

THE EFFECT OF INTRAVENOUS FLUIDS
AND OTHER FACTORS ON
PATIENT RECOVERY FOLLOWING
ELECTIVE ABDOMINAL SURGERY

Graham J. MacKay

MBChB MRCS

A thesis submitted in June 2008
to the University of Glasgow
for the degree of Doctor of Medicine

from the University Departments of Surgery,
Western and Royal Infirmarys, Glasgow

© Graham J. MacKay 2008

Copies of this thesis may be produced by photocopying

SUMMARY

The subject matter for this research work is the area of perioperative recovery for patients undergoing major abdominal surgery. During clinical studies we have investigated some of the factors influencing postoperative recovery as well as suggesting strategies to improve patient care.

The main focus of the scientific work of this thesis is the role of intravenous fluids in the perioperative management of patients undergoing abdominal surgery. We found that restriction of intravenous fluid in the postoperative period does not significantly improve recovery in terms of gastrointestinal function (4.2 (3.2-6.9) versus 4.7 (3.7-6.1) days; $p=0.80$) or hospital stay (5.9 (4.0-7.9) versus 5.8 (4.1-7.3) days; $p=0.90$). Analysing our findings in the context of what is already known suggests that the immediate perioperative period when the effect of the metabolic-endocrine response is at its greatest is the most important period for fluid management. During this period fluid optimisation has an important role in patient recovery but following this period the body's own homeostatic mechanisms are more able to cope with any fluid excess. We also found that using a 'fast-track' regime we could reduce hospital stay to levels comparable with other studies in the published literature.

Our work using a multi-modal rehabilitation regime in association with both laparoscopic and open surgery suggests that it is the postoperative care package which has the more major influence on recovery. Our findings are in agreement with other small

sized studies beginning to appear in the literature and indicate that further large scale studies are required to determine the role of laparoscopic surgery and any potential benefits.

One of the most significant causes of morbidity for patients undergoing abdominal surgery is postoperative ileus. During the course of our studies we found that the extent of surgery and particularly handling and exposure of the intestines seems to have little effect on the duration of postoperative ileus. These findings add to the previously contradictory findings of other groups.

Our experience with 'fast-track' postoperative programmes was also applied to liver surgery, an area where it has not previously been reported, to show that a variety of abdominal procedures may benefit from this approach. By comparing our results with series published in the medical literature we found that hospital stay can be significantly reduced (4 *versus* 5-8 days).

CONTENTS

	Page:
Title page	1
Summary	2
Contents	4
List of tables	7
List of figures	9
Acknowledgements	10
Statement of collaboration	12
List of work published and presented	14
List of abbreviations	18
Chapter 1: Introduction – review of relevant literature	19
1.1 Perioperative recovery	20
1.2 Nasogastric tubes	23
1.3 Intra-abdominal drains	29
1.4 Mechanical bowel preparation	35
1.5 Prophylactic antibiotics	40
1.6 Midline versus transverse incisions	47
1.7 Bladder catheterisation	50
1.8 Nutrition	53
1.9 Postoperative ileus	57
1.10 Analgesia	65
1.11 Laparoscopic colorectal resection	71
1.12 Intravenous fluids	78
1.13 Fast-track surgery	88

CONTENTS (continued)

		Page:
Chapter 2:	Study aims	96
Chapter 3:	Effect of postoperative intravenous fluid and sodium restriction on patient recovery after elective colorectal surgery: A pilot study.	99
	3.1 Introduction	100
	3.2 Patients and methods	103
	3.3 Results	106
	3.4 Discussion	109
Chapter 4:	Effect of postoperative intravenous fluid and sodium restriction on patient recovery after elective colorectal surgery: An observer blinded randomised clinical trial.	112
	4.1 Introduction	113
	4.2 Patients and methods	115
	4.3 Results	119
	4.4 Discussion	132
Chapter 5:	Effect of laparoscopic colonic resection in fast-track patients after elective surgery.	135
	5.1 Introduction	136
	5.2 Patients and methods	138
	5.3 Results	141
	5.4 Discussion	148
Chapter 6:	Early discharge following liver resection for colorectal liver metastases	150
	6.1 Introduction	151
	6.2 Patients and methods	153
	6.3 Results	155
	6.4 Discussion	159

CONTENTS (continued)

	Page:
Chapter 7: The effect of colonic resection on recovery of gastrointestinal function following major abdominal surgery	161
7.1 Introduction	162
7.2 Patients and methods	164
7.3 Results	166
7.4 Discussion	172
Chapter 8: Conclusions	174
Appendix I: Fluid and sodium restriction study patient information sheet	185
Appendix II: Fluid and sodium restriction study consent form	187
Appendix III: Telephone randomisation protocol for fluid and sodium restriction study	188
Appendix IV: Patient folder abbreviated fluid and sodium restriction study protocol	189
Appendix V: Junior doctors' room fluid and sodium restriction study protocol	190
Appendix VI: Fluid prescription sheet for fluid and sodium restriction study	192
Appendix VII: Data collection sheet for fluid and sodium restriction study	193
Appendix VIII: Short form 36 questionnaire	199
Appendix IX: Randomisation questionnaire for fluid and sodium restriction study	202
References	204

LIST OF TABLES

		Page:
Table 3.1	Baseline characteristics for patients in fluid and sodium restriction pilot study	107
Table 3.2	Intravenous fluid and sodium daily quantities and cumulative totals for patients in the fluid and sodium restriction pilot study	108
Table 4.1	Baseline Characteristics for patients in the fluid and sodium restriction study	122
Table 4.2	Intravenous fluid and sodium daily quantities and cumulative totals for patients in the fluid and sodium restriction study	123
Table 4.3	Serum urea and creatinine for patients in the fluid and sodium restriction study	124
Table 4.4	Times to study endpoints for patients in the fluid and sodium restriction study	125
Table 4.5	Complications for patients in the fluid and sodium restriction study	126
Table 4.6	Mean Short Form 36 (SF-36) scores at 3 months after surgery for patients in the fluid and sodium restriction study	127
Table 4.7	Baseline Characteristics comparing non-randomised patients with patients randomised to the fluid and sodium restriction study	128
Table 4.8	Intravenous fluid and sodium cumulative totals comparing non-randomised patients with patients randomised to the fluid and sodium restriction study	129

LIST OF TABLES

		Page:
Table 5.1	Baseline characteristics for patients in the laparoscopic/ open surgery study	143
Table 5.2	Times to study endpoints for patients in the laparoscopic/ open surgery study	144
Table 5.3	Complications for patients in the laparoscopic/ open surgery study	145
Table 6.1	Baseline characteristics for patients in fast-track liver resection series	157
Table 6.2	Blood parameters for patients in fast-track liver resection series	158
Table 7.1	Baseline characteristics for patients undergoing colonic/ liver resection	168
Table 7.2	Opioid and intravenous fluid intake for colon/ liver resection patients	169
Table 7.3	Blood parameters for patients undergoing colonic/ liver resection	170

LIST OF FIGURES

	Page:	
Figure 4.1	Trial profile for the fluid and sodium restriction study	130
Figure 4.2	Estimated mean daily weight change compared to baseline with 95% CIs, for patients in the fluid and sodium restriction study	131
Figure 5.1	Trial profile for patients in the laparoscopic/ open surgery study	146
Figure 5.2	Estimated mean daily pain scores at rest and on moving, in the mornings or afternoons, with 95% CIs for patients in the laparoscopic/ open surgery study	147
Figure 7.1	Time to return of gastrointestinal function: boxes show median and interquartile range; whiskers give range by study group for patients undergoing colon/ liver resection	171

ACKNOWLEDGEMENTS

I would like to acknowledge the support and advice of the following people who made the experience such an enjoyable one. Without their encouragement this thesis would not have been possible.

My wife Catherine and my children Emily and Finlay for their love and patience and for allowing me the time and space to complete this work.

Prof. Patrick O'Dwyer (Professor of Surgery, University Department of Surgery) who acted as my supervisor for the work included in this thesis. I would like to thank him in particular for his constant encouragement and enthusiasm which I found invaluable during my research. I would also like to record my gratitude to Dr Michael Serpell (Consultant Anaesthetist, Western Infirmary) and Mr Richard Molloy (Consultant Surgeon, Gartnavel General Hospital) who not only participated enthusiastically in the trial but gave me good advice along the way.

Mr Felix Duffy (Research Nurse, Western Infirmary) who worked exclusively on the randomised trial helping with randomisation, data collection and follow-up of patients.

Mr Joseph Crosier (Research Fellow, Royal Infirmary) who helped with randomisation of patients at the Royal Infirmary including data collection for patients during their in-patient stay.

The following surgeons who allowed their patients to be entered into the randomised trial: Mr David Galloway (Consultant Surgeon, Gartnavel General Hospital), Mr Paul Horgan (Senior Lecturer in Surgery, Royal Infirmary), Dr Ruth McKee (Consultant Surgeon, Royal Infirmary), Mr John Anderson (Consultant Surgeon, Royal Infirmary) and Mr David Deardon (Consultant Surgeon, Western Infirmary).

Alex McConnachie (Statistician, Robertson Centre for Biostatistics) for his advice regarding the statistical design and analysis. I would also like to thank the staff at the Robertson Centre for helping to set up the telephone randomisation system used in the main trial and for keeping the backed-up patient database.

ACKNOWLEDGEMENTS (continued)

Prof. Ken Fearon (Professor of Surgery, University Department of Surgery, Edinburgh Royal Infirmary) for his fresh perspective on the results of the trial.

The anaesthetists at the Western Infirmary, Royal Infirmary and Gartnavel General Hospital for adhering to the protocols involved in the trial.

The ward staff in all three hospitals but particularly in Ward 10 East and the High Dependency Unit in Gartnavel General Hospital for their care and attention to data collection for patients in the trial.

The majority of this work was carried out while I was employed as a research fellow in the University Department of Surgery, Western Infirmary, Glasgow. The randomised controlled trial which makes up the main body of my research was funded by the Chief Scientist Office of the Scottish Executive.

STATEMENT OF COLLABORATION

The randomised trial comparing the effect of restricted and standard postoperative intravenous fluids on recovery was initially conceived by Prof. Patrick O'Dwyer. I was involved at an early stage in the submissions for both ethical approval and funding of the trial. In conjunction with Prof. Patrick O'Dwyer I helped to plan the pilot study including designing the data collection sheets and all other material used in the running of the trial. The design of the randomised trial was then further refined prior to commencing in November 2003.

I supervised the day to day running of the trial including data collection with help at the Western Infirmary and Gartnavel General Hospital by Felix Duffy and at the Royal Infirmary by Joseph Crozier. Follow-up of patients following their inpatient stay was performed by both myself and Felix Duffy. The data collected from patients during their in-patient stay and out-patient follow up was collated and entered into a database by myself and Felix Duffy.

The content of the postal questionnaires was agreed with Prof. O'Dwyer and were posted by Felix Duffy.

Analysis of the results of the trial was carried out by myself including the statistical analysis. The statistics for the main randomised trial were repeated by Alex McConnachie at the Robertson Centre for Biostatistics which was a condition of the funding received from the Chief Scientist's Office. The telephone randomisation system and critical incident monitoring of the randomised trial were also handled by the Robertson Centre for Biostatistics. A back-up of the patient database was kept at the Robertson Centre for Biostatistics.

The first draft of the fluid trial paper was reviewed by Prof. K C Fearon who offered a fresh perspective on the results prior to submission for publication in the British journal of Surgery.

The composition of this thesis is entirely my own work and has not been submitted previously for another degree or to any other institution. The thesis was typed by me using a Windows PC running Windows XP operating software. The following software programs were used in the production of this work: Microsoft Word 2003, Microsoft Excel 2003, Reference Manager 10, Minitab version 14 and SPSS version 15. All references used in the text were reviewed by me personally.

LIST OF WORK PRESENTED AND PUBLISHED

Original Articles:

1. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, K C Fearon, P J O'Dwyer. Randomised clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* 2006; 93: 1469-1474.
2. G, MacKay, K Fearon, A McConnachie, M G Serpell, R G Molloy, P J O'Dwyer. Effect of postoperative intravenous fluid and sodium restriction on patient recovery after elective colorectal surgery: An observer blinded randomised trial. *Focus on Research. Scottish Executive Health Department Chief Scientist Office. CZH/ 4/ 98.*
3. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, P J O'Dwyer. Laparoscopic colonic resection in fast-track patients does not enhance recovery after elective surgery. *Colorectal Dis* 2007; 9 (4): 368-372.
4. G MacKay, P J O'Dwyer. Effect of colonic resection on recovery of gastrointestinal function following major abdominal surgery. *Journal of Chinese Clinical Medicine* 2007; 2 (12): 667-670.
5. G MacKay, P J O'Dwyer. Early discharge following liver resection for colorectal liver metastases. *Scott Med J* 2008; 53 (2): 22-24.
6. G MacKay, R G Molloy, P J O'Dwyer. Fast-track colorectal surgery and perioperative outcomes. *Semin Colon Rectal Surg* 2008; 19 (1): 16-19.

Book Chapters:

Fluid balance and Shock.

Davidson's Foundation Handbook for Clinical Practice. (*In Press*)

Letters:

1. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, P J O'Dwyer. Laparoscopic colonic resection in fast-track patients does not enhance recovery after elective surgery. *Colorectal Dis* 2007; 9 (8): 758-761.
2. G MacKay. Randomised clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg* 2007; 94(3): 383.

Published Abstracts:

1. G MacKay, M Downey, R G Molloy, P J O'Dwyer. Early discharge following liver resection for colorectal liver metastases. *Colorectal Disease* 2004; 6 (Supp 2): 50.
2. G MacKay, R G Molloy, P J O'Dwyer. The effect of colonic resection on gastrointestinal recovery following major abdominal surgery. *Br J Surg* 2005; 92: 154.
3. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, P J O'Dwyer. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery. *Br J Surg* 2006; 93: 896-902.
4. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, K Fearon, P J O'Dwyer. Intravenous fluid and sodium restriction has no effect on recovery from colorectal surgery: An observer blinded randomised clinical trial. *Br J Surg* 2006; 93: 896-902.
5. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, K C Fearon, P J O'Dwyer. Intravenous fluid and sodium restriction has no effect on recovery from colorectal surgery: An observer blinded randomised clinical trial. *Colorectal Disease* 2006; 8 (Supp 2): 29.

6. G MacKay, U Ihedioha, A McConnachie, M Serpell, R G Molloy, P J O'Dwyer. Laparoscopic colonic resection in fast-track patients does not enhance recovery after elective surgery. *Colorectal Disease* 2006; 8 (Supp 2): 31.
7. G MacKay, U Ihedioha, A McConnachie, M Serpell, R Molloy, K C Fearon, P J O'Dwyer. Laparoscopic colonic resection in fast-track patients does not enhance recovery after elective surgery. *Surg Endosc* 2007; 21 (Suppl 13): 1-106.

Presentations to Learned Societies:

1. Early discharge following liver resection for colorectal metastases. European Association of Coloproctology, Geneva, Switzerland. September 2004
2. The effect of colonic resection on recovery of gastrointestinal function following major abdominal surgery. Association of Surgeons of Great Britain and Ireland, Glasgow. April 2005
3. The effect of colonic resection on recovery of gastrointestinal function following major abdominal surgery. Glasgow GUT club Scientific Meeting. February 2005
4. Postoperative intravenous fluid and sodium restriction has no effect on patient recovery following elective colorectal surgery. West of Scotland Surgical Association, Royal College of Physicians and Surgeons of Glasgow, October 2005.
5. Postoperative intravenous fluid and sodium restriction has no effect on patient recovery following elective colorectal surgery. Patey Prize session, Surgical Academic and Research Society, Royal College of Surgeons of Edinburgh, January 2006.
6. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery. Surgical Academic and Research Society, Royal College of Surgeons of Edinburgh, January 2006.

7. Perioperative Care – Taking the Fast-Track.
Hospital Meeting, Royal Alexandra Hospital, Paisley, April 2006.
8. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery.
Tissue Science Laboratories Runner-up prize. Association of Coloproctology of Great Britain and Ireland, Sage Centre, Gateshead, July 2006.
9. Intravenous fluid and sodium restriction has no effect on recovery from colorectal surgery: an observer blinded randomised clinical trial.
Association of Coloproctology of Great Britain and Ireland, Sage Centre, Gateshead, July 2006.
10. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery.
European Association of Endoscopic Surgeons, Estrel Congress Complex, Berlin, Germany, September 2006.
11. Enhanced recovery after surgery.
Critical Care Nurses Group, Glasgow Royal Infirmary, Glasgow, May 2007.
12. Enhanced recovery after surgery.
Scottish Colorectal Cancer Nurses Group, Isle of Skye Hotel, Perth, August 2007.
13. Enhanced recovery in Colorectal Surgery
South Glasgow Colorectal Surgical Unit, Victoria Infirmary, Glasgow, March 2008.

ABBREVIATIONS

ACTH	Adrenocorticotrophic Hormone
ALT	Alanine transaminase
Alb	Albumin
ASA	American Society of Anesthesiologists
AST	Aspartate transaminase
Bil	Bilirubin
BMI	Body Mass Index
CI	Confidence Interval
Cr	Creatinine
CT	Computed Tomography
DVT	Deep Venous Thrombosis
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GI	Gastrointestinal
Hb	Haemoglobin
HR	Hazard Ratio
IQR	Interquartile range
IV	Intravenous
Kg	Kilogram
L	Litres
MBP	Mechanical Bowel Preparation
Na	Sodium
NG	Nasogastric
NSAID	Non-steroidal anti-inflammatory
PCA	Patient Controlled Analgesia
PONV	Postoperative Nausea and Vomiting
PVC	Polyvinyl Chloride
RCT	Randomised Controlled Trial
UCLA	University of California, Los Angeles
UTI	Urinary Tract Infection

CHAPTER 1

REVIEW OF THE LITERATURE

1.1 PERIOPERATIVE RECOVERY

The development of modern surgery has focused on several different elements with the aim of improving overall outcome. One of the primary areas of interest has been the technical aspect of surgery which includes not only the precise methods for carrying out a procedure but also training and technological advances. For as long as the importance of technique has been recognised, clinicians have also been aware that the perioperative care of the patient has a significant influence on the overall outcome from surgery. In particular over the last decade there has been a sustained interest in the medical literature regarding both individual interventions and processes and pathways relating to recovery.

The renewed interest in perioperative recovery has been driven by a number of different factors not least of these the increasing pressure on resources in healthcare systems struggling to meet the cost of new technology and the demand of an ageing population. Particularly in the United Kingdom with the restraints of a National Health Service funded through taxation, rising costs have led to reduced bed numbers, higher bed occupancy rates and drives toward cost-efficiency. An ageing population has only added to these challenges as excellence in the face of significant co-morbidity has come to be expected. The development of ‘day-surgery’ has been a timely answer to many of these problems. Borne out of the improvements already realised in perioperative care and in conjunction with shorter-acting anaesthetic agents, day-surgery has changed expectations with principles being applied to a growing number of procedures.

When discussing perioperative care a number of phases have to be taken into account. In the preoperative phase it is clear that preparation for theatre is an important aspect. Firstly the baseline state of the patient needs to be assessed and optimised which will include attention to co-morbid illnesses and also the effect their presenting condition may exert on nutrition and general wellbeing. With respect to abdominal surgery preoperative interventions such as bowel preparation, nutritional supplementation and fluid balance may all have a bearing on the postoperative outcome. In addition to these factors it is clear from the literature that the psychological preparation of the patient preoperatively can also have an effect postoperatively reducing pain and analgesic use^{1,2}.

During the intraoperative phase both surgical and anaesthetic technique play a vital role. Through the work of early pioneers such as Sir David Cuthbertson we now understand that the response to injury, which includes the insult of surgery, involves activation of the hypothalamic-pituitary axis and autonomic nervous system with an overall catabolic effect³. It has therefore been postulated that intervention focused on reducing the stress of surgery may in turn reduce the inflammatory response and improve recovery. This has led to surgeons embracing the ideas of minimal access techniques with precise and limited dissection. Anaesthetic technique has also been influenced with studies examining analgesic regimes aimed at reducing perioperative pain and stress. Methods to block the afferent pathways involved in the metabolic-endocrine response have also been investigated.

Many of the interventions made in the intraoperative phase such as fluid management, analgesia and placement of monitoring devices will continue into the postoperative phase. During this phase management of the surgical patient can become even more complex as a number of different members of the multi-disciplinary team become involved. Furthermore the interventions made in this phase have been especially influenced by decades of surgical tradition rather than the principles of evidence-based practice. The use of surgical drains, nasogastric tubes and postoperative feeding regimes have until recently been guided purely by practice handed down through the apprenticeship model of training. Recently these traditions have been challenged and it is in these areas that some of the most significant advances in perioperative recovery have been made.

Along with the increased knowledge base regarding individual interventions it is also clear that on their own their success in modifying the surgical stress response and end organ dysfunction is limited. From this realisation has come the idea of an integrated care pathway aiming to bring together evidence-based practice with a synergistic effect. A large proportion of the work in this area termed 'fast-track surgery' has come from Professor Henrik Kehlet's group in Denmark. They suggest that by using a multimodal rehabilitation regime the stress response to surgery can be significantly reduced and along with this hospital stay and time taken to return to normal activities. They further highlight that the success of areas such as feeding and mobilisation is intimately linked to other parts of the regime such as a dynamic analgesic and antiemetic regime. By approaching the problem in this way they argue that the result may be more than just the sum of its parts.

Despite reports of initial success using a fast-track regime many clinicians have expressed concern that safety may be compromised. If patients are to be discharged sooner from hospital this may lead to patients developing significant complications at home and so delaying their presentation. Moreover the burden of health provision may simply be shifted from secondary care in hospital to primary care and general practitioners. In response to these concerns a number of groups have published their experience of fast-track surgery as well as refocusing their attention on the individual elements making up the multimodal programme.

1.2 THE USE OF NASOGASTRIC TUBES IN ABDOMINAL SURGERY

Introduction

The use of a nasogastric tubes is said to date back to 1790 when John Hunter stretched the skin of an eel over a whale bone to deliver enteral feeding to a patient with dysphagia⁴. The use of a tube to decompress the stomach was described much later in 1884 by Kussmaul and further by Levin in 1921 who designed a single lumen tube^{5,6}. The routine use of nasogastric tubes in abdominal surgery is widely attributed to Wangenstein following a number of experiments on patients with small bowel obstruction reported in 1932⁷. Because of the perceived reduction in mortality attributable to the use of nasogastric tubes they became routine not only in bowel obstruction but in all abdominal procedures.

