure for this form of surgery. One consistent criticism, quite fairly levelled at the pursestring closure trial presented in this thesis, is that the trial was closed early and as a result potentially underpowered. The implication is that it is quite possible that the trial outcome represents a false positive outcome and this needs to be borne in mind when deciding whether to implement the technique as part of routine practice. It is fair to say that purse string closure would still not be considered standard practice at most institutions, but based on the available evidence, it is the routine form of closure performed by the author and other surgeons at his institution.

Many trials have highlighted the advantage of TAP blocks for abdominal surgery. There has only been one other RCT, to the author’s knowledge, examining the effect of a ‘single shot’ TAP block for laparoscopic colorectal surgery, and this emerged following completion of the trial in this PhD. This trial was smaller in number (n=79) and found improvements associated with TAP blockade in the form of reduction in pain scores, but found no improvement in analgesic consumption, nausea, vomiting, length of hospital stay and readmission rates. The ‘neral plane’ wound infusion paper presented in this PhD identified a significant improvement in respiratory function associated with a post-operative infusion following laparoscopic colorectal surgery. It is the only trial of this nature, to the author’s knowledge, and potentially represents a superior way to manage post-operative pain in this group of patients, compared to ‘single shot’ TAP blockade. It is possible though that this trial, like the ileostomy closure trial, is underpowered. The difference in opiate use between the two groups would be considered clinically relevant and is of the magnitude used for the power calculation, highlighting the fact that the pre-trial power calculation may have been based on an ‘unrepresentative’ sample. A larger sample size for power calculation may have resulted in a superior trial than the one performed by the author. In view of the findings of both trials, however, it is the author’s practice to utilise neural plane infusions following laparoscopic colorectal surgery.

Finally, the role of sham feeding after colorectal surgery remains controversial. There is no doubt that this intervention is safe and cheap, but the questions remain as to how effective it is, and whether it is a useful adjunct for patients that are placed on early feeding programs following their surgery. In addition to the RCT presented in this
PhD examining this topic, the author has performed and published a systematic review and meta-analysis on sham feeding following colorectal surgery. This meta-analysis, performed on all RCTs assessing the role of sham feeding following colorectal surgery (10 RCT’s n=612), highlighted a real, but limited effect, associated with sham feeding. This effect does not appear to be present when accelerated feeding is employed as part of an ERAS program. A separate analysis was performed as part of this systematic review, examining only trials looking at the effect of sham feeding in addition to post-operative feeding. There are only two RCTs (including the author’s) examining this aspect of sham feeding. Both of the trials and the combined analysis of them, failed to find evidence to support sham feeding in terms of accelerating the return of gut function when patients are placed on a diet immediately post-operatively. Given the results of this meta-analysis and the RCT presented in this PhD (the largest on the topic), it is the author’s practice to provide early feeding for all post-operative colorectal patients, while reserving sham feeding for those who cannot, or are unable to tolerate routine feeding, for any reason.

In summary, care of the colorectal surgical patient has been changed as a result of the trials that make up this PhD. It is the philosophy of the author that ERAS implies utilising current science surrounding aspects of surgical care applicable to your current patient, in order to minimise their peri-operative morbidity. In addition, it provides a standard template on which to base ongoing research in order to evaluate objectively and prospectively, advances in surgical care. It could be said in view of this philosophy, that enhanced recovery after surgery simply implies that your current surgical patient receives the best possible surgical care, while ensuring the next patient receives better care.
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