The prophylactic use of nasogastric tubes remained part of 'standard practice' in abdominal surgery for more than 50 years despite people questioning its routine use as early as the 1960s^{8,9}. Advocates of the practice believe that the use of a nasogastric tube reduces postoperative ileus and the resultant nausea, vomiting and abdominal bloating. Furthermore it has been suggested to reduce other postoperative complications such as aspiration, wound dehiscence and anastomotic leak.

The proposed mechanism is that the nasogastric tube drains secretions and gas from the upper gastrointestinal tract and thereby relieves nausea and vomiting, abdominal bloating and reduces the duration of ileus; however there are a number of problems with this. In the presence of an intact pylorus the tube is only likely to drain the stomach and we know from clinical and manometric studies that contractile activity returns to the stomach within a few hours¹⁰. The last part of the gastrointestinal tract to recover from postoperative ileus is the large bowel which can take a number of days and this is likely to account for the majority of the abdominal distension¹⁰. We also know that the nasogastric tube will only ever drain a fraction of the 8.5L estimated to be produced by the intestinal tract every 24 hours and so small bowel absorption must be present soon after the operation. It has also been previously theorized that the swallowing of air or aerophagia has a significant contribution to abdominal bloating and ileus and that the use of a nasogastric tube would avoid this, however nasogastric tubes themselves may promote aerophagia^{11,12}.

It is well recognized that nasogastric tubes cause a significant amount of discomfort for patients in the postoperative period and so many have looked again at the evidence with multiple randomised and non-randomised trials as well as reviews and editorials suggesting that routine nasogastric decompression is unnecessary after elective abdominal surgery^{8, 12-28}.

The evidence

The evidence for the use of prophylactic decompression has been widely studied with particular attention paid to the difference between certain abdominal procedures. In colorectal surgery one of the largest prospective randomised trials was by Wolff et al. from the Mayo Clinic and published in the *Annals of Surgery*²¹. The study included 535 patients undergoing elective colorectal surgery and found that there was no difference in hospital stay, pulmonary or wound complications between the group who were decompressed and the group who were not. They did note that there was an increase in abdominal distension, nausea and vomiting in the group who were not decompressed which amounted to around 10%. Moreover, 13% of this group required subsequent re-insertion of the tube compared with 5% in the other group. Despite this increase in minor complications the authors concluded that 'routine nasogastric decompression is not warranted after elective colon and rectal surgery'.

Further evidence has been produced in upper gastrointestinal surgery where the use of nasogastric tubes has been uniform owing to the higher incidence of anastomotic leakage with proximal anastomoses. Furthermore truncal vagotomy and skeletonisation of the

coeliac plexus is thought to interfere significantly with upper gastrointestinal motility. A study looking at 136 patients undergoing radical (D2) gastrectomy for malignancy found that patients in the no decompression group had a reduced time to first flatus, time to liquid diet and hospital stay²⁴. There was also no difference in fever, atelectasis, anastomotic leak rate or postoperative complications. 2 (3%) patients in each group required further insertion of a nasogastric tube. Another study looked at patients (n=66) undergoing total gastrectomy with oesophago-jejunal anastomosis and found that there was less sore throat, nausea, fever and pulmonary complications in the group without nasogastric decompression²⁵. Finally in the largest series published of patients undergoing Roux-en-Y gastric bypass for obesity without nasogastric decompression (n=1015) the authors from UCLA report an anastomotic leak rate of 1% which suggests that the practice is safe²⁹.

As well as numerous studies looking at the use of nasogastric tubes following gastrointestinal surgery data is also available regarding its use in both Vascular and Gynaecological surgery. An American study looking at 80 patients undergoing elective abdominal aortic aneurysm surgery found no difference in postoperative outcomes with or without the use of nasogastric decompression³⁰. They also reported that only 3 patients (7%) in each group required intubation in the postoperative period. A further study of patients undergoing gynaecological surgery for malignancy found patients experienced less pain and a quicker return of bowel function in the group without nasogastric decompression and no difference in any other complications³¹.

Criticisms of previous randomised and non-randomised trials published on the prophylactic use of nasogastric tubes have mainly focused on the number of patients involved in these trials especially when comparing rates of low incidence complications such as anastomotic leakage. Perhaps the most compelling evidence on the use of nasogastric tubes comes from two meta-analyses that have been carried out. The first of these was published in 1995 in the *Annals of Surgery* by Cheatham et al³². They included 26 trials with a total of 3,964 patients undergoing a variety of abdominal procedures and looked at the main postoperative outcomes. They found that patients without routine nasogastric decompression had fewer episodes of postoperative fever, atelectasis and pneumonia and faster return to oral intake. There was an increased rate of abdominal bloating and vomiting but no overall increase in complications and the authors concluded that for every 1 patient requiring a nasogastric tube for postoperative nausea and vomiting 20 patients could be spared the discomfort. This showed that routine use of nasogastric tubes was not required and that a policy of selective use for patients who develop symptoms does not prolong hospital stay or increase complications.

The meta-analysis by Cheatham et al. was updated in 2005 by Nelson et al. and published in the *British Journal of Surgery*³³. Since the first meta-analysis in 1995 a number of randomised trials had been published and the updated meta-analysis included almost double the number of randomised-controlled trials of the original. Furthermore in contrast to the original analysis no non-randomised trials were included. This analysis included 28 trials and 4194 patients. It found an earlier return of bowel function in the group without tubes with a reduced rate of pulmonary complications approaching statistical

significance. There were no differences seen in the rates of ventral hernia however only one study reported this endpoint and there were no differences seen in anastomotic leak rate. More discomfort was found with the routine use of the tube.

Conclusion

Over the last 20 years the routine use of nasogastric decompression in elective abdominal surgery has been challenged by a number of trials and at least 2 large meta-analyses.

Despite this wealth of evidence the traditions of surgery are often deeply ingrained and in a U.K. survey of 259 general surgeons carried out in 1991 92% of surgeons still used nasogastric decompression after Polya gastrectomy, 72% after small bowel resection and 49% after large bowel resection¹⁷. A similar survey carried out in 1994 of American Colon and Rectal surgeons revealed that only 30% were still using routine nasogastric decompression³⁴. This may represent a difference between general and specialist colorectal surgeons or indeed the difference between British and North American surgeons or possibly that at last the evidence regarding the prophylactic use of nasogastric tubes is being recognized.

It is clear from the literature that nasogastric tubes do not prevent any of the complications that their advocates propose. They may well increase respiratory complications and there is no doubt that they cause significant discomfort to the patient. Furthermore there is no evidence of any increase in postoperative complications when their routine use is avoided.

1.3 THE USE ON INTRA-ABDOMINAL DRAINS IN ABDOMINAL SURGERY

The history of drains in medicine

The use of drains in medicine dates back to the Hippocratic era when, in his writings, Hippocrates describes using a drain to release pus from an empyema of the chest. Prophylactic drainage of the peritoneal cavity was first described much later in the mid-nineteenth century by Sims and for almost as long there has been debate over their use. Theodore Billroth³⁵, one of the fathers of gastrointestinal surgery, was convinced that drains had saved the lives of many of his patients while others such as Von Ott³⁶ and Delbert³⁷ argued that drainage of the general abdominal cavity was impossible. Tait, a great antagonist of Lord Lister (himself an advocate of drains), for once agreed when he stated ‘when in doubt, drain!’³⁸.

By the early twentieth century Yates, a surgeon from Chicago, in his seminal paper on the effects of peritoneal drainage, wrote: ‘There is probably no detail in modern surgical pathology that deserves more thorough comprehension, that which is less definitely understood by the average teacher, practitioner, and student than the reaction of the peritoneum to drainage; nor is there another that so often savors as strongly of pioneer mysticism, if expressed opinions written or spoken, may be taken as criteria.’ In over 30 experiments Yates concluded that drainage of the general peritoneal cavity was impossible due to early encapsulation of the drain and that the serous exudates from drains were caused by their own foreign body reaction³⁹⁻⁴¹.

How do drains work?

The use of drains in colorectal surgery has been proposed for a number of theoretical reasons. Those who advocate the use of drains argue that it allows drainage of serous fluid and haematoma at the operative site which is at risk of becoming infected, forming an abscess and causing disruption of the anastomosis. They would also suggest that a drain close to the anastomosis will give an early indication of leakage by draining pus or faeces and possibly limiting the severity of the leak. On the opposing side of the argument those against prophylactic drainage suggest that drains may impede the healing of anastomoses and do not give an early indication of anastomotic breakdown or ameliorate the clinical effect.

The healing of colorectal anastomoses depends on a number of local factors including adequate blood supply, the absence of tension on the anastomosis and good surgical technique. The contribution to healing from a number of other local factors is a matter of some debate. For intra-peritoneal anastomoses it is thought that access to omentum, peritoneum and bowel serosa is important for healing as they may provide additional blood supply in the presence of ischaemia and seal some anastomotic defects^{42, 43}. The situation is thought to be different for anastomoses below the peritoneal reflection where the bowel is surrounded by a large dead space. This dead space fills postoperatively with sero-sanguineous fluid produced by the raw surfaces following dissection and the absence of peritoneum means that resorption of fluid is markedly reduced. It is thought that this collection of fluid which provides a rich culture medium for bacteria is at risk of becoming infected and leading to abscess formation and anastomotic breakdown.

Anastomoses in the pelvis are also much more likely to be formed under tension and are less accessible for the omentum.

Experimental trials

A number of experimental trials have been carried out on the use of prophylactic abdominal drains. Berliner performed studies on dogs and observed leaks in 11 out of 20 where the drain was found interposed between anastomosis and omentum suggesting that the drain forms a physical barrier to the omentum⁴⁴. Manz carried out similar experiments finding that after left sided colonic anastomosis 9 of 20 dogs with drains died compared with 0 of 15 dogs without drains⁴⁵. Nora and colleagues found that 9 out of 10 splenectomized dogs in which drains were placed developed obvious signs of infection compared with none of the dogs in the group without drains⁴⁶.

Crowson and Wilson carried out one of the most detailed experimental studies into the use of prophylactic drains after intra-peritoneal colonic anastomosis in dogs. They found that in the absence of a drain the peritoneum appeared capable of controlling bacteria but when a drain was added to the contaminated area of an anastomosis the incidence of sepsis was significantly increased. They noted that anastomotic burst pressure was doubled in the group without drains suggesting an inhibition to local healing caused by drains. They also observed that due to the marked inflammatory response to the drain the tract was almost completely obliterated. This meant that in 8 dogs abdominal wall abscesses were present which were unable to drain as the tract no longer communicated with the peritoneal cavity. Of the different drain types used they found that silastic drains

produced less foreign body reaction than latex or PVC⁴⁷. Smith et al. also investigated the effect of different drain materials in rats and found that latex inhibited local healing and lead to a significantly higher anastomotic leak rate³⁹.

Randomised clinical trials

A number of clinical trails have been published which have tried to answer the question of whether prophylactic abdominal drainage is beneficial for patients. All of these studies have suffered from a similar problem which is that the outcome measure of anastomotic dehiscence is so rare a very large sample size is required to prove that there is no difference between the groups. Previous researchers have calculated that with a baseline leak rate of 5%, ruling out a 20% relative risk reduction in leak rate with a 5% significance level and 80% power would require 1080 patients in each treatment arm⁴⁸. Many studies to date also include patients with intra-peritoneal and extra-peritoneal anastomoses and patients who have had defunctioning stomas making interpretation difficult.

Sehapayak published a retrospective analysis of 44 patients undergoing extra-peritoneal anastomosis with or without suction drainage and found an increased complication rate and hospital stay in the group without drainage⁴⁹. Collins and Talbot published a similar series of 39 patients and it was suggested that suction drainage was a useful adjunct during low anterior resection⁵⁰.

Allen-Mersch carried out a randomised study of 30 patients and using CT measured fluid collections in the pelvis on the seventh postoperative day. He showed that despite the presence of a functioning drain residual collections were still present in the pelvis and the addition of suction made no difference to the size of the collection. He also noted that the lower the anastomosis the larger the collection of fluid⁵¹.

Galandiuk and Fazio investigated whether the addition of irrigation to suction drainage had any effect on local septic complications randomizing 200 patients to their study. They did not observe any effect from irrigation with regard to pelvic sepsis or hospital stay⁵².

Some of the strongest evidence on the issue of prophylactic drainage comes from a meta-analysis published in the *Annals of Surgery* in 1999 by Urbach and colleagues⁴⁶. The analysis included 414 patients undergoing both intra-peritoneal and extra-peritoneal anastomoses. It concluded that prophylactic drainage of colonic and rectal anastomoses does not reduce the rate of adverse events including clinical leaks. The studies included in the meta-analysis also reveal some other interesting findings. One study showed that there was no difference in the size of fluid collections between patients with or without drains⁵³. It is also clear from these studies that drains are unlikely to ameliorate the clinical effects of a leak as in only 1 of 20 patients with an anastomotic leak did pus or faeces pass through the drain⁵⁴⁻⁵⁶.

Since the publication of this meta-analysis there have been 3 further studies which seem to concur with the results. Merad et al. in a study of 319 patients found that drains did not

reduce either the rate or severity of complications and that there was no difference between suction and non-suction drains⁵⁷. In a series of 707 patients undergoing large bowel resection with intra-peritoneal anastomosis Alves found that on multivariate analysis abdominal drainage was significantly associated with a higher risk of anastomotic leakage⁵⁸. Finally, Yeh and colleagues recently published a series of nearly 1000 patients undergoing anterior resection. They found that prophylactic drainage was not associated with a reduced rate of anastomotic leakage after anterior resection. They showed that irrigation-suction sump drainage was associated with a higher rate of leak independent from other risk factors⁵⁹.

Conclusion

The varied experimental and clinical trials looking at the question of abdominal drainage have revealed a number of important findings. Drains when placed in the peritoneal cavity become rapidly encapsulated making their use limited. Certain materials such as latex may have local inhibitory effects on healing increasing the chance of dehiscence although whether they act as a physical barrier to the body's natural defences is unclear. The placing of drains for intra-peritoneal anastomoses appears to be contraindicated by current evidence although the case in extra-peritoneal anastomosis is less clear. Drains do not appear to reduce the size of pelvic fluid collections and may themselves produce serous exudates through a foreign body reaction. The addition of suction or irrigation to pelvic drains seems to make little difference. In summary, the current evidence does not support the view that drains have any effect on rates of anastomotic dehiscence or that drains control the clinical effect of a leak.

1.4 MECHANICAL BOWEL PREPARATION FOR ABDOMINAL SURGERY

Introduction

In the early part of the 20th century mortality rates from surgery on the gastrointestinal tract were high at around 20% mainly due to septic complications. For as long as bowel surgery has been possible surgeons have been looking at ways of trying to sterilise the contents of the colon to try to reduce the risk of infective postoperative complications. It is not exactly clear when the use of bowel cleansing first began but it may well have been introduced by military surgeons during the Second World War. Following this in 1966 Plumley described a new regimen and mechanical bowel preparation (MBP) became widely accepted in the early 1970s⁶⁰. Its use was further cemented into surgical dogma by a retrospective study of the aetiology of disruption of intestinal anastomoses by Irvin and Goligher in 1973 suggesting that poor MBP led to increased anastomotic leak rates⁶¹.

The theoretical advantages of MBP include decreased intra-luminal bacterial counts, avoiding hard faeces from physically disrupting anastomoses and improving bowel handling by emptying the colon. Although the use of MBP has been seen by most as a 'standard of care' there is very little hard evidence to support its use with expert opinions and clinical experience making up the bulk of the evidence base. Furthermore despite the introduction of routine prophylactic antibiotics surgeons were still reluctant to review the role of MBP. Since its widespread introduction in the 1970s almost no studies were carried out into the efficacy over the next 20 years, but rather concentrated on different

preparations to empty the bowel⁶²⁻⁶⁵. It was not until Irving and Scrimgeour published a series in 1987 of 72 patients undergoing a wide range of elective and emergency colorectal procedures without MBP and with low rates of infective complications (8.3% wound infection) that serious attention was given to the use of MBP⁶⁶. This series was followed by a number of others all reporting excellent results without the use of MBP and so in 1992 Brownson published the first large randomised controlled trial on the use of MBP in elective colorectal surgery⁶⁷⁻⁶⁹.

Experimental data

Experimental data regarding the use of MBP is largely contradictory⁷⁰. The use of animal models to investigate bowel cleansing is made more difficult by the differences in bacterial flora composition between species and also brought about by differences in dietary intake⁷¹.

Studies carried out on both animal and human models have found that the use of MBP only reduces the total faecal mass but does not reduce the concentration of faecal micro-organisms and so the concept of sterilising the bowel is misleading. Some authors have found that far from reducing the microbial counts, within 12-18 hours the concentrations are actually higher than pre-treatment levels⁷¹⁻⁷³.

A further study of 36 dogs undergoing low anterior resection, an operation with a higher rate of anastomotic dehiscence, found that in the group without MBP anastomotic bursting pressures were lower when compared with MBP (150mmHg vs. 250mmHg)⁷⁴.

However in manometric studies of human colon in the postoperative period the maximum pressures reached across the anastomosis were around 45mmHg and so intra-luminal pressure seems unlikely to be implicated in the aetiology of anastomotic breakdown⁷⁵.

Trial evidence

Through clinical experience many surgeons are aware that MBP can be poorly tolerated by the patient. In a questionnaire study of 58 patients by Solla et al. 88% found the procedure distressing to some degree and 41% complained of nausea, vomiting and/ or abdominal pain⁷⁶. 10 patients stopped taking their preparation due to discomfort and 34% were still passing faecal fluid at the end of the procedure. This survey highlights very nicely the practical problems encountered with bowel cleansing not to mention the burden on nursing staff. For this reason alone the omission of MBP if it were safe would likely be welcomed by patients and clinicians alike.

Aside from the patient's experience of bowel preparation studies have looked at the other complications involved with the procedure. A number of studies have shown that MBP can cause significant electrolyte abnormalities, in particular reductions in serum calcium and potassium with a rise in serum urea⁷⁷⁻⁷⁹. While these changes are small and probably not significant for healthy individuals they may have important implications for a more elderly population such as those undergoing colorectal resection. MBP also causes significant weight loss of up to 1.2kg and postural changes in blood pressure due to dehydration and typically requires between 2-3L of fluid to compensate for the effect⁷⁹.

One study also showed a reduction in exercise tolerance by 9% following the use of MBP⁷⁸.

As mentioned previously the first large randomised controlled trial to investigate the effect of MBP was by Brownson published in the British Journal of Surgery in 1992⁶⁹. They looked at 179 patients undergoing colorectal resection with or without MBP and found a higher leak rate in the group who received MBP with no difference in wound infection rates. In 1994 a study by Santos et al. of 149 patients found an increase in wound infection rates in patients having MBP (24 vs. 12%, $p < 0.05$)⁸⁰. However complication rates in this study were high and the authors themselves suggest this may be due to the experience of the surgeon carrying out the procedures. Another study in the same year by Burke et al. of 186 patients found no difference in outcomes between the two groups⁸¹.

Since these first trials were published several similar studies have been reported in the world literature. A study by Zmora et al. of 380 patients found no differences in infective complications⁸². They also reported that postoperative diarrhoea was more common in the MBP group (7% vs. 0.5%, $p < 0.001$). Spillage of bowel content was more common as was the presence of liquid faeces with fluid or semi-solid content reported in over 50%. Studies by Miettinen et al.⁸³, Fa-Si-Oen et al.⁸⁴ and Ram et al.⁸⁵ have all failed to show any significant difference in outcome measures between groups with or without MBP. A recent study by Bucher et al. published in the British Journal of Surgery and looking only at patients having left sided colorectal resections (n=153) found an increase in infective

complications (22% vs. 8%, $p=0.028$) and in anastomotic leak (6% vs. 1%, $p=0.021$) with the use of MBP⁸⁶. This translated to an increase in hospital stay (15 vs. 10 days, $p=0.024$) which was also significant for those patients not experiencing complications. In one of the largest trials of its kind Contant et al. carried out a multicentre randomised trial of 1431 patients with no difference seen between groups in anastomotic leak rate (4.8% with MBP versus 5.4% without)²⁸⁹.

One of the difficulties with trying to prove a negative effect particularly when the incidence of complications is low (<3% anastomotic leakage) is that very large numbers of patients are required for adequate power. This is difficult to achieve even in a multi-centre setting without introducing further problems such as inter-operator variability. For this reason some of the best data is derived from meta-analyses and there have been several carried out on the subject of MBP. Bucher et al. first published their analysis in a Swiss medical journal, updating it for publication in the Archives of Surgery in 2004^{87, 88}. This included 7 RCTs and 1297 patients and found a significant increase in anastomotic dehiscence in the MBP group (5.2% vs. 2.8%, $p=0.03$). They did not find a difference in any other outcome measures. Wille-Jorgenson et al. also produced a meta-analysis for a Cochrane review in 2005 which was further published in Colorectal Disease^{89, 90}. Looking at 9 RCTs with 1592 patients it also showed a significant increase in anastomotic leak with the use of MBP (6% vs. 3.2%, $p=0.003$). In this analysis wound infection rates showed a trend towards significance in favour of no MBP (5.4% vs. 7.4%, $p=0.07$). There was no difference in mortality.

Conclusion

In a survey of North American colorectal surgeons carried out in 1990, 100% of the 352 respondents used some form of mechanical bowel preparation⁷⁶. In the last decade however with growing evidence suggesting at the very least no significant benefit and possibly an increase in the rate of anastomotic dehiscence opinions are starting to change. In national guidelines published in 2003 the Scottish Intercollegiate Guideline Network concludes that ‘current evidence...does not support its routine use’⁹¹. With even more evidence having been published since the introduction of these guidelines it is now clear that the omission of MBP is safe and may even be beneficial to the patient.

1.5 PROPHYLACTIC ANTIBIOTICS

Introduction

Since the advent of colonic surgery in the 19th century the most significant cause of postoperative morbidity and mortality has been infective complications. Even before colonic resection was commonplace the infective potential of colonic content was well recognised. The resident bacterial flora of the colon consists of high concentrations of both aerobic and anaerobic organisms. This bacterial reservoir can become a potential source of infection once the normal mucous membrane barrier has been disturbed by surgery. Recognising this risk has led to surgeons investigating numerous strategies to try to reduce the rates of postoperative infective complications.

Prophylactic antibiotic use describes the practice of administering antibiotics before there is any evidence of contamination or infection. The primary aim of prophylactic antibiotic use is to reduce the incidence of postoperative infective complications, but to be adopted into routine clinical practice it must fulfil additional criteria. The benefits should outweigh the risks particularly relating to drug toxicity. The antibiotic used should be site-specific with antimicrobial coverage directed at the likely pathogenic organisms. This should not only increase the efficacy of the treatment but also reduce selective resistance. Furthermore the antibiotic should have the appropriate pharmacokinetic properties to allow it to be present in the tissues for the duration of the period of maximum risk.

The first recorded use of antimicrobial prophylaxis in colorectal surgery was in 1939 by Garlock and Seley⁹². They reported 21 patients undergoing colonic resection with oral sulphonamides for prophylaxis with only one resultant wound infection. It was not until the 1960's that the first randomised controlled trial was carried out to look at the efficacy of prophylactic antibiotics but in the following decades it has been a common theme throughout the surgical literature. Risk factors for postoperative infections are now well known with extremes of age, malnutrition, obesity, diabetes, malignancy and steroid use among the most common. It is known that mortality rates are 2-3 times higher for patients who develop surgical-site infections. Patients will also stay in hospital on average 1 week longer with an increase of 10-20% in the cost of hospitalisation^{93,94}. With such significant consequences of postoperative infective complications on patient recovery, the potential benefits of prophylaxis are substantial.

Efficacy

Since the first randomised trials looking at the effects of antibiotic prophylaxis in surgery in the 1960s there have been numerous trials in the literature providing strong evidence. Research has been carried out not only on the efficacy of prophylaxis but also on different regimes of antibiotics, the timing, dosing and route of administration as well as the duration of the antibiotic course.

In a trial of 400 patients undergoing gastrointestinal or biliary procedures patients were treated with either an intramuscular cephalosporin or placebo. Wound infection rates fell from 22% to 4% for gastric surgery, from 11% to 2% for biliary procedures and from 16% to 6% for colorectal surgery⁹⁵. A further study of 350 patients by Coppa and Eng concentrated particularly on colorectal surgery. They found that wound infection was directly related to the length of procedure and also that surgery below the peritoneal reflection carried a significantly higher risk than colonic procedures. They also found that prophylaxis with a combination of oral neomycin and erythromycin in combination with a cephalosporin significantly reduced wound infection rates⁹⁶.

In a review of all the best trials to look at antibiotic prophylaxis in colorectal surgery between 1965 and 1980 Baum et al. found that 22 of the 26 trials meeting the inclusion criteria showed a significant benefit with antibiotics compared to no treatment^{97,98}. Wound infection rates were reduced from 36% to 22% and mortality rates fell from 11.2% to 4.5%. Following the results of the review the authors concluded that the

evidence for antibiotic prophylaxis was so strong that 'no treatment' controls were no longer ethical.

More recently the evidence has been looked at again in a systematic review by Song and Glenn of studies carried out between 1984 and 1995. This looked at the efficacy of prophylactic antibiotics in colorectal surgery examined in 147 trials. The review found the overall rate of wound infection to be 11% with prophylaxis and confirmed the effectiveness of prophylaxis⁹⁹.

Timing

With the efficacy of antibiotic prophylaxis well proven further trials have looked at the issue of timing of administration. In the study by Stone et al. 400 patients undergoing either gastrointestinal or biliary procedures were randomised to receiving intramuscular Cefuroxime, either 12 hours before operation, immediately before the procedure or after the procedure⁹⁵. They found no great difference between the preoperative doses but that the postoperative doses showed no efficacy in comparison.

These findings are supported by a large retrospective review which was reported in 1985 in the Archives of Surgery¹⁰⁰. In a review of 2847 patients undergoing a variety of operations classed as 'clean' or 'clean-contaminated' 1708 patients were found to have received prophylactic antibiotics within 2 hours of their procedure with a resultant wound infection rate of 0.6%. 282 patients received antibiotics less than 3 hours after their procedure with 1.4% developing wound infections (p=0.12). 488 patients received

antibiotics over 3 hours after their operation with an infection rate of 3.3% ($p < 0.0001$) and 369 had antibiotics more than 3 hours before operation with 3.8% developing wound infections ($p < 0.0001$). This clearly showed that the best time to receive prophylactic antibiotics is in the 2 hours before the operation.

In a further retrospective study of 2651 patients undergoing surgery Silver et al. found that although up to 94% of patients received prophylactic antibiotics, 27-54% did not receive them at the right time (i.e. less than 2 hours prior to surgery)¹⁰¹. These results were mirrored in a later review of practice in 2005 by Bratzler et al. who found that out of 2965 patients only 55% received antibiotics within 1 hour of surgery¹⁰².

The timing of antibiotic administration was further highlighted as an important issue in a study by DiPiro et al. who compared regimes using Cefazolin and Cefoxitin¹⁰³. By carrying out serial blood measurements as well as muscle biopsies they showed that of the two drugs Cefoxitin has a shorter elimination half-life with 90% being eliminated in 3 hours. This highlights the need to know the pharmacodynamic properties of the antibiotics being used for prophylaxis as certain regimes may not provide cover for the duration of maximum risk to the tissues. Furthermore it has been shown that long operations using antibiotics with a short half-life leads to more postoperative infective complications and repeated dosing intra-operatively may be required⁹⁶.

Duration

Another area of debate regarding the use of prophylactic antibiotics has been the duration of administration and whether a single dose or multiple doses are more effective. In a study of 311 patients undergoing both elective and acute colorectal surgery a single dose regime of cefuroxime and metronidazole was compared with giving 3 doses with no difference found between the two¹⁰⁴. Another trial published in the British Medical Journal looked at 943 patients undergoing elective colorectal surgery comparing the same antibiotic regimes. It also found no difference in wound infection rates (7.1% versus 7.3%) or mortality rates (6.6% versus 5.5%) between a single dose and a triple dose regime¹⁰⁵. It concluded that there are practical and financial advantages to the single dose regime.

Since these trials were published a systematic review has been carried out to draw together all the available evidence¹⁰⁶. This included 28 trials with a total of 9478 patients with no difference between single and multiple dose prophylaxis. There was also no difference in shorter or longer than 24 hour extended dosing.

Regimen

The exact regimen used for prophylaxis is an issue too wide to be addressed in the course of this short review. Trials to look at drug regimens have mainly been driven by commercial research. There are however clear broad principles. The antibiotics used should be site-specific to cover the likely pathogenic organisms. This means that there will be different regimes for different procedures. In general studies have shown that for

gastrointestinal procedures the combination of either a cephalosporin and metronidazole or gentamicin and metronidazole are of equivalent efficacy. There are a number of other regimes of comparable efficacy with a few notable regimes having been shown to be inadequate including metronidazole alone, oral neomycin and erythromycin alone, gentamicin alone and cefotaxime alone. It has also been shown that first generation cephalosporins have comparable efficacy to the newer generations^{99, 107}. There is also no difference between oral and parenteral regimes¹⁰⁸.

Conclusion

With a wealth of evidence to support its use prophylactic antibiotics are now a routine part of surgical practice and have been adopted into national guidelines for good practice⁹¹. Prophylaxis is particularly important in colorectal surgery where the risk of postoperative infective complications is high and the effect on patient recovery can be severe. Antibiotic prophylaxis should be administered immediately before induction of anaesthesia and a single dose regime offers the most practical and cost-effective method. The route of administration does not seem to be important. The exact regime used will vary and depend not only on pharmacodynamic and microbiological characteristics but also on the results of local infection control surveillance. The most commonly used regime remains the combination of a cephalosporin and metronidazole and other regimes while proving equivalent have not shown superior efficacy.

1.6 MIDLINE VERSUS TRANSVERSE INCISIONS

Introduction

Currently the choice of abdominal incision used for major abdominal surgery is dictated primarily by the preference of the surgeon. The incision should allow ease of access to the structures of interest as well as being quick to perform and secure when closed. The effect of incision type on patient recovery and postoperative morbidity is another important aspect which has been studied to try to find the optimal incision.

The main area of debate with regard to incision type is between transverse and vertical incisions. Because the fibres of the fascial layers of the abdominal wall run transversely, tension from suture closure of a transverse wound will be at 90 degrees to the fibres rather than pulling along the line of the fibres which some argue should lead to a more secure closure. Transverse incisions should also achieve a better cosmetic result as they are parallel with Langer's lines of cleavage. Furthermore a vertical incision crosses more segmental nerves which may lead to a more painful wound.

To try to find the optimal wound for abdominal surgery a number of studies have been undertaken. There are however methodological problems with the studies published to date. Many of the studies are retrospective which raises the problem of selection bias with surgeons likely to use transverse wounds only in the most favourable situations. The studies performed have also looked at patients undergoing a variety of procedures and so the heterogeneity of the studies means that it is problematic to try to generalise the results

for all abdominal surgery. The other problem has been blinding of both the patient and carers to the type of incision which is difficult to achieve for obvious reasons. This again introduces an area of possible bias.

Pulmonary function

One aspect which has been investigated is the effect of incision on postoperative respiratory function. We know that in the immediate postoperative period patients respiratory function in terms of vital capacity and forced expiratory volume in 1 second is reduced and that it recovers over the following few days. The effect of abdominal pain and the incision is that patients splint their abdominal wall to avoid pain and therefore their expiratory excursion is reduced. This can also lead to reduced clearance of respiratory secretions, atelectasis and even pneumonia.

In a study of 13 patients with respiratory disease and 13 patients with 'normal' lungs Becquemin et al. found that, although there was no difference in normal patients with either a transverse or a midline wound, in patients with respiratory disease postoperative lung function was significantly improved in patients with a transverse wound¹⁰⁹. A further study of 132 patients undergoing biliary surgery found that respiratory function was less depressed postoperatively in patients with a transverse incision although the differences were small¹¹⁰. These results were again confirmed in a study of 40 patients undergoing right hemicolectomy in a study by Lindgren et al¹¹¹. Despite the differences between the two groups in terms of respiratory function studies have failed to show consistent differences in pulmonary complications such as pneumonia¹⁰⁹⁻¹¹⁴. Therefore

with no differences in significant clinical endpoints it is difficult to know whether the changes in FVC and FEV1 are of any great importance.

Pain

One area where more robust conclusions can be drawn is that of postoperative pain. In a study of 60 patients undergoing cholecystectomy through either a midline or subcostal incision there was a significantly reduced usage of analgesics in the transverse group¹¹². Halasz also found transverse wounds to cause less pain in a study of 100 patients having biliary surgery¹¹³. Studies have looked at the effect of the wound size on postoperative pain and in a study comparing 6cm subcostal wounds with 15cm wounds O'Dwyer et al. showed significantly reduced analgesic intake as well as hospital stay in the 6cm group¹¹⁵.

Overall morbidity

Despite the evidence of reduced depression of respiratory function and less pain with transverse abdominal wounds studies have not shown any difference in hospital stay or in terms of postoperative complications^{110-112, 114, 116}. Publications relating to pulmonary and wound complications have been contradictory and a recent Cochrane review of the literature reports no significant differences between the two groups¹¹⁴. One review of the available literature published in 2001 by Grantcharov suggested that transverse wounds had a lower rate of wound dehiscence, both early and late, however the review includes a number of retrospective series with a very high possibility of selection bias¹¹⁷. In the

more recent Cochrane review no difference in terms of burst abdomen or incisional hernia was found when looking at prospective, randomised trials¹¹⁴.

Conclusions

The evidence available on the optimal incision for abdominal surgery suffers from poor methodological quality and contradictory results. What evidence is available suggests that while transverse wounds may be less painful there is no difference in hospital stay, respiratory or wound complications. There is also no evidence available relating to patient satisfaction or cosmetic outcome.

1.7 THE ROLE OF BLADDER CATHETERIZATION IN COLORECTAL SURGERY

Introduction

Urethral catheterisation is commonly used in the perioperative period following abdominal surgery to monitor urine output and to avoid postoperative retention which can occur in between 10-60% of patients^{118,119}. Causes for urinary retention are multifactorial and include the effect of drugs, operative damage to pelvic autonomic nerves and possible loss of anatomical support for the bladder. Despite the well established role of urethral catheterisation there is very little evidence available concerning its effect on

patient recovery and postoperative morbidity. Complications related to the procedure include urinary tract infection, discomfort, urethral stricture and the need for re-catheterisation if spontaneous voiding fails. To reduce postoperative morbidity studies have looked at alternative routes of bladder catheterisation and also at the duration for which it is required.

Suprapubic catheterisation

Kronberg et al. reported the first large series using suprapubic catheterisation routinely for colorectal patients^{120, 121}. In a series of 399 patients they found that in 31 patients they failed to insert the catheter and in a further 19 a urethral catheter was placed subsequently for recurrent or persistent retention. The average length of suprapubic catheterisation was 7 days. Having shown that suprapubic catheterisation was a viable alternative other groups have looked in closer detail to compare the morbidity related to each procedure.

Catheter-related discomfort

In a randomised trial of 137 patients undergoing rectal surgery by Perrin et al. 14% of patients with a suprapubic catheter experienced morbidity compared with 32% in the urethral group¹²². Most of the increased morbidity was accounted for by catheter-related discomfort (12% vs. 29%). These findings seem to confirm the findings of a previous randomised study by O'Kelly et al. of 57 patients which found that more patients with urethral catheters complained of catheter-related pain (13 vs. 2, $p < 0.01$) and on more days (37 of 126 cf. 6 of 142, $p < 0.001$) than in the suprapubic group¹²³.

Urinary tract infection

Despite studies suggesting that discomfort is increased with urethral catheters the evidence regarding urinary tract sepsis, the most important morbidity, remains contentious. In the studies by both O'Kelly¹²³ and Ratnaval et al.¹²⁴ no difference in urinary sepsis was seen between the two methods. Perrin¹²² found that there was almost a twofold increase in significant bacteriuria in the urethral group however the clinical consequences of this remain unclear. A further study of 66 patients by Sethia et al. did show a significant difference with 16 out of 34 patients developing a urinary tract infection in the urethral group and 2 out of 32 in the suprapubic group ($p < 0.001$)¹¹⁸. However the validity of this result is questionable due to the very high infection rate in the urethral catheterisation group.

Duration of catheterisation

The issue of urinary tract infection and duration of catheterisation was addressed in a study of 126 patients undergoing rectal resection with patients randomised to drainage for either 1 day or 5 days¹²⁵. Benoist et al. found that with only 1 day of urethral catheterisation urinary retention increased from 10% to 25% but UTI reduced from 42% to 20%. It was also seen that the vast majority of the patients who went into retention were patients with low rectal cancers. A follow up to this study by Kehlet et al. found that in a series of 100 patients undergoing colectomy with epidurals in-situ only 9 patients needed re-catheterisation and 4 developed UTI with the urethral catheter removed 24 hours after surgery¹¹⁹. These studies suggest that it is possible to remove the urinary

catheter much earlier than has traditionally been the case and by doing so significantly reduce the risk of urinary tract infection.

Conclusion

The evidence that exists relating to bladder drainage following abdominal surgery and its relationship to postoperative morbidity and recovery is fairly limited. The evidence that is available suggests that urethral catheters cause more discomfort for patients and may increase rates of urinary sepsis. While some would argue that suprapubic catheterisation offers a safe alternative the technique has not gained widespread acceptance. It is also possible that simply reducing the duration of urethral catheterisation is safe and can significantly reduce the rate of urinary tract infection which is the major post-procedural morbidity.

1.8 NUTRITION AND ITS EFFECT ON RECOVERY FROM SURGERY

The importance of nutrition in surgical patients has been recognised for many years. It has been estimated that almost half of all surgical patients suffer from malnutrition which is compounded by surgery and the reduced intake of protein and energy¹²⁶. Malnutrition is clearly associated with increased morbidity and mortality after major gastrointestinal surgery. Furthermore the catabolic response to surgery can lead to delayed wound

healing, fatigue, depression of the immune system and prolonged convalescence¹²⁷. It has also been postulated that this catabolic response can lead to a compromise in gut barrier function and bacterial translocation due to increased intestinal permeability and mucosal atrophy¹²⁸.

The often dual effect of malnutrition and the response to surgery has led to a number of studies looking at the effect of nutrition on recovery. They have concentrated on two main areas: the role of supplementation in combating malnutrition; and the effect of postoperative feeding on short term recovery.

Despite sustained interest in supplementation for patients undergoing gastrointestinal surgery there is little evidence to suggest a major clinical benefit except in a very select group. In a study of preoperative oral supplements for at least 7 days in 179 colectomy patients Smedley et al. found that although supplemented patients lost less weight there was no difference in major complications and no overall clinical benefit¹²⁹.

One of the largest studies carried out in the area of preoperative feeding was the Veterans Administration study which looked at the effect of preoperative parenteral nutrition in patients with GI malignancy undergoing elective colorectal resection. 395 malnourished patients were randomised in total however only those with severe malnutrition showed any benefit in terms of morbidity with parenteral nutrition lasting between 7-15 days¹³⁰. A number of other studies have also failed to show significant benefit in favour of preoperative feeding and the few that suggested a positive difference have suffered from high complication rates in the control arm making the conclusions questionable¹³¹⁻¹³⁶.

Perhaps more controversial is the area of postoperative feeding and when this should be introduced. Traditionally feeding has only started once ileus is deemed to have resolved. These restrictions on oral intake have been based primarily on clinical experience rather than any scientific evidence. The difficulty with such an approach is the assessment of ileus. We know from experimental studies that listening for the return of bowel sounds is merely an indication of migratory myoelectric complexes in the starved state and is not a good indicator of gastrointestinal function in the fed state^{137, 138}. We also know that ileus lasts only a matter of hours in the stomach and small intestine with the rate limiting step being return of peristalsis in the left colon, taking between 2-4 days^{10, 139}. This has led many to question whether patients should be fed early in an attempt to ameliorate the catabolic response and improve recovery. Moves toward early feeding have also been encouraged by the introduction of laparoscopic surgery and the pressures of early discharge.

A large number of trials have attempted to look at the efficacy and safety of postoperative feeding. These have included a wide variety of feeding methods in a fairly heterogenous group of patients in terms of their nutritional status making comparison difficult.

In a study of 105 patients undergoing abdominal surgery randomised to delayed (traditional) or self-directed feeding, patients given the choice commenced diet significantly earlier (3 vs. 5 days, $p < 0.001$). No differences were seen in complications or overall hospital stay¹⁴⁰. A further randomised trial by Feo et al. of 100 patients

undergoing colectomy also found no difference in outcomes or complications with 80% of those in the early group tolerating oral diet from day 1 postoperatively¹⁴¹. This proportion of patients who tolerate early re-introduction of diet is fairly constant in the literature at around 80%. In a randomised trial of 197 patients with upper GI malignancy by Heslin et al. it was evident that the symptoms associated with initiation of diet were the same for both groups and only the timing was different due to the difference in when the gut was challenged. This study also showed no difference in hospital stay, complications or mortality¹⁴². Finally a study by Reissman et al. of 161 patients undergoing colorectal procedures found that diet was tolerated earlier in the early feeding group although there were no differences in duration of ileus, complications or hospital stay and they concluded that early feeding is indeed safe¹⁴³.

In an attempt to draw together the available evidence Lewis et al. carried out a meta-analysis of 11 randomised controlled trials including 837 patients undergoing gastrointestinal surgery¹⁴⁴. They found a reduction in septic complications, particularly wound infections and a reduction in hospital stay of 1 day. They also found risk reductions for anastomotic dehiscence, pneumonia, abscess and mortality approaching statistical significance ($p < 0.10$). A significant increase in postoperative vomiting was found in the early feeding group. They concluded that early feeding may be beneficial although there was no clear advantage.

Further evidence of the safety of early feeding has come more recently with the incorporation of early feeding into 'fast-track' recovery regimes with no increase in

complication rates reported in the literature¹⁴⁵⁻¹⁴⁸. Therefore while it is certainly safe to feed patients early following colorectal surgery with the majority of patients tolerating it well it is not clear whether it has any overall advantage in terms of patient recovery.

1.9 POSTOPERATIVE ILEUS

Introduction

Following surgery the gastrointestinal tract takes time to recover its coordinated propulsive activity. This delay in the functional recovery of the bowel is often referred to as postoperative ileus. Through experimental studies we know that the pace of recovery is different in different parts of the alimentary tract. The first to recover is the small bowel in only a matter of hours followed by the stomach within 12-24 hours and then finally the colon at between 3-5 days. In the colon the right side is the first to resume peristalsis with the left colon being the rate-limiting step^{10, 137}. Ileus can often be prolonged past 3 days and this is often referred to separately as postoperative paralytic ileus although many see the conditions as a continuum rather than separate entities¹⁴⁹.

Ileus is a major cause of postoperative morbidity especially following colorectal surgery with which it is most commonly associated. The condition is characterised by abdominal pain, distension, absent bowel sounds and delayed defaecation and can lead to nausea and vomiting. The result of postoperative ileus can be a reluctance to mobilise, delay in the

institution of oral diet and ultimately prolongation of hospital stay and increased healthcare costs.

The pathophysiology of ileus is multifactorial and contributing factors are still a matter for debate and ongoing research. Inhibitory reflex arcs with afferents from somatic, visceral and parietal fibres are thought to play a part. Important also in the reflex arc is the interplay between the sympathetic and parasympathetic nervous system as well as the intrinsic nervous system of the gastrointestinal tract. In 1899 Bayliss and Starling demonstrated the role of sympathetic activity in gastrointestinal function by ablating the splanchnic nerves of dogs and recording the improvement in bowel activity¹⁵⁰. As well as the inhibitory reflexes inflammatory mediators are thought to play a role along with endogenous and exogenous opioids.

This review will examine some of the factors thought to be important in relation to the duration of ileus. Some of these areas will be covered in greater detail in other chapters. Furthermore as a major rate-limiting step in postoperative recovery from colorectal surgery ileus will be a major focus of the experimental work contained in this thesis.

Extent, site and duration of surgery

Ileus was first described by Pal in 1890 when he reported a reduction in intestinal motility following surgery¹⁵¹. Since then studies have looked at many contributory factors using various techniques and in different models. Much of our knowledge regarding ileus has come from experimental studies primarily using animal models. Woods et al. carried out

experiments on monkeys where electrodes were attached to the stomach, small intestine, right colon and sigmoid colon to get information on the pattern of recovery of ileus¹³⁷. They found that even the laparotomy incision itself led to a reduction in myoelectrical activity. They also found that peristaltic inhibition was short lived in the stomach and small bowel but lasted 24 hours on the right side of the colon and 72 hours in the sigmoid. They showed good correlation between the return of myoelectrical activity in the sigmoid and the passage of the first bowel motion which is often used as a more clinical endpoint for the resolution of ileus.

The same group continued their research in the monkey model and found no difference in the duration of ileus with the extent, site or duration of operation¹⁵². These findings are in contrast to traditional views held by many surgeons that ileus is made worse by prolonged exposure and handling of the intestines. The authors suggest that the parietal peritoneum plays an important role in the pathogenesis rather than the visceral peritoneum. This view is supported by the findings of Lindquist who reported that blood, turps or pus injected into the retroperitoneum produces prolonged ileus implicating the peritoneum as a major part of the process¹⁵³. Following these animal experiments similar studies were carried out using implanted seromuscular electrodes in human patients with complete validation of the previous animal work¹³⁸. As well as studies measuring myoelectrical activity, investigators have used radiotelemetry capsules to measure intra-luminal pressure and radio-opaque markers to look at transit through the gastrointestinal tract. Using these techniques Wilson also found no relation between duration of operation and length of ileus¹³⁹.

In contrast to these studies there have been experimental studies which have suggested a link between manipulation of the bowel and ileus. Kalff et al. found that in the rat model there was an increase in inflammatory cell infiltrate within the intestinal muscularis proportionate to the degree of trauma to the intestines¹⁵⁴. They also demonstrated a progressive decrease in muscle function in response to increasing degrees of manipulation. The findings are consistent with those of Beuno et al. who found that handling of small intestine in rats led to a reduced electrical activity compared with laparotomy alone¹⁵⁵. The link between manipulation and inflammatory response in the small intestine is further demonstrated in a study by Schwarz et al¹⁵⁶. It is also suggested that the increased wall permeability and bacterial overgrowth related to ileus leads to bacterial translocation and further morbidity¹⁵⁷⁻¹⁵⁹.

It is difficult to reconcile these contradictory findings, however the studies which support the role of manipulation in ileus come from animal studies of small bowel. We know that the rate-limiting step in the recovery of function is the left side of the colon. Furthermore the colon is more dependent on the extrinsic nervous system and does not act as a 'peristaltic syncytium' lacking the gap junctions of small bowel smooth muscle. This may well explain the lack of correlation between the experimental data and clinical studies.

Analgesia

The role of postoperative analgesia in the duration of ileus has been found to be one of the most important therapeutic targets. It has previously been mentioned that opioids play a part in the pathogenesis of ileus. Experimental work has shown that the effects of opioids are mediated primarily at receptors within the GI tract and that spinal and cerebral receptors have less of a role¹⁶⁰⁻¹⁶². Endogenous opioids are released as part of the stress response to surgery and act at mu-receptors in the bowel lead to inhibition of peristalsis. This natural effect can be further increased by the use of exogenous opioids in the postoperative analgesic regime. In an attempt to reduce the use of opioids other anaesthetic techniques have been employed to good effect.

The use of epidural analgesia and its effect on the duration of ileus will be expanded on in a future chapter but it has proved the single most effective strategy to reduce the duration of ileus. Epidural local anaesthetics appear to block the inhibitory afferents involved in the spinal reflex. In 6 of 8 studies looking at the effect of epidural local anaesthetics ileus was found to be significantly reduced¹⁶³⁻¹⁷⁰. In the 2 studies which did not show a significant difference, one used low thoracic epidurals which may not have covered all of the necessary dermatomes for abdominal surgery and the other used the epidural for only 24 hours rather than the 72 hours used in the other trials.

Minimally invasive surgery

With the introduction of laparoscopic surgery in the early 1990's surgeons noticed as a result a reduction in ileus. It is suggested that this reduction in ileus is due to both

reduced manipulation and exposure of the bowel and a reduction in the inflammatory response. However following laparoscopic surgery postoperative recovery methods have often been very different to traditional care following open surgery making it difficult to determine which is exerting the most significant effect.

In a study of 12 dogs subjected to laparoscopic or open right hemicolectomy Fazio's group found a more rapid recovery of myoelectrical activity and a shorter time to first bowel motion in the laparoscopic group¹⁷¹. This was despite the duration of the procedure being double that in the open group. These findings have been validated by other studies using the same animal model¹⁷².

Although an effect in relation to laparoscopic surgery seems clear its relative importance is still difficult to determine as studies on patients undergoing laparoscopic surgery with standardisation of the postoperative care package do not appear to show a difference in the duration of ileus^{173, 174}.

Early feeding and mobilisation

The effect of early oral feeding following surgery is controversial and to some extent depends on the endpoints used to measure ileus. Some investigators prefer to combine the functional clinical endpoints of passage of bowel motion but also the time taken for patients to tolerate oral diet. With this in mind there is no doubt that patients who are offered food earlier in their recovery tolerate it more quickly than those who are offered diet only when there are indicators of bowel activity^{140, 175}. Using only the endpoints of

passage of flatus or bowel motion oral feeding does not appear to play a major part in the duration of ileus¹⁴⁴.

Linked to the institution of oral diet is the traditional view that as well as fasting patients, nasogastric intubation reduced abdominal distension and the length of ileus. There is now strong evidence available that the routine use of NG tubes after elective colorectal surgery may prolong ileus and also increases the risk of other complications such as fever and atelectasis³³.

Another strongly held view with little scientific evidence to support it is that ambulation reduces the duration of ileus. It is in no doubt that early postoperative ambulation reduces the risk of other morbidities including deep venous thrombosis, chest infections and muscle wasting. However studies looking at the effect of ambulation on ileus do not support a significant effect. In a study of 34 patients who had electrodes placed at laparotomy there was no difference seen in myoelectrical activity between those who ambulated from day one and those who were kept on bed rest until day 4¹⁷⁶.

Therapeutic interventions

Various therapeutic strategies have been employed to try to reduce ileus and too many to cover in the course of this review. It has been suggested that perioperative fluid excess can lead to gastrointestinal mucosal oedema with prolongation of ileus¹⁷⁷. This will be covered in greater detail later in this introduction.

It has also been suggested that higher centre control of GI function can be affected by patients' expectations and the way they are prepared for surgery. In a novel study of 20 volunteers by Disbrow and colleagues, patients were counseled preoperatively to expect an early return of GI function and compared to a control group. They found that in the counseled group both ileus (2.6 days versus 4.1 days) and hospital stay (6.5 days versus 8.1 days) were reduced¹⁷⁸.

A number of pharmacological agents have also been studied including propranolol, neostigmine, erythromycin, laxatives, metoclopramide and cholecystokinin, to name only a few, with either equivocal or negative results¹⁷⁹. One class of drug with initially encouraging results with respect to ileus is peripherally selective opioid antagonists. As we have already seen the effect on peristalsis of both endogenous and exogenous opioids is inhibitory and mediated at receptors on the bowel wall. By blocking these receptors it is suggested that ileus could be reduced while still allowing adequate analgesia which is mediated through more central opioid receptors. The first of this class of drug to be trialed on patients was Alvimopan. In a study by Wolff et al. involving 510 patients Alvimopan was found to reduce time to recovery of GI function by 22-28 hours and reduced hospital stay by 20 hours¹⁸⁰. They also found no significant difference in analgesia between groups suggesting that the systemic absorption of the drug was low.

Conclusions

Ileus remains a significant cause of postoperative morbidity for patients undergoing surgery and particularly for colorectal patients. It is one of the main delaying factors

affecting patient recovery and as such has been a target for research. The pathogenesis is multifactorial and the relative contribution of various factors is still controversial.

Epidural local anaesthetics have certainly been shown to reduce ileus but the importance of minimally invasive techniques, early oral feeding and opioid sparing analgesic regimes is still unclear. While a variety of pharmacological therapies have been trialled few have shown any efficacy but recent work on peripherally selective opioid antagonists has been encouraging.

1.10 ANALGESIA

Introduction

Postoperative analgesia is an important component of any perioperative care regime. The ideal analgesic should be effective in treating postoperative pain, reduce the effects of the stress response and be safe to administer without significant complication.

Following major abdominal surgery the majority of patients will require strong parenteral analgesia and the area of most interest in the recent literature has been the method of delivery for adequate analgesia. The two main strategies used have been either parenteral opioid analgesia delivered intravenously, intramuscularly or by the subcutaneous route, or epidural analgesia which delivers local anaesthetics and/ or opioids through a fine cannula into the epidural space.

Epidural analgesia was first described in 1900 and there are a number of theoretical advantages relating to its use in abdominal surgery¹⁸¹. Epidurals work by blockade of both nociceptive afferents and sympathetic efferent nerves and therefore may reduce pain and opioid requirement which may lead to reduced postoperative nausea. It is also suggested that by blocking the spinal reflex arc thought to be a major cause of ileus that bowel motility may well be improved.

In support of the theoretical advantages experimental work has shown that epidural local anaesthetics suppress perioperative adrenaline and noradrenaline production¹⁸²⁻¹⁸⁴. In addition plasma levels of ACTH, cortisol, aldosterone and glucose are all reduced postoperatively in patients with epidural analgesia as opposed to other forms of analgesia indicating an attenuation of the stress response¹⁸⁵. Despite these encouraging experimental results when looking at more clinically based endpoints the efficacy of epidural analgesia is less clear cut.

Ileus

The one area where the effect of epidural analgesia is not in question is with regard to intestinal motility postoperatively. As mentioned previously postoperative ileus is a frequent cause of morbidity for patients undergoing major abdominal surgery and can lead to nausea, vomiting, abdominal distention and abdominal pain as well as a delayed discharge from hospital.

In a recent Cochrane review 9 studies reported duration of ileus as an endpoint when comparing epidural analgesia with parenteral opioids¹⁸⁶. These studies included a total of 406 patients and only one of the studies did not report a statistically significant difference between the groups. The other studies all showed a consistent reduction in the duration of ileus in favour of epidural analgesia and this has been supported in subsequent trials^{165, 167, 169, 188, 189}. The trials considered in the meta-analysis were all on patients undergoing open surgery however there is some evidence that the advantages may in fact disappear when considering laparoscopic colorectal surgery. One recent study which looked at 38 patients undergoing laparoscopic colectomy found no difference in duration of ileus with the use of epidural analgesia¹⁸⁹. Similar results were found by a separate centre which looked at 20 patients undergoing laparoscopic sigmoid colectomy¹⁷⁰.

Analgesia

With respect to the analgesic effects of epidurals, trials have considered a number of different areas. Firstly people have looked at the most effective regimen for delivering epidural analgesia. These have been using an opioid, a local anaesthetic or a combination of the two. It is fairly clear from the literature that on current evidence the combination of a local anaesthetic and an opioid gives superior analgesia to other regimens and that because of a synergistic effect doses can be reduced which in turn reduces the side effects^{169, 186, 190}.

It is also evident that the level of insertion of the epidural catheter is important so that the dermatomes crossed by the abdominal incision are included in the block. For most

abdominal surgery this requires an epidural to be placed around the level of the 8th thoracic vertebrae. Thoracic epidurals have been shown to give better analgesia than lumbar epidurals and postoperative analgesia is not affected by insertion before or after surgery¹⁹⁰.

When comparing the analgesic effect between epidural analgesia and patient-controlled analgesia with morphine the majority of trials suggest an improvement in analgesia with the epidural route. Absolute certainty of superior analgesia with an epidural is difficult to claim, primarily because the majority of studies to look at this area have suffered from poor methodology. Blinding of subjects has been a particular criticism and may well have lead to significant bias in the reporting of results. A number of studies also do not adequately report patients who either withdraw from the trial or incidences when epidural analgesia failed. Because of the lack of an intention-to-treat policy this is a further area where bias could be introduced. Despite these reservations the majority of trials do support superior analgesia with the use of epidurals.

As part of a systematic review in the Cochrane Database, 5 out of 8 studies reported that combination epidurals provided better analgesia on day 1 when compared with PCA morphine¹⁸⁶. No difference in postoperative nausea and vomiting was found between the two methods. In the Veterans Affairs Co-operative study, one of the largest single trials which included 1021 patients, epidural again proved better in terms of analgesia than the opioid alternative¹⁹¹. Finally in a meta-analysis of 100 articles published between 1966 and 2000 epidural analgesia was found to give superior analgesia on each postoperative

day when compared to a variety of opioid regimes¹⁹⁰. This trial included not only abdominal procedures but also orthopaedic and thoracic surgery but results were significant for each area individually.

Complications

The hope of those who have encouraged the use of epidural analgesia has been that with improved analgesia postoperatively an effect on morbidity and mortality would be realised. With the theoretical advantages and the changes in plasma markers suggesting an attenuation of the stress response, as well as improved analgesia allowing deeper respiration and patient mobilisation, a reduction in postoperative complications was expected. These theoretical advantages have not however been supported by clinical evidence. The MASTER trial looked at 915 patients deemed to be at high-risk of postoperative complications because of preoperative co-morbidity¹⁹². It found no overall difference in major morbidity or mortality when comparing epidurals to other analgesic techniques in patients undergoing major abdominal surgery. There was a difference seen in favour of epidural with respect to respiratory failure but this has not been confirmed in other trials. In a study of 150 patients undergoing abdominal surgery for cancer Jayr et al. found no difference in pulmonary complications or chest X-ray changes with the use of epidurals although forced vital capacity was less reduced postoperatively¹⁸⁸. In the Veterans Affairs study no difference in complications or mortality was shown and this was further confirmed in the large meta-analysis by Block et al¹⁹⁰.

The one area with respect to complications and epidural analgesia which is often not considered and is poorly reported in clinical trials is the complications relating to the technique itself. Studies report failure rates of anything between 4-50% of patients. In the MASTER trial detailed reporting of complications showed that of the 447 patients randomised to the epidural group only 225 managed to keep the epidural in for 72 hours. Of those who did not there were 13 failed insertions, 4 patients refused epidural, 45 had inadequate analgesia, 26 catheters dislodged, 5 leaked, nursing issues accounted for 5, 1 patient had a high block, 1 catheter blocked, in 61 no reason was given and 66 gave other reasons¹⁹². This fairly clearly shows the range of problems associated with epidural analgesia.

Conclusion

Postoperative analgesia is an important part of the perioperative management of patients undergoing abdominal surgery. Epidural analgesia offers improved pain management at least in the first 24 hours when compared to parenteral opioid regimes and also reduces postoperative ileus in certain circumstances. However epidurals do not significantly reduce postoperative morbidity or mortality and the technique is not without its own complications. Despite this it has been widely adopted into colorectal practice in both the United Kingdom and in North America.

1.11 LAPAROSCOPIC COLORECTAL RESECTION

Introduction

The first experimental laparoscopy dates back to 1901 when a German surgeon, George Kelling, used a cystoscope to examine the abdominal cavity of a dog. Since then the technique has steadily increased in its surgical application. Gynaecologists were among the first to apply the use of laparoscopy in humans using it first as a diagnostic tool and then proceeding to carry out tubal sterilisation. The first use of the laparoscope in General Surgery was again by a gynaecologist, Kurt Semm, who performed a laparoscopic appendectomy in 1983¹⁹³. However it was not until Phillippe Mouret carried out the first video-laparoscopic cholecystectomy in Lyon in 1987 that the technique was rapidly adopted into general surgical practice. Within 5 years laparoscopic cholecystectomy had largely replaced the open procedure because of the perceived benefit of speed and recovery time. In the enthusiasm to use the new technique adequate training was overlooked leading to reports of increased operative complications. In one report investigators found a 5-fold increase in bile duct injury following laparoscopic cholecystectomy compared with the open approach¹⁹⁴.

Despite the initial problems the use of the laparoscope has been applied to almost every abdominal procedure with varying degrees of success. The first report of a laparoscopic colectomy was in 1991^{195, 196}, however due to the steep initial learning curve conversion to the open procedure was common at around 40%^{197, 198}. The use of minimally invasive surgery was further questioned with a number of reports in the literature of metastases at

port-sites following resection for colorectal cancer^{199, 200}. This was postulated to be due to specimen retrieval through the wound but metastases were also seen at distant port-sites with incidences from 1-21% reported²⁰¹. Because of these early concerns laparoscopic colorectal surgery has been introduced mainly in the setting of randomised controlled trials which have given us a growing evidential basis for its use. Following the results of both large series and multi-centre randomised trials there is now a wealth of information regarding not just the short-term outcomes of recovery but also the long-term outcomes relating mainly to colorectal cancer.

Long-term outcomes

The delay in widespread adoption of laparoscopic colorectal surgery has primarily been due to the unknown effect on long-term outcomes in the treatment of malignant disease which forms the main part of colorectal practice. In the 15 years since the first laparoscopic colectomy there have been numerous series published with fairly large numbers of patients. These have to a great extent eased the fears of compromising the oncological resection using laparoscopy.

In probably the largest single series experience to be published Di Palo et al. reported on 599 patients treated with laparoscopic colectomy for colorectal cancer²⁰². They give figures for morbidity (23.3%) and 5-year survival (81%) comparable with those for open surgery. They also report low rates of local recurrence for rectal cancers at 4.4% and only one port-site metastasis. Furthermore the conversion rate of 7% is a testament to their considerable experience and skill with the technique.

Lacy et al. published a randomised study of 219 patients with non-metastatic colon cancer treated by either laparoscopic or open surgery²⁰³. They found no significant difference in overall mortality but reported a significant improvement in cancer related mortality of 9% versus 21% in favour of the laparoscopic technique. The majority of the benefit seen was due to an increased loco-regional recurrence rate in the open group running at 14% which most would see as abnormally high. Despite this there was certainly no adverse effect on long-term outcome and there was again only 1 port-site metastasis identified.

In a later randomised study by Braga et al. of 391 patients with colorectal cancer no difference in cancer-related survival or disease-free recurrence were noted between the two groups²⁰⁴. This study did report a difference in both postoperative complications (17.9% versus 36.3%, $p=0.0005$) and long-term morbidity (6.8% versus 14.9%, $p=0.018$) in favour of laparoscopic surgery. These differences were mainly attributable to wound infection postoperatively and higher rates of postoperative intestinal obstruction and incisional hernia. Braga also reported an improvement in quality of life scores up to 1 year following surgery but further studies have failed to confirm these differences²⁰⁵.

Another large trial published in the Lancet in 2004 from Hong Kong randomised 403 patients undergoing sigmoid resection for colorectal cancer²⁰⁶. Again they found no difference in operative mortality, morbidity, cancer-related survival or lymph node retrieval rate between the two surgical techniques. The authors concluded that the use of

laparoscopic resection depends primarily on the perceived benefits in short-term recovery.

Mega-trials and meta-analyses

With the results of these series and medium-sized trials alleviating fears regarding the long-term outcomes for cancer patients some of the best evidence for both short and long-term outcomes come from two large multi-centre trials as well as two meta-analyses which have drawn together all of the available information to date.

The first of these is the COST trial which was a North American trial which randomised 872 patients with colon cancer to open or laparoscopic surgery²⁰⁷. The median follow-up for the trial was 4.4 years. To try to avoid the problems of the learning curve for the technique only surgeons with at least a 20 case experience were included in the trial. They found with regard to recovery the median hospital stay was 5 days versus 6 days in favour of the laparoscopic group ($p < 0.001$) and also that there was a shorter use of narcotics (3 versus 4 days, $p < 0.001$). There was no difference in the postoperative complication or mortality rates. With regard to the oncological resection the study found no difference in resection margin or lymph node retrieval and rates of recurrence at 3 years were similar (16% versus 18%) with $< 1\%$ wound recurrence in both groups. 3-year survival also showed no significant difference. The COST study therefore showed no difference with regard to long-term outcomes in colorectal cancer but did show marginal benefits in terms of short-term recovery.

The other large multi-centre trial is the British CLASICC trial which randomised 794 patients on a 2:1 basis to laparoscopic or open surgery respectively²⁰⁸. The findings were very similar to that of the COST study. There was a shorter duration of ileus noted as well as a shorter time to resumption of normal diet. This translated into a difference in hospital stay of 9 days versus 11 days in favour of the laparoscopic group. No difference was seen in quality of life or complications postoperatively and there was no difference in the completeness of resection or lymph node retrieval. The cautionary note to come out of the trial was that there was a high conversion rate of 29% and the patients who required conversion suffered both a delayed recovery and also an increase in the rate of complications. This led the authors to suggest that selection of patients for laparoscopic resection is crucial to reduce conversions and overall morbidity.

Finally two meta-analyses have drawn together the available evidence from around 24 published trials including nearly 7000 patients between them^{209, 210}. These further confirm the benefits in terms of recovery with reduced duration of ileus, less pain and analgesic use, and shorter hospital stay. Furthermore the equivalence with respect to postoperative mortality, disease recurrence and cancer-related survival is no longer in doubt.

Cost-effectiveness

Despite showing short-term benefits for patient recovery incorporation of laparoscopic resection into widespread surgical practice depends also on its cost-effectiveness. Cost-analysis of the laparoscopic technique has found the direct cost to be significantly higher, estimated at around \$2100 (£1400) per procedure in one study²⁰⁶. This increase in cost is

due not only to the increased use of disposable instruments but also because the procedure takes significantly longer^{207, 208}. This increased direct cost has been justified in several studies by savings made in relation to a shorter hospital stay with no significant difference in overall cost to the healthcare system²¹¹. However in a randomised trial of laparoscopic versus open colorectal resection from Sweden hospital stay was not significantly different between the two groups which led to a difference in cost to the healthcare system of €2244 (around £1500) per patient²¹².

The influence of perioperative care

It is clear from the evidence to date that the main benefits of the minimally invasive technique are focused on improvements in short-term recovery. It is also clear that these benefits particularly in relation to reduced hospital stay are important for the cost-effectiveness of the procedure. Recently the short-term benefits on which the procedure is based have been brought into question by work carried out using multi-modal rehabilitation programmes. These regimes draw together different areas of perioperative care with a solid evidence base and combine them in a protocol to standardise and enhance patient recovery. This so-called ‘fast-track’ surgery has led to dramatic improvements in short-term recovery with hospital stay following open surgery of around 3 days which is comparable to the best laparoscopic trials in the literature²¹³.

In a study by Kehlet’s group from Denmark 60 patients were randomised to either laparoscopic or open colorectal surgery with full patient and observer blinding¹⁷⁴. They found no difference in pain score, fatigue, motor activity or cardiopulmonary function between the two groups. The median hospital stay was 2 days in each group. The results

from the study suggest that using an enhanced recovery programme may negate the benefits derived from laparoscopic surgery alone.

In response to this study a further trial by King et al. was published in the British Journal of Surgery with 62 patients randomised on a 2:1 basis to either laparoscopic or open surgery²¹¹. They found that despite the use of a fast-track regime patients in the laparoscopic group had a shorter hospital stay (5 days versus 8 days, $p=0.018$). It could however be argued that the stay of 8 days postoperatively in the open group is much longer than that of other trials looking at fast-track recovery and the study suffered from the lack of blinding.

With such contradictory results it is not clear whether there are still benefits to using laparoscopic surgery with multi-modal rehabilitation or whether the use of enhanced recovery will mean that laparoscopic resection is no longer cost-effective. The results of further trials looking at laparoscopic colonic resection with the use of an enhanced recovery regime are awaited.

Conclusions

Laparoscopic colorectal surgery has gained cautious acceptance from the surgical community since it was first described 15 years ago. It is well established that the oncological results for resection of colorectal cancer are comparable to that of the open technique. Port-site wound recurrence which was one of the initial concerns has been shown to be a rare complication and one which is also associated with the open

technique. The main benefits of the procedure, apart from the difference in cosmesis, which have been taken for granted rather than proven in large scale trials, has been in relation to patient recovery. In trials using traditional perioperative care laparoscopic resection has been shown to reduce ileus, pain and hospital stay however the benefits when using enhanced recovery protocols are a matter of current debate and ongoing research. It is also clear that laparoscopic resection is not for all-comers but rather if any benefit is to be derived patients must be well selected.

1.12 THE EFFECT OF INTRAVENOUS FLUIDS ON RECOVERY

Introduction

Fluid and electrolyte balance and the administration of intravenous fluids is an important but still poorly understood part of perioperative management. Despite a comprehensive understanding of some of the physiological principles involved the effect of co-morbidity in addition to the surgical stress response make fluid prescribing difficult. These difficulties are further exacerbated by contradictory findings throughout the medical literature. The effect not only of the volume, timing and route of fluid administration but also of the ideal composition of the fluid is still a matter of debate.

Despite the complexity of the problem and the lack of agreement in the scientific journals the day-to-day management of surgical patients' fluid requirements is often left to the

most junior member of the surgical team^{214,215}. Surveys of prescribing practice suggest that fluid charts are often not checked during daily ward rounds and may be inaccurate mainly due to shortages of nursing staff²¹⁶. Furthermore the composition of different intravenous fluids is poorly understood with patients often prescribed water and salt grossly in excess of their normal maintenance requirements²¹⁷.

To begin to investigate the effect of intravenous fluid replacement on patient recovery during the perioperative period we must understand not only a patient's requirements under normal conditions but also the effect of surgery. Normal water requirements are estimated at around 20-40mls/kg/day which is achieved through drinking (approximately 1200mls), eating (1000mls) and water of oxidation (300mls). Of the 2L of oral intake and 6-8L of gastrointestinal secretions only around 150mls is lost in the faeces. The rest is reabsorbed in the gastrointestinal tract although this may be altered by certain disease processes or following surgery. Important changes to normal homeostasis occur during the perioperative period. Preoperative fasting and anorexia can lead to water and salt depletion. There may be increased G.I. fluid losses through diarrhoea, bowel preparation or vomiting. So called 'third space losses' can result from the inflammatory response to surgery causing fluid to pool in the extra-vascular/ interstitial space and anaesthetic drugs can lead to reduced flow through the circulation with vasodilatation and reduced cardiac output. All of these factors need to be taken into account when addressing the problems of perioperative fluid management.

Recent evidence in the medical literature regarding the use of intravenous fluids and their effect on recovery has renewed interest in this vital component of patient management. Studies have examined the differing effect of type of fluid used in the perioperative context and also protocols for volume replacement. Both areas still require a lot of work before a final solution is reached however interesting advances have been made which we hope to investigate further during the course of our scientific work.

What type of fluid is best?

The type of fluid chosen depends on both the biological and physicochemical properties. The two types of fluid which are commonly compared are crystalloids and colloids. A crystalloid is an aqueous solution of mineral salts and other water-soluble molecules whereas a colloid solution contains larger non-soluble molecules such as gelatin and stays in the intravascular space for a much longer period of time. Crystalloids are thought to lead to significantly more tissue oedema which will theoretically increase diffusion distances, compress small capillaries and reduce organ perfusion. In a study which looked at crystalloid resuscitation during Whipple's procedures Prien found that the jejunal specimen had increased water content when compared to using colloid²¹⁸. Further studies suggest that colloids may cause less nausea, vomiting and postoperative pain which could all be attributable to reduced tissue oedema^{219, 220}. Despite these positive findings the most recent meta-analysis to compare the use of crystalloids and colloids concluded that 'methodological limitations preclude any evidence-based clinical recommendations'²²¹.

There is also controversy over the composition of fluids used. Recent evidence suggests that large volume administration of salt containing fluids, particularly normal saline but also including colloids dissolved in isotonic saline may be detrimental to patient recovery. When compared to more balanced solutions such as Hartmann's and Ringer's lactate, saline has been found to cause renal vasoconstriction and reduced glomerular filtration rate which means that it takes significantly longer to get rid of the excess sodium load²²²⁻²²⁴. Furthermore saline is associated with the development of hyperchloraemic acidosis due to the high concentration of chloride. This metabolic acidosis can cause a reduction in gastrointestinal perfusion as measured by gastric tonometry and has been shown in pigs to reduce gastric motility^{225, 226}. Excessive sodium administration has also been associated with increased postoperative complications in colorectal patients although this study was a retrospective review and so does not prove a causal link²²⁷.

How much fluid should be given?

Most clinicians would agree that fluid administration for surgical patients is a fine balance between dehydration on one side and fluid excess on the other but there is continued discussion over which abnormality is predominant during the perioperative period. The argument for fluid restriction is that the metabolic-endocrine response to surgery is water and salt conservation mediated by aldosterone, the renin-angiotensin system and anti-diuretic hormone. Others would argue that because of the inflammatory response 'third space losses' dictate that you become relatively dehydrated and require extra fluid. This process would presumably be proportionate to the surgical insult and

may vary depending on the type of surgery. Shoemaker in the 1970's and 80's proposed a policy of resuscitating patients to supra-normal levels of circulatory function however excess fluid in the intravascular space can lead to increased fluid in the interstitial space and in turn to pulmonary and peripheral oedema with reduced systemic and local tissue oxygenation²²⁸.

As previously mentioned the balance between inadequate fluid administration/ dehydration and excess fluid with oedema formation will vary depending on the type of surgery and the different components of the perioperative care package used. Studies carried out on day-surgery patients who received a pre-load of intravenous fluid to compensate for their period of fasting found that patients had significantly less PONV as well as postoperative pain^{229, 230}. Patients receiving bowel preparation with no intravenous fluid replacement had a postural decrease in arterial blood pressure as well as a reduced urine output and increased creatinine when compared to patients who received a 2L crystalloid infusion⁷⁹. These studies demonstrate clearly that fluid and electrolyte balance relating to different perioperative interventions can have a significant effect on recovery. Although this role in recovery is now recognised the best way to achieve optimal fluid balance remains unclear.

The two competing theories of fluid restriction and maximal fluid resuscitation are often linked with different methods of managing perioperative fluid balance. While many use a standard fluid regime for uncomplicated elective patients with additional boluses guided by clinical endpoints, an alternative approach is the so called 'goal-directed fluids'.

Although seen as competing strategies it is true to say that both are in fact goal-directed. Fluid regimes can be altered to make them biased towards a 'conservative' approach but always include the administration of additional fluid based on clinical endpoints such as blood pressure, pulse and urine output. The 'goal-directed' approach incorporates a more invasive assessment of circulatory function using an oesophageal Doppler monitor to calculate cardiac output. This method involves the placement of an ultrasonic probe in the oesophagus to calculate blood flow and cardiac output. Fluid is then titrated until the maximal stroke volume is reached which it is argued gives a more accurate and immediate method for responding to changes in fluid balance. Those who are sceptical of this method suggest that for patients who are often elderly with extensive co-morbidity this maximal cardiac workload throughout the intraoperative period may be detrimental.

Fluid restriction

The first to suggest a delay in recovery due to excess fluid was Mecray who carried out an animal study on dogs²³¹. He found that gastric emptying time was significantly delayed in response to saline and low protein. He also showed that the change in motility was reversible using salt and water restriction and high protein intake. At autopsy dogs were found to have mucosal oedema affecting the gastrointestinal tract in response to excess saline and it was postulated that the oedema was the cause of the motility changes observed.

These findings were tested in a clinical setting by Lobo who randomised 20 patients undergoing colectomy to either 'restricted' intravenous fluids or a 'standard' regime²³².

The main difference in fluid administration occurred on the day of operation with a difference of 3L between the groups (3L versus 6L, $p < 0.0001$). Patients in the restricted group gained significantly less weight in the postoperative period. Lobo reported a significant reduction in solid and liquid phase gastric emptying in the restricted group as well as a reduced time to first bowel motion (3 versus 4 days, $p = 0.001$) and a shorter hospital stay (6 versus 9 days, $p = 0.001$). He concluded that reducing postoperative gastrointestinal mucosal oedema was the mechanism for the improvement in GI function. The trial was criticised for the small number of patients and also due to the lack of blinding of those assessing eligibility for discharge which may have been a source of bias. Patients involved in the trial underwent a limited range of procedures meaning the results may not be generalisable.

Following on from the Lobo trial Brandstrup et al. carried out a randomised, observer blinded trial of 141 patients undergoing colonic resection receiving standard or restricted (weight neutral) postoperative fluids²³³. As in the Lobo trial there was a significant difference in weight gain with the standard group gaining around 3kg on average. The difference in mean fluid volume on the day of theatre was 2.7L in the restricted group compared with 5.4L in the standard group ($p < 0.0005$). They found a reduction in postoperative complications in the restricted group (33% versus 51%, $p = 0.013$) with cardiopulmonary (7% vs 24%, $p = 0.007$) and tissue healing (16% vs 31%, $p = 0.04$) complications accounting for the major difference. They also demonstrated a dose dependent relationship between fluid volume and frequency of complications. Brandstrup's group did not report duration of postoperative ileus or hospital stay.

In the final study to look at fluid restriction Nisanevich randomised 152 patients undergoing elective abdominal surgery to restrictive or liberal intraoperative fluids²³⁴. Again there was a significant difference in fluid volumes on the day of theatre (1408 versus 3878mls, $p<0.001$) and also in patient weight gain (0.5 versus 2kg, $p<0.01$). Patients in the restrictive regime were found to have less complications (mainly infectious or cardiovascular), faster return of bowel function and shorter hospital stay (8 versus 9 days, $p=0.01$). In this study the surgical team used a traditional recovery protocol which is evident from the duration of hospital stay.

Goal-directed fluids

One of the first studies to use goal-directed fluids using an oesophageal Doppler was carried out on patients with normal left ventricular function undergoing coronary bypass grafting²³⁵. The study found a significant reduction in intensive care and overall hospital stay in the protocol group. The next study looked at using the technique in patients undergoing surgery for proximal femoral fracture and also showed a reduction in hospital stay²³⁶. As we know maintenance of fluid balance is different for different types of surgery and so perhaps more relevant data comes from studies using the technique for patients undergoing colorectal resection.

The first of these was a study of 57 patients randomised to either oesophageal Doppler management or standard fluids during bowel surgery²³⁷. There was no statistically significant difference in the volumes of fluid used although more colloid was used in the Doppler group. The authors reported fewer complications in the Doppler group although

the study is not powered for this endpoint. They did not find any difference in time to tolerating diet or time to discharge.

The next study was of 100 patients undergoing gynaecological, urological or GI surgery with an estimated blood loss of greater than 500mls²³⁸. Patients were randomised to either standard or goal-directed fluids with only a small difference in overall volume (5420 versus 4775mls). The difference in fluid volume is due to a difference in colloid solution infused. Gan et al. reported an earlier return to diet (3 versus 5 days, $p=0.01$) and a shorter hospital stay (6 versus 7 days, $p=0.03$). Information was not given on differences in postoperative fluid management and a traditional care pathway was used making it difficult to interpret the results. The difference in fluid shifts among the population studied (blood loss of greater than 500mls) would not be expected in a standard elective colorectal population but may indicate a benefit to the technique when fluid shifts are less predictable.

In one of the most recent trials Wakeling et al. looked at 128 colorectal patients managed with either intraoperative oesophageal Doppler or central venous pressure monitoring²³⁹. Patients in the Doppler group received more fluid (5 versus 4L) although again postoperative fluid management is not recorded. The authors report a shorter hospital stay (10 versus 11.5 days, $p<0.05$), shorter time to tolerating diet (6 versus 7 days, $p<0.001$) and reduced GI morbidity (45 versus 14%, $p<0.001$). One possible criticism of the trial is that there were more left sided colonic resections and more stomas formed in the control

group which could account for the difference in hospital stay which was also longer than hospital stays seen in most other studies.

Finally Horgan et al. published a double-blind randomised trial of 108 patients undergoing elective colonic resection²⁹⁰. They compared Doppler-guided fluid therapy to fluids given at the discretion of the anaesthetist and found shorter hospital stay (7 versus 9 days, $p=0.005$), and reduced postoperative complications (2 versus 15%, $p=0.043$) in the intervention group.

Conclusions

It is difficult to come to firm conclusions regarding the best method to optimize perioperative fluid management. While studies have so far been inadequate to show any clear difference between colloids and crystalloids the differences in which fluid is used may be a confounding factor in studies of fluid volume. It is clear that fluid management can have an effect on postoperative recovery and that management needs to be tailored to the exact nature of the surgery being carried out.

In relation to colorectal surgery the evidence seems to suggest that if large fluid shifts can be avoided patient recovery may be improved. This may be achieved by compensating for the dehydrating effect of bowel preparation and preoperative fasting or by avoiding the use of bowel preparation and limiting the duration of fasting. Initial studies looking at conservative intraoperative fluid protocols suggest that postoperative ileus, complications

and hospital stay may all be reduced and that the possible mechanism is through reduced gastrointestinal and tissue oedema.

Studies looking at the effect of goal-directed fluids using oesophageal Doppler monitoring suggest that the technique may be of use in higher risk patients and when the potential for large fluid shifts is greater. It is difficult to compare the results with those of fluid restriction trials as the postoperative management of patients is so variable between the studies. It is also difficult to explain how such small differences in fluid volumes in these trials can lead to the differences suggested in postoperative recovery.

1.13 FAST-TRACK SURGERY

Introduction

The idea of 'fast-track' surgery has been developed primarily by Professor Kehlet's group in Denmark. The aims of the approach are to attenuate the surgical stress response and reduce end organ dysfunction through an integrated recovery pathway. This pathway should incorporate perioperative strategies with a proven evidence base to reduce hospital stay following surgery and allow a quicker return to baseline function. In recent times many of the individual elements which make up perioperative care have been studied with traditional practice challenged. Mechanical bowel preparation for instance does not appear to have any significant benefit and may simply make optimisation of fluid balance more difficult by adding to the dehydration experienced during the period of preoperative

fasting^{79, 89, 90}. Nasogastric tubes have been shown to increase respiratory complications, cause significant discomfort and delay the introduction of oral diet³³. This change in practice has allowed others to introduce early oral feeding which has proven safe and well tolerated following abdominal surgery¹⁴⁴. Other factors which have allowed the successful introduction of early oral diet have included better antiemetic strategies and epidural local anaesthetics which reduce the duration of postoperative ileus¹⁸⁶. With the use of dynamic pain regimes and the introduction of early oral diet patients may also be more able to comply with early mobilisation, regaining their independence necessary before considering discharge home. It is clear then from this wealth of evidence that the success of a single strategy in isolation may be limited but that as part of a multimodal rehabilitation regime the potential benefits are significant.

The initial evidence

Before the birth of fast-track surgery others had already recognised the potential benefits of using a coherent pathway to direct and standardise perioperative care. By introducing a clinical pathway with many traditional recovery principles Pritts et al. found that patients were discharged from hospital up to 2 days earlier following colonic surgery²⁴⁰. The length of hospital stay was still around 8 days as more modern interventions were not employed but it served to show that the protocol approach to recovery had merit. They also showed through a cost-analysis that the shorter hospital stay reduced cost from around \$20,000 to close to \$14,000.

Much of the experience with fast-track surgery comes from case series and single unit experience. In one of their first publications on fast-track Kehlet's group studied 57 consecutive patients undergoing elective colonic resection²⁴¹. They reported that the majority of patients moved their bowels within 48 hours of surgery and that the median hospital stay was 2 days. Of the 57 patients, 9 patients required readmission but the authors stated that no life-threatening complications were delayed in their presentation.

Following this early experience Kehlet later published a larger series of patients undergoing colonic resection and treated in a single centre using a fast-track regime²¹³. He compared 260 patients of which half had been treated at another University hospital in Copenhagen using a more traditional strategy. After analysis of the two groups he found that the fast-track group was comprised of patients with a significantly higher ASA grade and that there was a preponderance for left sided colonic surgery both of which it could be argued would delay recovery in the fast-track group. Despite these differences the fast-track group had a shorter time to first bowel motion (2 versus 2.5 days, $p < 0.05$) and a significantly shorter median hospital stay (2 versus 8 days, $p < 0.05$). In addition they found that patients in the fast-track group had less postoperative complications (25% versus 45%, $p < 0.05$) due to a reduction in cardiopulmonary and wound complications. Readmissions were higher in the fast-track group at 20% versus 12% in the traditional group ($p > 0.05$).

Following on from these studies other groups around the world attempted to translate the benefits experienced with fast-track recovery into their own practice. One of the largest

of these series was a French study of 132 elective colorectal patients treated with fast-track rehabilitation²⁴². They reported hospital stay of 4 days and a readmission rate of 11%. This was significantly quicker when compared with historical controls with a reduction in complications also seen. As well as the French study further series from Germany, Italy, Sweden, the United Kingdom and North America have all reported reductions in hospital stay to between 3 and 5 days^{145, 148, 243-245}. Although other investigators have failed to achieve hospital stays as short as 2 days significant improvements have been duplicated and readmission rates have been reduced to more acceptable levels.

As well as a growing experience in other units the principles of fast-track surgery have been applied to an increasing number of procedures and disciplines²⁴⁶⁻²⁴⁸. Initial criticisms of fast-track studies included the selective population with only straightforward colonic resections included and in an otherwise young, fit population. Similar benefits have since been demonstrated when fast-track is applied to more major surgery including major colorectal, pelvic and re-operative surgery^{249, 291}. Studies looking at fast-track in elderly surgical populations have also found that recovery can be significantly enhanced although suggest that the age group less than 70 years gain the most benefit from the approach^{145, 250, 292}. Fast-track principles have been applied to nephrectomy, aortic abdominal aneurysm repair and gynaecological surgery with similar benefits in recovery recorded²⁵¹⁻²⁵⁴.

The aims of a multimodal rehabilitation programme are to reduce the stress response to surgery which leads to hypermetabolism and an overall catabolic result. Those sceptical of fast-track recovery have argued that the majority of the evidence in support of fast-track is from non-randomised series from units with an enthusiastic interest which may introduce significant bias. Blinding trials in this setting has also proven difficult. In addition it is argued that simply looking at the endpoint of hospital stay does not necessarily reflect an improvement in recovery and a reduction in the metabolic-endocrine response to surgery. It may simply be that clinicians are discharging patients earlier in their recovery. Evidence to refute this argument comes from studies which have looked at a range of other endpoints rather than simply hospital stay. In a study comparing gastrointestinal motility in fast-track surgical patients compared to healthy volunteers using scintigraphy Basse found no difference in excretion of tracer between the groups¹⁴⁷. These findings suggest that strategies to reduce the duration of ileus are proving successful and that the differences in time to first bowel motion are not simply due to sigmoid emptying. In a non-randomised study comparing 14 fast-track patients with 14 control patients after colonic resection Basse et al. found that lean body mass and postoperative exercise performance were preserved with fast-track recovery while the control group noticed significant reductions in both²⁵⁵. In a further study looking at patients after discharge from hospital Hjort et al. reported that fast-track patients experienced an earlier resumption of normal activities, a reduced need for daytime sleep and no increased use of primary care when compared to a control group²⁵⁶. It has also been suggested that 'fast-track' rehabilitation can lead to improved preservation in cell-

mediated immunity postoperatively²⁹³. These more objective findings it has been suggested support the claims of a reduction in the surgical stress response.

Randomised trials

While there is a wealth of experience of multimodal rehabilitation through case-controlled series the number of truly randomised trials has been limited. The first randomised controlled trial was carried out by Delaney et al. and comes from the Cleveland Clinic in Florida¹⁴⁵. They randomised 64 patients to either a fast-track regime or a traditional care package following colorectal resection and showed that hospital stay was reduced (5.4 versus 7.1 days, $p=0.02$). They found no difference in readmission rates, pain scores or quality of life between the two groups including no difference in complications, although the study is not powered for this endpoint. Interestingly they found that patients managed by surgeons with an experience of fast-track regimes spent significantly less time in hospital regardless of which group they were randomised to. This shows not only that readiness for hospital discharge has a subjective element to it but also that there is a learning curve with the approach. The benefits demonstrated are more modest than in other studies which may be due to the use of PCA morphine rather than epidural analgesia. However the authors go on to suggest that despite this modest difference 1.2 million hospital days could be saved in the United States using this approach for colorectal surgery alone.

Two further randomised trials using fast-track recovery with colorectal surgery come from McFie's group in Scarborough, U.K. The first trial to be published randomised 25

patients to fast-track or control and found that hospital stay was reduced from 7 to 3 days ($p=0.002$)¹⁴⁸. They also found that pain scores and fatigue were reduced and that there was earlier tolerance of oral diet in the fast-track group. This study was criticised as the control group were not treated with epidurals and so it was argued the study was really a study of epidural analgesia over PCA morphine. It is a common difficulty with fast-track trials to separate the effects of single interventions from the whole pathway. McFie followed this trial by reporting a second similar study of 39 patients with both groups treated with epidural analgesia¹⁴⁶. In support of his previous findings hospital stay was reduced from 7.5 days to 5 days ($p=0.027$) although no explanation was given for the increased length of stay in the fast-track group in comparison with the previous trial.

Conclusion

Fast-track recovery protocols have been shown to significantly enhance perioperative recovery in a range of different settings. Following colorectal surgery hospital stays of 2-3 days have been reported where previously 8-10 days would have been normal practice. Multimodal rehabilitation appears to positively influence the surgical stress response with reductions shown in duration of ileus, complications, pain, postoperative exercise tolerance and activities of daily living. The advances in recovery found using fast-track regimes following open abdominal surgery have also led clinicians to question the additional benefits of laparoscopic surgery. The application of laparoscopy to colorectal surgery has been based primarily on improvements in short-term recovery however if discharge after open surgery is possible after 2 days then the additional expense of laparoscopy may be difficult to justify. In one randomised and blinded trial comparing

laparoscopic and open surgery in patients enrolled in a fast-track programme no difference was found in cardiopulmonary function, gastrointestinal function, pain, fatigue scores or hospital stay¹⁷⁴.

Research into perioperative recovery continues to be a rapidly changing field. As different parts of the fast-track regime are investigated further, new strategies are adopted to reflect changing knowledge. Pharmacological strategies to further reduce ileus such as peripheral opioid antagonists have shown promise. Although the area of fluid optimisation has been shown to exert an effect on recovery the ideal fluid regime is yet to be defined. Further research in manipulation of the numerous cascades resulting from injury is ongoing with the aim of attenuating the deleterious effects while enhancing those that are beneficial. Technological advances will also play an increasing role through laparoscopic surgery and beyond but in all these areas evidence-based practice should remain the foundation on which any advances are built.

CHAPTER 2

STUDY AIMS

INTRAVENOUS FLUID THERAPY

The main focus of this research work is in the area of intravenous fluid therapy. Our aim is to determine the effect of postoperative intravenous fluid restriction on recovery following elective colorectal surgery. The first part of the work will be to carry out a pilot study. The aim of the pilot study will be to assess whether a postoperative fluid and sodium restriction regime can be applied safely and effectively to our clinical practice. The secondary aim of the pilot study will be to ensure that the relevant systems and data collection methods are in place prior to the commencement of a randomised trial.

The aim of the randomised trial will be to investigate the effect of postoperative fluid restriction on recovery following elective colorectal surgery in patients managed with intraoperative fluid restriction. The primary endpoint for the trial will be length of hospital stay. Secondary endpoints will include duration of ileus, complications, pain and nausea scores, analgesic and antiemetic requirements.

LAPAROSCOPIC-ASSISTED SURGERY

Following the randomised trial looking at the effect of intravenous fluid restriction we will look at other factors involved in recovery following major abdominal surgery. The first of these factors is the use of laparoscopic-assisted surgery. The aim of this study will be to investigate whether laparoscopic-assisted colorectal surgery improves recovery with the use of a multi-modal rehabilitation regime. This will be achieved by comparing the

outcome data for patient randomised to the intravenous fluid trial who had either open or laparoscopic-assisted colorectal resection. From these results we hope to be able to determine whether the type of surgery or the perioperative recovery pathway is the most important factor in immediate postoperative outcome.

FAST-TRACK LIVER RESECTION

Following on from our experience using ‘fast-track’ recovery we want to investigate the effect of a multi-modal recovery regime in an area of surgery where it has not previously been applied. The aim of this study is to determine the effect of fast-track recovery on patients undergoing liver resection for colorectal liver metastases. We will analyze outcome data for a consecutive series of patients undergoing open liver resection using a fast-track regime and compare this with other series published in the medical literature.

COLONIC RESECTION

The aim of our final area of research is to investigate the effect of the colonic resection itself on recovery of colonic function following major open abdominal surgery. We will compare a series of patients undergoing open liver resection with no intestinal manipulation or colonic resection to a series of patients undergoing open colorectal resection. The primary endpoint of the study will be the duration of postoperative ileus.

CHAPTER 3

EFFECT OF POSTOPERATIVE INTRAVENOUS FLUID AND SODIUM RESTRICTION ON PATIENT RECOVERY AFTER ELECTIVE COLORECTAL SURGERY: A PILOT STUDY

3.1 Introduction

Intravenous fluids play an important role in the perioperative management of patients undergoing major abdominal surgery. Until recently there was little evidence available on the effects of intravenous fluids in the perioperative period to guide clinical practice. This has since changed due to two main factors. Firstly the introduction of multimodal rehabilitation programs has led to clinicians re-examining interventions made around the time of surgery to assess their effect on recovery. In addition there have been two trials published in the surgical literature on the area of intravenous fluid administration which have stimulated renewed interest.

The first paper by Lobo was published in the *Lancet* in 2002 and was the catalyst for the multi-centre randomised controlled trial reported in this thesis²³². The study by Lobo was based on observations made in the clinical nutrition unit in Nottingham that elimination of oedema in postoperative patients led to an increase in serum albumin and possibly an earlier return of gastrointestinal function. The investigators postulated that restricting intravenous fluid may lead to a more rapid recovery from surgery. These findings were supported by previous animal studies by Mecray which found that gastric emptying was prolonged in dogs infused with saline to provoke hypoalbuminaemia²³¹. The changes in gastric emptying time were then reversed by salt and water restriction.

Lobo et al. carried out a randomised controlled trial comparing 10 patients treated with intravenous fluid restriction and 10 patients treated with 'standard care' following

elective colorectal surgery. Patients in the restricted group were limited to 2 litres of intravenous fluid and 77mmol of sodium per day while patients in the control group received fluids in accordance with the standard practice in the unit. The primary endpoint of the study was gastric emptying measured using radio-labeled contrast. The investigators found a significantly reduced gastric emptying time in the restricted group (difference between medians for solid and liquid phase T₅₀ of 56mins and 52mins respectively, p=0.017). They also reported a significant difference in return of gastrointestinal function (median 4 vs. 6.5 days, p<0.001) and hospital stay (median 6 vs. 9 days, p<0.001) in favour of the restricted group. These findings suggested that both ileus and hospital stay could be dramatically reduced in colorectal patients using a restricted intravenous fluid and sodium regime.

Since its publication the Lobo trial has drawn a number of criticisms. In the introduction to the paper the authors admit that the study was prompted by observations they had already made which would suggest bias towards the restriction regime. The study was non-blinded which makes any potential for bias in the results even greater, especially as the endpoint of hospital stay is often dependent on a subjective assessment of patient recovery. The study was further criticized for having a small patient population all of whom were fairly fit and undergoing a limited number of procedures.

The second study by Brandstrup in the *Annals of Surgery* was published after the commencement of our own fluid trial in late 2003²³³. This study examined the effect of a restricted intravenous fluid regime on postoperative complications following elective

colorectal surgery. No data regarding duration of ileus or hospital stay was presented. The findings of the trial suggested that there was an increase in postoperative complications in the standard group, particularly respiratory and wound complications.

In response to the Lobo trial and taking into account its limitations we decided to undertake a multi-centre, single-blinded, randomised controlled trial to test the hypothesis that restriction of intravenous fluid and sodium leads to a more rapid return of gastrointestinal function and shorter hospital stay for patients undergoing elective colorectal surgery.

While submitting applications for the funding of the trial and following ethical approval in the coordinating centre we commenced a pilot study to confirm that the fluid restriction regime could be applied to our clinical practice both safely and effectively. The pilot study also allowed us to ensure that the necessary systems were in place to run the subsequent randomised controlled trial successfully.

3.2 Patients and methods

We carried out a prospective case-controlled series of 10 consecutive patients undergoing elective colorectal surgery using a restricted intravenous fluid and sodium regime and compared this with a retrospective series of 10 consecutive patients managed with 'standard care'. The study was carried out in one surgical centre and with a single operating surgeon over a 4-month period preceding the commencement of the multi-centre randomised trial reported later in this thesis. All patients undergoing elective colorectal resection with primary anastomosis were eligible unless they had significant renal impairment, suffering severe physical disability and in long-term care, an insulin dependent diabetic or undergoing total colectomy, abdominoperineal resection of the rectum, or low anterior resection requiring a defunctioning stoma.

Patients were consented after receiving a patient information sheet devised for the randomised trial (See Appendix I, II). Patients were allowed to drink up to 2 hours prior to their operation. Patients did not receive bowel preparation except for those having left-sided surgery who had a phosphate enema the night before and the morning of surgery. This regime was a change in practice instituted in line with recent evidence and avoided preoperative dehydration as a factor in patients' perioperative fluid balance. All patients received antibiotic and DVT prophylaxis.

A standardized anaesthetic protocol was used in all patients and normothermia was maintained throughout the procedure. Patients were given a restricted intraoperative fluid

regime consisting of 4 per cent dextrose, 0.18 per cent saline at 10ml/kg/hr plus 3 x measured blood loss. No nasogastric tubes or drains were placed.

An analgesic protocol was developed which utilized PCA morphine (1mg bolus, 5 minute lockout) for the first 48 hours. Regular Paracetamol was prescribed (1g four times daily, orally or rectally) and oral NSAIDs were used for breakthrough pain after the PCA had been discontinued.

Oral fluids were encouraged in all patients immediately following anaesthesia and oral diet was commenced on the first postoperative day as tolerated. All patients were treated with a postoperative fluid and sodium restriction regime consisting of 2 litres of 4 per cent dextrose and 0.18 per cent saline per day. The intravenous fluid protocol closely mirrored the regime used in the Lobo trial. Intravenous fluids were stopped after the first postoperative day unless otherwise clinically indicated. Patients had daily biochemistry and haematology measurements. Active mobilization and chest physiotherapy was commenced on the first postoperative day.

Patients were discharged by the consultant surgeon once all discharge criteria had been met. To be considered fit for discharge patients had to be afebrile, fully mobile, passing flatus or faeces and using oral analgesics only for pain. The pilot study allowed all members of the team time to adjust to the changes in discharge practice as changing expectations of both medical staff and patients is a major part of fast-track recovery. A new follow-up policy was also instituted during the pilot study which involved the

research nurse phoning patients at home daily for the first two weeks followed by an outpatient review at 30 days. This ensured that complications out of hospital were not missed.

The results from the pilot study were compared to retrospective data for 10 patients undergoing elective colorectal surgery immediately prior to the start of the pilot study. The results were not analysed statistically as the aim of the study was not to prove significance but rather to assess the ability to use a fluid restriction regime and follow a fast-track protocol in preparation for a larger randomised controlled trial.

3.3 Results

Of the 10 patients treated using the fluid restriction regime the median age was 72 (i.q.r. 64-81) years compared with 75 (70-85) years in the control group. There were no obvious differences in sex ratio or ASA grades between the two groups. There were a greater number of left-sided resections in the fluid restriction group (Table 3.1).

Patients in the fluid restriction group had their intravenous fluids discontinued earlier than the control group (median day 1 (1-1) *versus* day 3 (2-3)). The cumulative total intravenous fluid volume from day 0-3 was 4.5 (4-5) litres in the restricted group *versus* 8.05 (6.5-11.5) litres in the control group. The cumulative total intravenous sodium from day 0-3 was 362 (306-428) mmol in the restricted group *versus* 763 (533-1056) mmol in the control group. No patients required a perioperative blood transfusion. There were no adverse events related to the use of the fluid and sodium restriction regime (Table 3.2).

The trend suggested a shorter time to first bowel motion (4 (3-5) days *versus* 5.5 (4-8) days) in the restricted group. The median day of discharge for patients in the restricted group was day 6 (5-6) *versus* day 7.5 (6-9) in the control group. 1 patient in the restricted group developed an enterocutaneous fistula and another patient suffered a postoperative myocardial infarction. There were no complications in the standard care group. No patient developed a complication following discharge from hospital and there were no readmissions during the pilot study. There were no postoperative deaths within 30 days of surgery.

Table 3.1 Baseline Characteristics for patients in fluid and sodium restriction pilot study

		Fluid restriction patients	Control patients
N		10	10
Age (years)		72 (64-81)	75 (70-85)
Sex	Male	7	6
	Female	3	4
ASA Grade	1	1	0
	2	6	7
	3	2	3
	4	1	0
Operation	Right hemicolectomy	2	5
	Left hemicolectomy	3	1
	Anterior resection	5	4
	Reversal of Hartmann's	1	0

Values are median (interquartile range)

Table 3.2 Intravenous fluid and sodium daily quantities and cumulative totals for patients in the fluid and sodium restriction pilot study

		Fluid restriction patients	Control patients
		Median (IQR)	Median (IQR)
Day of operation	IV Fluids (l)	2.45 (2.00, 2.50)	3.00 (2.00, 3.50)
	Na ⁺ (mmol)	246 (169, 317)	339 (302, 456)
Day 1 post-op	IV Fluids (l)	2.00 (2.00, 2.50)	2.50 (2.00, 3.50)
	Na ⁺ (mmol)	60 (60, 77)	187 (77, 308)
Day 2 post-op	IV Fluids (l)	0 (0, 0)	2.00 (2.00, 2.50)
	Na ⁺ (mmol)	0 (0, 0)	154 (154, 231)
Day 3 post-op	IV Fluids (l)	0 (0, 0)	0.50 (0, 1.50)
	Na ⁺ (mmol)	0 (0, 0)	0 (0, 154)
Cumulative total	IV Fluids (l)	4.50 (4.00, 5.00)	8.05 (6.50, 11.50)
	Na ⁺ (mmol)	362 (306, 428)	763 (533, 1056)

Values are median (interquartile range)

3.4 Discussion

The results of the pilot study confirmed that using the protocol developed for the randomised controlled trial we were able to safely restrict intravenous fluid and sodium during the perioperative period. It also suggested that using a restricted fluid regime may reduce the duration of postoperative ileus and allow a more rapid discharge from hospital. We did not encounter any adverse events with respect to abnormal renal function relating to the use of the intravenous fluid and sodium restriction regime. Furthermore there were no readmissions during the pilot study and no complications were missed due to early patient discharge. The follow up arrangements trialed during this period appeared to work well and allowed for extra reassurance while the clinical team adjusted to the new discharge policy. The running of the pilot study also allowed us to identify a number of areas where practice needed to be changed prior to starting the main trial.

Although the fluid restriction regime was instituted the results of the pilot study highlighted that patients in this group still received a median of 2.5 litres of fluid and 246mmol of sodium. This was higher than levels targeted in the protocol and was mainly due to inexperienced medical staff inappropriately prescribing saline to study patients with low one hour urine volumes. In response to these difficulties we decided to increase the visibility of abbreviated versions of the study protocol both in the junior doctors' room and in participating patients' observation folders (See Appendix IV, V). Fluid charts were pre-printed with the restriction regime to alert doctors to patients' inclusion in the trial (See Appendix VI). We also undertook training meetings with members of the

nursing staff and medical staff involved. The final alteration was to change to a policy of 4 hourly urine volumes to avoid doctors responding to single hourly urine volumes. The levels of intravenous fluid and sodium infused on days one to three were felt to be in keeping with those desired for the trial.

During the pilot study the hospital stay for patients in the fluid restriction group was 6 days compared to 7.5 days in the control arm. The median hospital stay in the restricted group was comparable with the results of the Lobo trial (median 6 (i.q.r. 5-6) *versus* 6 (5-7) days) however there were factors which suggested that even shorter hospital stays were achievable. The patients in the restricted group had a greater proportion of left sided resections which is likely to reduce the difference in hospital stay between the two groups. There were also 2 complications in the restricted group and one patient whose discharge was delayed due to social reasons. There were no complications in the control arm of the study. The median hospital stay of patients in the control arm was also shorter in our pilot study compared to the Lobo trail (7.5 (6-9) *versus* 9 (7.8-14.3) days). This is explained by the fact that many of the principles of fast-track surgery had already been adopted in the unit although they had not been formally described in a protocol.

The running of the pilot study allowed us to confirm the safety of the fluid restriction regime prior to its application during the larger randomised trial. Data collection procedures including forms to be used during the study were trialed and refined during this period (See Appendix VII). Follow-up arrangements were formalized and both nursing and medical staff gained in experience with both the restricted fluid protocol and

fast-track recovery. The results suggested a faster return of gastrointestinal function as well as earlier discharge in the restricted fluid group. The results were not analysed statistically as the pilot study was not powered to look for significance between primary endpoints.

CHAPTER 4

EFFECT OF POSTOPERATIVE INTRAVENOUS FLUID AND SODIUM RESTRICTION ON PATIENT RECOVERY AFTER ELECTIVE COLORECTAL SURGERY: AN OBSERVER BLINDED RANDOMISED CLINICAL TRIAL

4.1 Introduction

Use of intravenous fluids is an important part of perioperative management in patients undergoing elective or emergency surgery. It is known from clinical trials that excess use of intravenous fluid can significantly increase weight and complications²³²⁻²³⁴. More recently positive salt and water balance sufficient to cause a 3kg weight gain has been shown to delay return of gastrointestinal function and prolong hospital stay in patients undergoing elective colorectal resection^{232, 234}. Current opinion suggests that maintaining fluid balance such that the patient remains weight stable may reflect best practice in perioperative fluid management.

Fast-track recovery programmes are becoming increasingly popular after major abdominal surgery²⁵⁷. In order to achieve optimal fluid balance these programmes restrict the use of intravenous fluids intraoperatively and use little or no parenteral fluids after the first postoperative day^{145, 148, 241}. Patients are encouraged to drink protein drinks on the day of operation and resume normal food and oral liquids on day one postoperatively. Following colonic resection very short hospital stays (2-3 days) have been reported with the use of epidural anaesthesia/ analgesia whereas length of stay has tended to be longer with patient-controlled analgesia (PCA : 4-6 days). A recent randomised trial showed no benefit of thoracic epidural analgesia over PCA (length of stay 6 days in both groups) when used within a fast-track programme for patients undergoing colorectal resection²⁵⁸. Whatever the precise components of 'fast-track' programmes they require an intensive multidisciplinary approach by surgeons,

anaesthesiologists, nutritionists and physiotherapists. However the excellent results obtained by the enthusiasts have yet to be adopted widely.

Previous studies have focused mainly on restricting fluids given during the intra-operative period and have thus reduced total intravenous fluid load on the day of surgery from around 5-6 litres to about 2-3 litres^{233, 234}. Postoperative strategies have been less well defined and it has not been possible to separate the effect of intraoperative versus postoperative regimens. The aim of the present study was to investigate the effect of postoperative fluid restriction on recovery following elective colorectal surgery in patients managed with intraoperative fluid restriction.

4.2 Patients and methods

Patients

An observer blinded randomised trial was carried out between November 2003 and March 2005 with the approval of the relevant local Research Ethics Committee. All surgeons involved in the trial have a specialist interest in colorectal surgery. All patients undergoing elective colorectal resection with primary anastomosis were eligible unless they had significant renal impairment, suffering severe physical disability and in long-term care, an insulin dependent diabetic or undergoing total colectomy, abdominoperineal resection of the rectum, or low anterior resection requiring a defunctioning stoma. Patients who were ineligible for the study were recorded to allow subsequent outcome analysis.

Preoperative preparation

Informed consent was obtained and patients were randomised postoperatively by automated telephone randomization to either restricted intravenous fluids or standard care (See Appendix I-III). All patients were allowed free fluids and high calorie containing drinks for up to 2 hours before operation. Patients did not receive bowel preparation except for those having left-sided surgery who received a phosphate enema the night before and the morning of surgery. All patients received antibiotic and DVT prophylaxis.

Anaesthesia

A standardized anaesthetic protocol was used and all patients received a restricted intraoperative fluid regime consisting of 4 per cent dextrose/ 0.18 per cent saline at 10ml/kg/hr plus 3 x measured blood loss. Normothermia was maintained throughout surgery and all operations were carried out through the smallest incision necessary to complete the procedure. No nasogastric tubes or intra-abdominal drains were used.

Analgesia

PCA with morphine (1mg bolus, 5 minute lockout) was provided for 48 hours in both groups. Paracetamol (1g four times daily orally or rectally) was administered concurrently with Tramadol (50-100mg orally or intravenously) used for breakthrough pain. NSAID use was withheld until the morphine PCA was discontinued. Analgesia consumption for both groups was noted and visual analogue pain scores at rest and on movement were recorded twice daily.

Diet and Fluids

Oral fluids were encouraged immediately postoperatively in both groups with protein drinks (Fortisip® Nutricia Clinical, UK) and normal food introduced on day 1. Patients in the sodium and water restricted group received 4 per cent dextrose/ 0.18 per cent saline intravenously at 83ml/hr giving them in total 2 litres of water and 60 mmol of sodium per day. All intravenous fluids were stopped on day 1 in the restricted group unless there was a clinical reason to maintain them. The control group received 1 litre 0.9 per cent saline and 2 litres 5 per cent dextrose per day intravenously, equivalent to 3 litres water and 154

mmol sodium per day, until day 3 unless decided otherwise by the consultant. Patients in both groups had daily biochemistry, haematology and weight measurements between 0800 and 0900 hours. Nausea scores (0-4) were checked twice per day and antiemetic administration was recorded. Time to first flatus and bowel motion was recorded for both groups. All patients received chest physiotherapy and commenced active mobilization from the first postoperative day.

Patient Discharge

Decision on patient discharge was made by the consultant surgeon with responsibility for the patient who was blinded to the treatment group. This was achieved by covering the intravenous solution with an opaque bag while daily monitoring of events was undertaken by the consultant anaesthetist and surgical registrar. The consultant surgeon did not review the patient on the ward until the afternoon of day three, by which stage intravenous fluids were generally discontinued in both groups. To be considered fit for discharge patients had to be afebrile, fully mobile, passing flatus or faeces and using oral analgesics only for pain. Discharge delayed by social problems was recorded as such.

Complications

All adverse events were recorded during the first 30 postoperative days with phone follow-up until review at clinic on day 14. Patients were sent a Short Form 36 Health Questionnaire at three months²⁵⁹ (See Appendix VIII). Patients were also asked to state which study group they thought they had been randomised to (See Appendix IX).

Statistics

Based on previous studies^{148, 232, 241} it was estimated that 80 randomised patients would give an 80% power to reject the null hypothesis that patients in the two groups had equal length of stay using a two-sided Wilcoxon rank sum test at a 5% significance level. Time to event data was compared between groups using log rank tests. Daily measurements of continuous outcomes were analysed by repeated measures linear regression analysis with auto correlated errors, allowing for random patient effects and a global intervention effect; daily intervention effects were estimated by inclusion of intervention \times day interaction terms. Cumulative totals were compared between groups using bootstrap t-tests. Data was analysed on an intention-to-treat basis. The statistical software package S-Plus for Windows v 6.1® (Insightful Corporation, Switzerland) was used.

4.3 Results

During the study period 97 eligible patients were identified. Eighty patients gave their consent and were randomised (Figure 4.1). The main reasons for non-randomization were renal impairment (8), anaesthetic cancellations (6) diabetes (2) and patient refusal (1). The characteristics of the patients agreeing to randomization in both groups were similar at trial entry (Table 4.1).

Fluid and Sodium Management:

There were significant reductions in the amount of intravenous fluids administered to the restricted group on the day of surgery and for days 1,2 and 3 postoperatively (Table 4.2). Similar findings were observed for intravenous sodium although the difference was not significant by the third postoperative day. For each day of their hospital stay patients in the standard group were significantly heavier than those who had restricted intravenous fluids and sodium ($p=0.002$ – $p<0.001$) (Figure 4.2).

Analgesia and Pain

Patients in both groups used similar amounts of morphine, with a median of 69 (i.q.r. 32-103) mg in the standard care group compared to 69 (41-80) mg in the restricted group (mean difference 2.8 (95 per cent confidence interval -14.9, 20.8) mg; $p=0.75$). No significant differences were found between groups in terms of other analgesics: Paracetamol (global $p=0.93$), Ibuprofen ($p=0.94$) and Tramadol ($p=0.23$). Pain scores at rest and on movement were similar in both groups throughout the patients' hospital stay.

There were no significant global differences between groups in nausea scores. Similarly, there were no significant differences overall between groups in terms of antiemetic use.

Biochemistry and Haematology

There was marginal evidence of an overall difference in serum urea between groups ($p=0.077$), with a significant rise in the restricted group compared to the standard group from day 2 postoperatively (Table 4.3). This was mirrored by increases in serum creatinine on days 1 and 2 postoperatively ($p=0.065$ and $p=0.042$, respectively). These changes were most likely due to the dilutional effect of excess fluid in the standard group and within the range of normal. No patient developed renal failure or suffered any adverse effect as a result of the biochemical changes. There were no differences in the patients' postoperative haemoglobin (global $p=0.47$), haematocrit ($p=0.76$) or albumin ($p=0.43$) between the groups.

Patient Outcome

There were no differences in the time to passage of first flatus ($p=0.47$) or bowel motion ($p=0.80$) between study groups (Table 4.4). The time to which patients were considered fit for discharge and actual hospital discharge were also similar. There were no differences observed in complications between the groups ($p=0.31$) although the study was not powered to this endpoint (Table 4.5). 1 patient in either group died postoperatively due to respiratory failure (1) and a staphylococcus septicaemia secondary to a central line insertion (1). Follow-up SF-36 scores also showed no difference between the groups in any of the components measured. 2 patients required readmission within 30

days of surgery. Of the 69 patients who returned the questionnaire regarding randomization 40 said they did not know which group they were in, 14 chose incorrectly and 15 chose correctly. This suggests that patients were effectively blind to the randomization.

Non-entrants

Of the 17 patients who were not randomised into the trial during the study period follow-up data was available for 12. The reasons for non-randomization were renal impairment (6), anaesthetic cancellations (4) diabetes (1) and patient refusal (1). Baseline characteristics for patients not included in the trial were similar to those randomised except for the proportion of patients having right sided surgery which was greater in the non-randomised group (Table 4.7).

Patients who were not randomised to the trial received similar cumulative intravenous fluid volumes to patients in the standard arm of the trial although there was a trend toward higher cumulative intravenous sodium in the non-randomised patients (Table 4.8). Data on time to first bowel motion was not available for non-randomised patients. The median hospital stay for non-entrants was 8 (i.q.r. 6.8-18.0) days. 5 patients who were not randomised into the trial suffered complications: 3 patients developed anastomotic leaks all of which were treated by laparotomy and Hartmann's procedure; 1 patient suffered a myocardial infarction postoperatively; 1 patient developed atrial fibrillation and pulmonary oedema. There were no deaths within 30-days of surgery.

Table 4.1 Baseline Characteristics for patients in the fluid and sodium restriction study

		Standard Care	Restricted
N		41	39
Age (years)		72.6 (67.3, 82.9)	73.2 (65.3, 78.0)
Sex	Male	17 (41%)	20 (51%)
	Female	24 (59%)	19 (49%)
BMI (kg/m ²)		25.8 (23.2, 28.7)	26.8 (22.5, 30.7)
ASA Grade	1	2 (5%)	2 (5%)
	2	26 (63%)	30 (77%)
	3	12 (29%)	7 (18%)
	4	1 (2%)	0 (0%)
Operation	Right hemicolectomy	12 (29%)	14 (36%)
	Left hemicolectomy	4 (10%)	3 (8%)
	Anterior resection	23 (56%)	19 (49%)
	Hartmann Closure	2 (5%)	3 (8%)
Technique	Laparoscopic	11 (27%)	11 (28%)
	Open	30 (73%)	28 (72%)
Indication	Benign	9 (22%)	9 (23%)
	Cancer	32 (78%)	30 (77%)
Blood transfusion		3 (7%)	3 (8%)

Values are median (interquartile range) for continuous or N (%) for categorical data

Table 4.2 Intravenous fluid and sodium daily quantities and cumulative totals for patients in the fluid and sodium restriction study

		Standard Care	Restricted	Difference	p-value
		Median (IQR)	Median (IQR)	Estimate (95% CI)	
Day of operation	IV Fluids (l)	2.75 (2.50, 3.00)	2.00 (2.00, 2.62)	-0.45 (-0.76, -0.14)	0.004
	Na ⁺ (mmol)	169 (146, 266)	122 (60, 183)	-78 (-111, -46)	<0.001
Day 1 post-op	IV Fluids (l)	2.60 (2.50, 3.00)	2.00 (2.00, 2.00)	-0.58 (-0.89, -0.27)	<0.001
	Na ⁺ (mmol)	154 (154, 231)	60 (60, 80)	-83 (-116, -50)	<0.001
Day 2 post-op	IV Fluids (l)	2.50 (2.00, 3.00)	0.00 (0.00, 0.50)	-1.75 (-2.07, -1.44)	<0.001
	Na ⁺ (mmol)	154 (77, 216)	0 (0, 15)	-126 (-159, -94)	<0.001
Day 3 post-op	IV Fluids (l)	0.50 (0.00, 1.50)	0.00 (0.00, 0.00)	-0.56 (-0.87, -0.25)	<0.001
	Na ⁺ (mmol)	0 (0, 77)	0 (0, 0)	-23 (-56, 9)	0.16
Cumulative total (incl. day 4 post-op)	IV Fluids (l)	8.75 (8.00, 9.80)	4.50 (4.00, 5.62)	-3.39 (-4.48, -2.20)	<0.001
	Na ⁺ (mmol)	560 (477, 667)	229 (131, 332)	-316 (-442, -197)	<0.001

Table 4.3 Serum urea and creatinine for patients in the fluid and sodium restriction study

		Standard Care	Restricted	Difference	p-value
		Median (IQR)	Median (IQR)	Estimate (95% CI)	
Day of operation	Serum urea (mmol/l)	5.3 (4.3, 6.9)	5.5 (4.5, 6.4)	0.1 (-1.3, 1.5)	0.87
	Serum creatinine (mmol/l)	89.0 (77.0, 104.0)	94.0 (85.0, 107.0)	6.6 (-7.4, 20.6)	0.36
Day 1 post-op	Serum urea (mmol/l)	4.6 (3.8, 6.0)	5.3 (4.2, 7.6)	0.9 (-0.4, 2.3)	0.18
	Serum creatinine (mmol/l)	88.5 (79.8, 101.2)	95.0 (83.5, 116.0)	13.0 (-0.8, 26.8)	0.065
Day 2 post-op	Serum urea (mmol/l)	3.9 (3.1, 5.1)	5.4 (3.9, 7.1)	1.4 (0.0, 2.7)	0.046
	Serum creatinine (mmol/l)	81.5 (71.8, 90.0)	89.0 (77.5, 100.5)	14.4 (0.5, 28.2)	0.042
Day 3 post-op	Serum urea (mmol/l)	4.5 (3.8, 5.8)	5.7 (4.8, 8.0)	1.6 (0.3, 3.0)	0.020
	Serum creatinine (mmol/l)	77.0 (71.0, 93.0)	90.0 (77.0, 101.0)	11.0 (-2.9, 25.0)	0.12
Day 4 post-op	Serum urea (mmol/l)	5.2 (4.2, 6.8)	7.0 (5.2, 8.7)	1.5 (0.1, 3.0)	0.034
	Serum creatinine (mmol/l)	79.5 (68.2, 98.8)	88.0 (70.0, 97.0)	8.8 (-5.8, 23.5)	0.24

Table 4.4 Times to study endpoints for patients in the fluid and sodium restriction study

	Standard Care	Restricted	HR (95% CI)	p-value
Time to first flatus	2.9 (2.4,3.3)	2.9 (2.3,3.8)	0.85(0.54,1.32)	0.47
Time to first bowel movement	4.9 (3.2,6.9)	4.7 (3.7,6.1)	1.06(0.68,1.65)	0.80
Time to medical discharge	5.9 (4.0,7.9)	5.8 (4.1,7.3)	0.97(0.62,1.53)	0.90
Time to hospital discharge	6.2 (5.0,10.1)	6.2 (5.0,9.9)	1.02(0.65,1.60)	0.92
Total hospital stay	7.2 (6.1,11.2)	7.2 (6.1,11.0)	1.03 (0.66,1.61)	0.90

Values are median (interquartile range) for times (in days)

Table 4.5 Complications for patients in the fluid and sodium restriction study

	Standard (n=41)	Restricted (n=39)
Atrial fibrillation	-	1
Pulmonary oedema	1	-
Myocardial infarct	1	1
Respiratory failure	1	-
Chest Infection	-	1
Wound infection	3	2
Intra-abdominal sepsis	-	1
Central line sepsis	-	1
Wound dehiscence	-	1
Obstruction	1	-
Prolonged ileus	-	1
Intra-abdominal bleed	1	1
Upper GI bleed	-	1
*Acute renal failure	-	1
Rectovaginal fistula	-	1
Femoral nerve palsy	1	-
Death within 30 days	1	1
TOTAL	10	14

Occurred following intra-abdominal bleed

Table 4.6 Mean Short Form 36 (SF-36) scores at 3 months after surgery for patients in the fluid and sodium restriction study

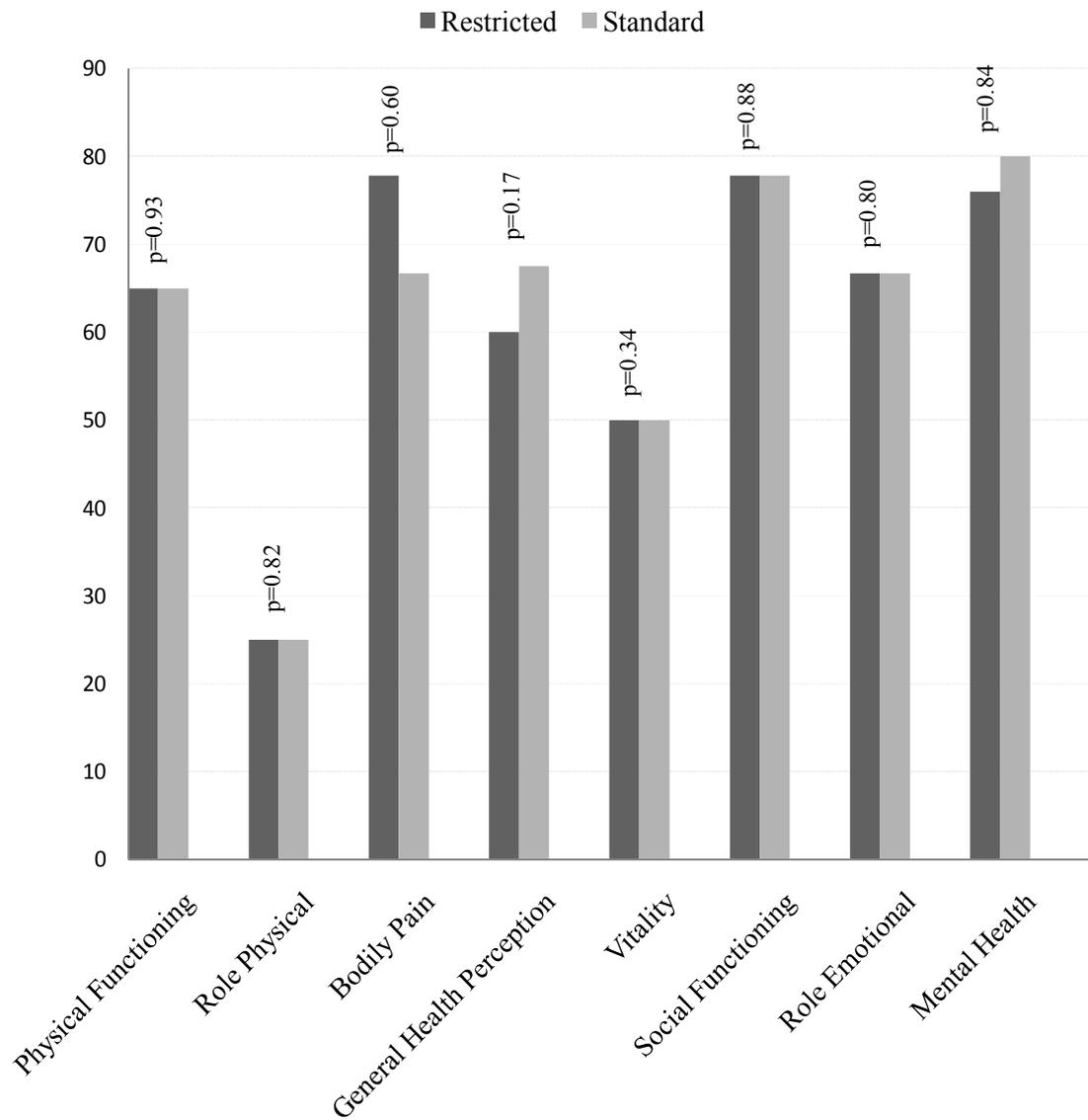


Table 4.7 Baseline Characteristics comparing non-randomised patients with patients randomised to the fluid and sodium restriction study

		Study	Non-entrants
N		80	12
Age (years)		72.8 (65.8, 81.0)	70 (63, 76)
Sex	Male	37 (46.2%)	5 (41.7%)
	Female	43 (53.8%)	7 (58.3%)
ASA Grade	1	4 (5%)	0 (0%)
	2	56 (70%)	11 (91.7%)
	3	19 (23.8%)	1 (8.3%)
	4	1 (1.2%)	0 (0%)
Operation	Right hemicolectomy	26 (32.5%)	5 (41.6%)
	Left hemicolectomy	7 (8.8%)	3 (25%)
	Anterior resection	42 (52.5%)	2 (16.7%)
	Hartmann Closure	5 (6.2%)	2 (16.7%)
Technique	Laparoscopic	22 (27.5%)	4 (33.3%)
	Open	58 (72.5%)	8 (66.7%)
Indication	Benign	18 (22.5%)	8 (66.7%)
	Cancer	62 (77.5%)	4 (33.3%)

Table 4.8 Intravenous fluid and sodium cumulative totals comparing non-randomised patients with patients randomised to the fluid and sodium restriction study

		Restricted	Standard Care	Non-entrants
		Median (IQR)	Median (IQR)	Median (IQR)
Cumulative total (day 0-3)	IV Fluids (l)	4.50 (4.00, 5.62)	8.75 (8.00, 9.80)	8.00 (6.50, 10.75)
	Na ⁺ (mmol)	229 (131, 332)	560 (477, 667)	921 (543, 1137)

Values are median (interquartile range) for continuous or N (%) for categorical data

Figure 4.1 Trial profile for the fluid and sodium restriction study

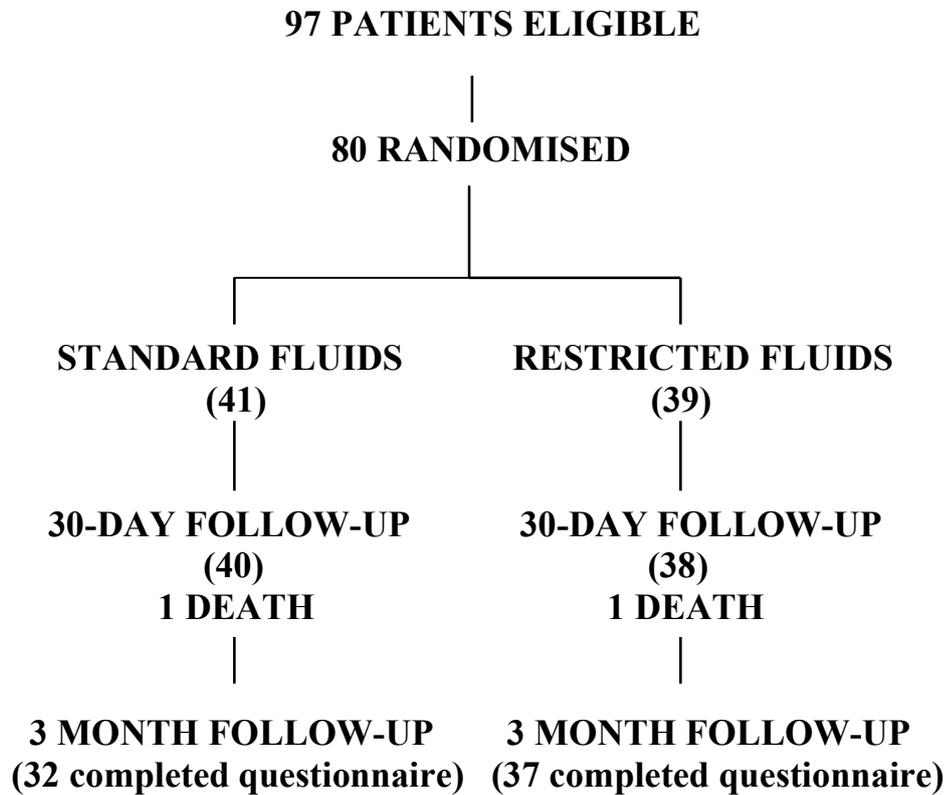
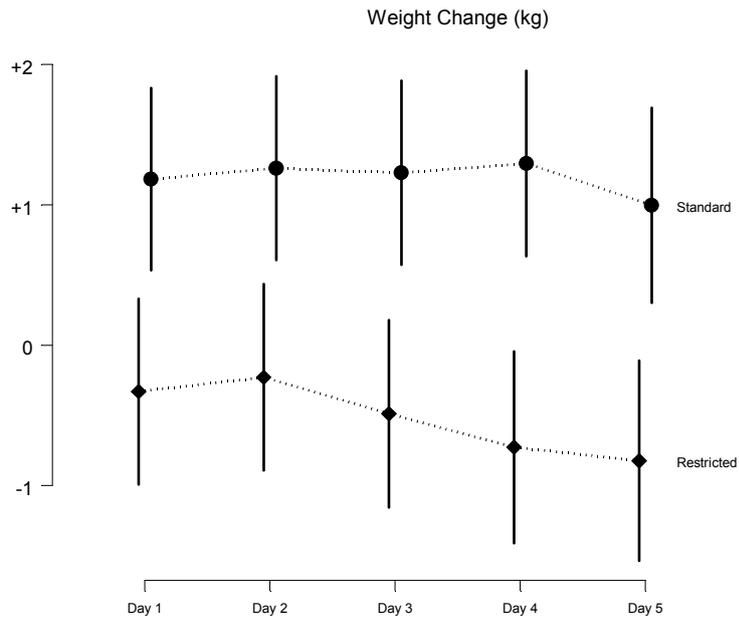


Figure 4.2 Estimated mean daily weight change compared to baseline with 95% CIs, for patients in the fluid and sodium restriction study



4.4 Discussion

This study shows that with a conservative intraoperative fluid protocol, postoperative restriction of fluids and sodium has no significant effect on postoperative gastrointestinal function or hospital stay in patients undergoing elective colorectal surgery.

When considering perioperative fluid management it is important to reach a balance between giving too little fluid with consequent hypovolaemia and organ dysfunction²⁶⁰ or too much fluid with resultant oedema and a different array of organ dysfunctions²³². Goal-directed intraoperative fluid administration guided by an oesophageal doppler monitor has been suggested as one method to maintain optimal stroke volume and achieve an earlier return to bowel function and decrease in postoperative hospital stay²³⁸. Simply following a standard protocol which sets limits on fluid and sodium load (as in the present study) is an alternative approach which can be further adapted by the use of more invasive monitoring for the high-risk patient.

The conservative intraoperative intravenous fluid and sodium regimen followed in the present study resulted in either group maintaining median body weight change within a kilogram of preoperative body weight on the first postoperative day. This is in marked contrast to the 'control' arms of trials examining the effects of fluid management where patients have gained 3-6 kg in the immediate postoperative period²³³. The lack of effect of the post-operative restriction regimen on clinical outcomes observed in the present study may be explained by the success of the intraoperative protocol in maintaining

weight-stability and avoiding such gross fluid gains. Equally, although the unrestricted postoperative regimen adopted in the present study resulted in patients receiving 4 litres more fluid (and > 300 mmol more sodium) than the restricted group, the timing and rate of administration was such that the patients were able to excrete most of the fluid in a timely fashion.

The factors that allow successful use of a restricted intraoperative fluid regimen include circumventing the patient coming to theatre in a dehydrated state by avoiding bowel preparation or excessive duration of preoperative fasting as undertaken in the present study. Equally the avoidance of epidural anaesthesia/ analgesia may contribute to the level of control that can be exerted over excessive fluid administration. Some centres use epidurals in 'fast-track' protocols and advocate the use of vasopressors or altered thresholds to manage epidural-related hypotension and thus avoid excessive fluid loading⁴. However, in routine practice it may be difficult to avoid some degree of increased fluid administration. By using a PCA-based regimen the present study avoided these issues which may have contributed to the ability to follow a relatively restricted fluid regimen in both arms of the protocol.

Total hospital stay, including convalescence, for patients in this study was a median of 7 days. This is shorter than that observed in clinical trials of laparoscopic surgery²⁰⁸ but longer than that reported where accelerated discharge protocols have been used^{145, 148, 241}. In a prospective study of 60 consecutive patients with similar co-morbidity to our population, Basse et al reported a median hospital stay of 2 postoperative days for

patients undergoing elective colorectal surgery²⁴¹. Similar results were obtained by Anderson et al in a randomised clinical trial comparing multimodal optimization and standard care¹⁴⁸. The readmission rate for patients in the Basse et al study was 15% while no patient in the Anderson study was re-admitted within 30 days of surgery. While better pain control in the form of epidural analgesia could account for some of the difference in hospital stay between these studies and our trial, it is likely that use of different discharge criteria, for example, the patients' ability to tolerate diet rather than waiting for the first bowel motion, may be more important in determining the length of hospital stay for the patient population¹⁴⁶.

The patients who were not randomised into the study had a longer hospital stay when compared with patients in the trial. This is unsurprising as the majority of patients were ineligible due to increased medical co-morbidity. The increased co-morbidity was not evident in patients' ASA grade which was similar between the groups but is suggested by the increased rate of significant complications in the non-randomised group.

It is clear from this and other studies that restriction of intravenous fluids intra and postoperatively is safe in well hydrated patients undergoing major elective abdominal surgery. Further clinical trials are required to identify the components of fast-track surgery that significantly influence hospital stay including the indications for more invasive fluid balance monitoring.

CHAPTER 5

EFFECT OF LAPAROSCOPIC COLONIC RESECTION IN FAST-TRACK PATIENTS AFTER ELECTIVE SURGERY

5.1 Introduction

Since the introduction of laparoscopic-assisted colorectal surgery over 10 years ago the technique has become increasingly popular. Data from randomised trials on outcomes following laparoscopic surgery has often lagged behind clinicians' enthusiasm to adopt the technique. There are now a number of randomised trials in the literature which seem to confirm the improved results seen in early studies. While it does not appear that laparoscopic resection adversely affects the oncological outcome in colorectal cancer, a significant effect on short-term recovery has been widely reported²⁰⁷⁻²¹⁰. Studies have shown that minimally-invasive surgery invokes a less pronounced inflammatory response and reduces the duration of ileus^{206, 210, 261, 262}. It has also been shown that duration of hospital stay can be reduced to around 4-8 days compared with 6-11 days with open surgery^{204, 206-210, 212, 262}.

Over almost the same period that laparoscopic surgery has been gaining acceptance, interest has been growing in the area of enhanced perioperative recovery protocols. Such protocols involve a multi-disciplinary approach adopting evidence-based practice to reduce the surgical stress response and enhance recovery. Studies of fast-track recovery have reported hospital stays of 2-3 days following colorectal resection which is comparable to any of the best laparoscopic trials in the literature^{174, 213, 263}. There is however little evidence comparing the effect of laparoscopic colorectal resection in fast-track recovery patients. One recent study has suggested that there is no difference in terms of return of gastrointestinal function and duration of hospital stay in fast-track

patients randomised to open or laparoscopic colorectal resection¹⁷⁴. This study has recently been challenged by another publication which suggests that hospital stay can be reduced by around 30% in fast-track patients using laparoscopic surgery²¹¹.

The aim of our study was to investigate whether laparoscopic colorectal resection improved recovery with the use of a multimodal rehabilitation program.

5.2 Patients and methods

We carried out a prospective audit between November 2003 and March 2005. Patients undergoing elective colorectal surgery with primary anastomosis at a University teaching hospital were included. Exclusion criteria included those with severe physical disability and in long term care, patients who were medically unfit for surgery and patients undergoing total colectomy, abdominoperineal resection or low anterior resection requiring a covering loop ileostomy. A decision on suitability for laparoscopic-assisted resection was made on a case by case basis by the operating surgeon. Both of the participating consultant surgeons carried out both open and laparoscopic procedures and were involved in all operations. A laparoscopic-assisted resection was defined as an operation where colonic mobilization and division of the vessels was performed laparoscopically. An extracorporeal anastomosis was fashioned for right sided lesions and an intracorporeal circular stapled anastomosis for sigmoid/ left sided lesions. Transverse, muscle splitting, single dermatome incisions were used for extraction of the specimen. The unit which is split over 2 sites has experience of around 50 laparoscopic colorectal procedures per annum and is a recognised centre for preceptorship.

Patients were given preoperative information and allowed free fluids and high calorie containing drinks for up to 2 hours before operation. Patients undergoing right hemicolectomy did not receive bowel preparation while those having left sided surgery received a phosphate enema the night before and the morning of surgery. All patients

received antibiotic and DVT prophylaxis and no nasogastric tubes or abdominal drains were used.

A standardized anaesthetic protocol was used with a conservative perioperative fluid regime consisting of 4 per cent dextrose/0.18 per cent saline at 10mls/kg/hr plus 3 times the measured blood loss. The postoperative analgesic regime was based around PCA Morphine which was continued for 48hours. Patients were also given regular Paracetamol with NSAIDs and Tramadol used for breakthrough pain. Oral fluids were pushed immediately postoperatively and normal diet was encouraged from day 1. Chest physiotherapy and active mobilization was also commenced on day 1. Urinary catheters were removed on day 2 unless there was a clinical reason for them to remain.

We recorded patients' weight, height, blood parameters, analgesic and antiemetic intake, visual analogue pain scores, nausea scores (0-4), time to first flatus and bowel motion and postoperative complications. Decision on patient discharge was made by the operating surgeon. To be considered fit for discharge patients had to be afebrile, fully mobile, passing flatus or faeces, using oral analgesics only for pain, and have a healing wound. Following discharge patients were phoned daily by a research nurse until review at clinic on day 14. At 3 months patients were asked to complete the Short Form 36 health questionnaire.

Statistical analysis was carried out using the Mann Whitney U test or Fisher's exact test where appropriate with measurements of continuous outcomes analyzed by repeated measures linear regression analysis.

5.3 Results

During the study period 80 patients who satisfied the inclusion criteria underwent elective colorectal surgery with primary anastomosis. A fast-track recovery protocol was employed in all of these patients. 22 patients underwent laparoscopic assisted colonic resection and 58 had open surgery (Figure 5.1). Patients were well matched for demographic data including age, sex, BMI, ASA grade and surgical site (Table 5.1).

Median incision size in the laparoscopic group was 9cm (i.q.r. 8-11 cm) compared to 21cm (17-24cm) in the open group. None of the patients in the laparoscopic group required conversion to an open procedure for colonic mobilisation. There was no significant difference in the use of morphine, with a median of 70mg (43-101mg) in the laparoscopic group compared to 67mg (33-91mg) in the open group (mean difference 4 (95 per cent confidence interval -14.6, 23.9) mg; $p=0.69$). There was no difference between the groups in use of Paracetamol (global $p=0.63$) and Tramadol ($p=0.96$). Patients in the laparoscopic group used significantly more Ibuprofen ($p=0.036$). There was no difference in visual analogue pain scores at rest or on movement between the 2 groups for the duration of their hospital stay (Figure 5.2).

We did not see any difference in the use of antiemetics, namely Metoclopramide (global $p=0.09$), Prochlorperazine ($p=0.24$) and Ondansetron ($p=0.28$). Nausea scores also showed no significant difference (global $p=0.39$ (morning) and $p=0.83$ (evening)).

Time taken to passage of first flatus ($p=0.36$) and time to first bowel motion ($p=0.07$) was similar between the two groups. Time to medical discharge and time to actual hospital discharge was not significantly different between the 2 groups with the median day of discharge on the 5th postoperative day (Table 5.2). Two patients in the open group were readmitted following discharge. One patient was readmitted with a late wound dehiscence and a 96 year old patient was readmitted with diarrhoea.

Postoperative complications were identified in 6 patients in the laparoscopic group and 13 patients in the open group. There was no difference in infective ($p=0.70$) or non-infective complications ($p=0.73$) between the 2 groups (Table 5.3). There were 2 deaths within 30 days of operation. One patient in the laparoscopic group died on day 1 from respiratory failure and another in the open group died on day 4 from a central line infection. There was no difference in short form 36 scores between the two groups for any of the components measured.

Table 5.1 Baseline Characteristics for patients in the laparoscopic/ open surgery study

		Laparoscopic	Open
N		22	58
Age (years)		72.0 (63.7, 78.8)	73.2 (66.8, 81.7)
Sex	Male	12 (54.5%)	25 (43.1%)
	Female	10 (45.5%)	33 (56.9%)
BMI		25.1 (23.4, 28.8)	26.2 (22.4, 30.4)
ASA Grade	1	3 (13.6%)	1 (1.7%)
	2	14 (63.6%)	42 (72.4%)
	3	5 (22.7%)	14 (24.1%)
	4	0 (0.0%)	1 (1.7%)
Operation	Right hemicolectomy	6 (27.3%)	20 (34.5%)
	Left hemicolectomy	0 (0.0%)	7 (12.1%)
	Anterior resection	16 (72.7%)	26 (44.8%)
	Hartmann Closure	0 (0.0%)	5 (8.6%)
Indication	Benign	2 (9.1%)	16 (27.6%)
	Cancer	20 (90.9%)	42 (72.4%)

Values are median (interquartile range) for continuous or N (%) for categorical data

Table 5.2 Times to study endpoints for patients in the laparoscopic/ open surgery study

	Laparoscopic	Open	p-value
	Median (IQR)	Median (IQR)	
Time to first flatus	2.9 (2.3, 3.2)	2.9 (2.3, 3.6)	0.36
Time to first bowel movement	5.3 (4.1, 6.2)	4.2 (3.1, 5.8)	0.07
Time to medical discharge	5.8 (4.1, 7.8)	5.9 (4.1, 7.8)	0.99
Time to hospital discharge	6.1 (5.0, 9.0)	6.2 (5.0, 10.0)	0.87

Values are median (interquartile range) for times (in days)

Table 5.3 Complications for patients in the laparoscopic/ open surgery study

	Open (n=58)	Laparoscopic (n=22)
Atrial fibrillation	1	-
Pulmonary oedema	1	-
Myocardial infarct	2	-
Respiratory failure	-	1
Chest Infection	-	1
Wound infection	3	2
Intra-abdominal sepsis	1	-
Central line sepsis	1	-
Wound dehiscence	1	-
Obstruction	1	-
Prolonged ileus	-	1
Intra-abdominal bleed	1	1
Upper GI bleed	1	-
*Acute renal failure	-	1
Rectovaginal fistula	1	-
Femoral nerve palsy	-	1
Death within 30 days	1	1
TOTAL	15	9

***Occurred following intra-abdominal bleed**

Figure 5.1 Trial profile for patients in the laparoscopic/ open surgery study

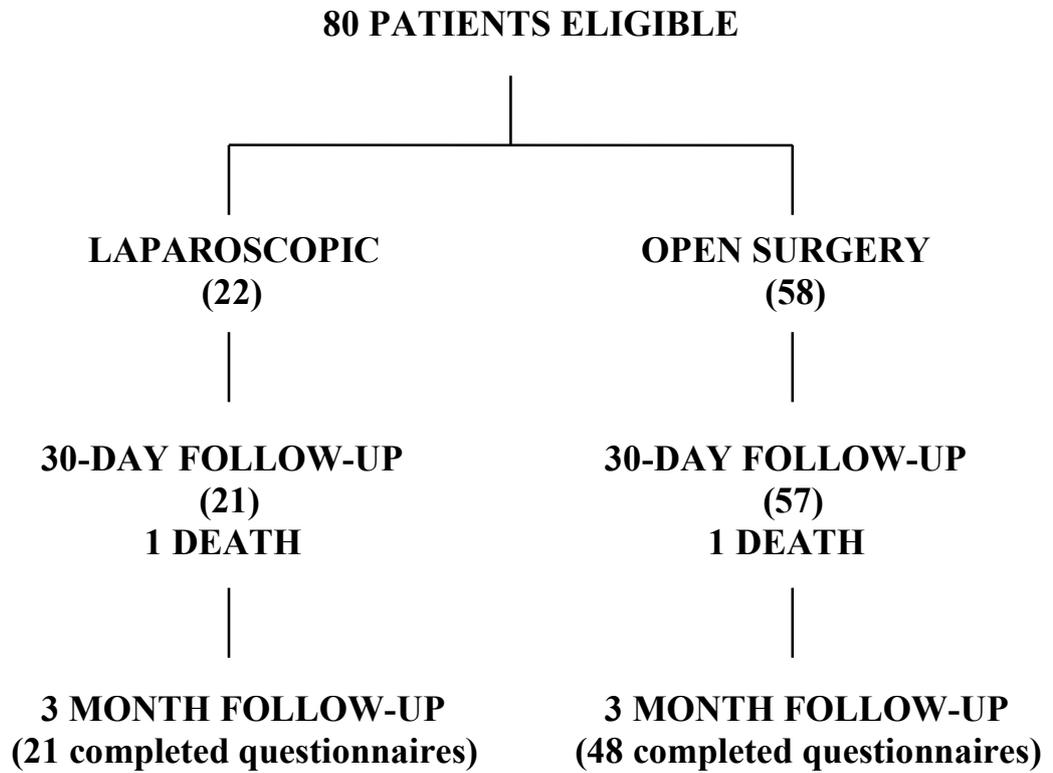
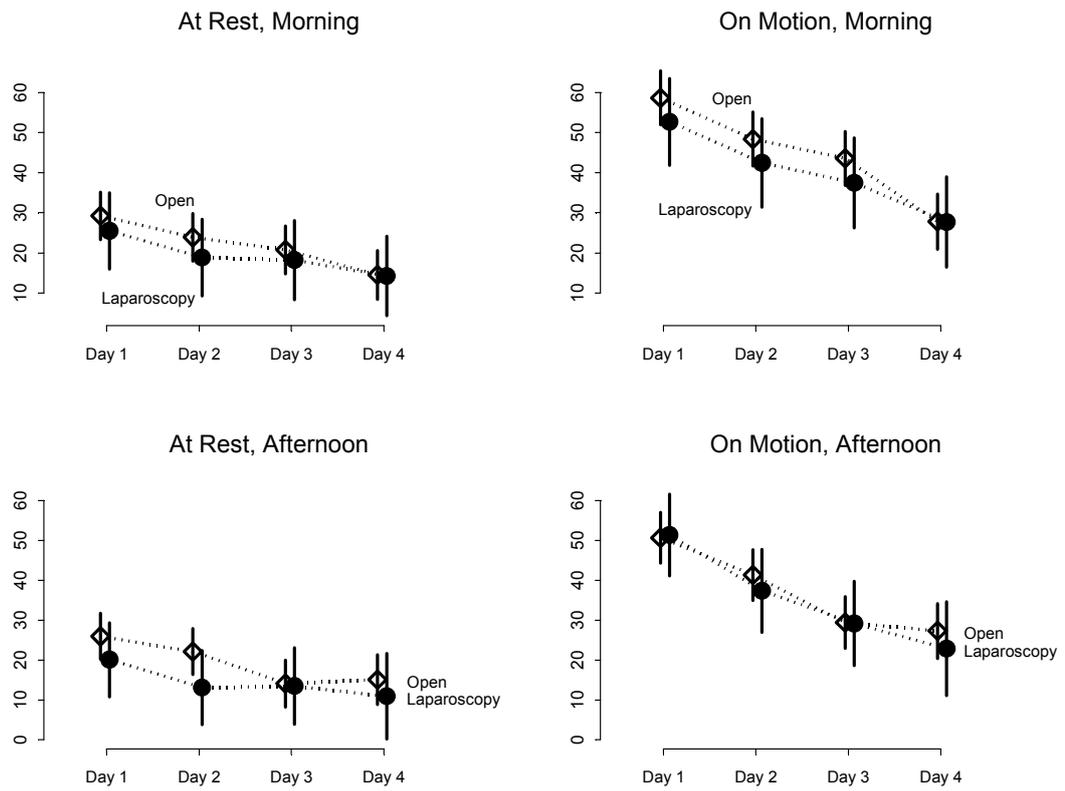


Figure 5.2 Estimated mean daily pain scores at rest and on moving, in the mornings or afternoons, with 95% CIs for patients in the laparoscopic/ open surgery study



5.4 Discussion

Laparoscopic colorectal surgery has gained increasing acceptance over the past decade. The arguments made for adopting the technique in spite of higher costs, longer operating times and a steep initial learning curve have been based around the improvements in patient recovery. The perceived advantages of less postoperative pain and a reduction in ileus and length of hospital stay are felt to outweigh any such disadvantages.

With the introduction of fast-track surgery dramatic improvements in perioperative care have been reported with hospital stays of between 2 and 3 days after open surgery¹⁷⁴. While individual interventions have been validated by randomised clinical trials, their relative importance in the context of a multimodal rehabilitation program remains obscure.

As in the study by Kehlet et al. we found no difference in pain scores or analgesic intake between the two groups¹⁷⁴. These results are obviously quite different from previous large trials and meta-analyses of traditional care which have consistently shown an improvement in analgesia with laparoscopic surgery²¹⁰. It may be that altering patients' expectations preoperatively has a significant effect on their perception of pain.

We also found no difference in duration of ileus or hospital stay with patients discharged on the 5th postoperative day. This is longer than in Kehlet's group which may be due to the use of PCA morphine rather than epidural analgesia however a recent randomised

trial showed no benefit of thoracic epidural analgesia over PCA morphine when used in a fast-track program for patients undergoing colorectal resection²⁵⁸. The difference in hospital stay may also reflect the use of different discharge criteria by waiting for the passage of the first bowel motion but it is offset by fewer readmissions in the current study. The only study to show a difference in fast-track patients between open and laparoscopic surgery is the study by Kennedy et al. however this may be due to hospital stays of 7 days in the open group which is longer than those in the current trial²¹¹. While we did not see any difference between the groups in term of complications or quality of life when assessed at 3 months the study is not adequately powered for these specific endpoints.

The number of patients in the current study is limited, as is the case with all the similar trials currently in the literature. While this series is non-randomised we would have expected any selection or observer bias to have benefited the laparoscopic group. We did not however see any significant difference in short term outcomes after colorectal surgery in fast-track patients treated laparoscopically. If laparoscopic resection does not improve short or long term outcomes then the significantly increased cost of the procedure may become difficult to justify²¹².

We believe that with the introduction of multi-modal rehabilitation programmes, the benefits of laparoscopic-assisted colonic resection remain to be proven and that further large randomised trials are necessary to investigate the current controversy in the literature.

CHAPTER 6

EARLY DISCHARGE FOLLOWING LIVER RESECTION FOR COLORECTAL LIVER METASTASES

6.1 Introduction

Liver resection is currently the recognised treatment for localised colorectal liver metastases. A large proportion of patients however will be unsuitable for resection either due to the extent of disease or their fitness for surgery. The prognosis without treatment is usually less than 12 months^{264, 265}. Following liver resection the 5-year survival ranges between 30-50% with operative mortality of around 3%²⁶⁶⁻²⁷¹. Recently published series of patients undergoing liver resection report hospital stays between 7-12 days²⁶⁹⁻²⁷² for open surgery and 5-8 days²⁷³⁻²⁷⁶ for laparoscopic resection.

As previously discussed there has been sustained interest recently in the use of ‘fast-track’ recovery protocols in major abdominal surgery. Efforts have focused on attenuation of the surgical stress response and improving physiological function to reduce postoperative complications and hospital stay. Such protocols commonly include early mobilisation and diet, optimised fluid and analgesic regimens, as well as avoidance of abdominal drains and nasogastric tubes. With recent advances and growing experience in liver surgery it is well suited to the introduction of such protocols to further enhance postoperative recovery.

As part of our clinical studies focusing on recovery following major abdominal surgery we were keen to introduce the principles of ‘fast-track’ recovery into our clinical practice. Multimodal rehabilitation has been applied to colorectal, orthopaedic, vascular and gynaecological procedures but has not previously been reported in liver surgery. By

comparing our results with data published in the medical literature, our aim was to measure the effect of a 'fast-track' recovery protocol on hospital stay following liver resection for colorectal metastases.

6.2 Patients and Methods

Data was prospectively collected from 12 consecutive patients undergoing open liver resection for colorectal metastases between August 2003 and September 2004 in one surgical centre.

All procedures were carried out by a single surgeon specialising in liver surgery. Patients were consented for surgery following a full discussion of the rehabilitation programme with both the patient and their family. All patients had open, segment-orientated liver resection carried out through a large sub-costal incision with full mobilisation of the liver. A standardised anaesthetic technique was used in all patients and normothermia was maintained throughout the procedure. Liver dissection was carried out with an ultrasonic dissector and Floseal® (Baxter International Inc. Deerfield, Illinois, USA) tissue glue was applied to the resection margins at the end of the procedure to aid haemostasis. Abdominal drains were not used in any patients following resection. Antibiotic prophylaxis consisted of a single dose of a cephalosporin administered intravenously at the beginning of the procedure.

A multi-modal optimisation package was employed in all patients. Patients were allowed to drink clear fluids until 2 hours before surgery to avoid preoperative dehydration. Oral fluids were encouraged on the night of surgery with diet introduced on the first postoperative day if tolerated. Patients received supplement drinks twice daily until discharge. An intravenous fluid regime using 2 litres of 4% Dextrose/ 0.18% Saline was

administered over the first 24 hours unless signs of salt or water depletion became evident. A protocol using small boluses of Gelofusine was employed for patients with signs of hypovolaemia. Intravenous fluids were stopped after 24 hours.

The analgesic regimen consisted of PCA Morphine for 24-48 hours with regular oral Paracetamol 1g four times daily. Following the cessation of PCA Morphine a non-steroidal was commenced in the form of oral Ibuprofen 600mg four times daily. Where non-steroidal analgesia was contraindicated patients were commenced on Tramadol 50-100mg four times daily.

Urinary catheters were removed after 24-48 hours to aid mobilisation. Early mobilisation was encouraged and an intensive physiotherapy regime was employed. Blood samples were taken preoperatively, on the night of surgery and daily for the first 4 postoperative days. Decision regarding discharge from hospital was taken by the Consultant in charge of the patients care. Prior to discharge patients were required to be tolerating full diet, mobilising unaided and experiencing good analgesia with oral medication. Data on postoperative complications and hospital stay was recorded for each patient. Patients were seen in the outpatient clinic 2 weeks following their discharge.

6.3 Results

12 patients with a median (i.q.r.) age of 60 (55-66) years underwent open liver resection for colorectal metastases. Resection consisted of 1 hepatic lobectomy, 2 trisegmentectomy, 3 bisegmentectomies and 6 segmentectomies. Mean operating time was 130 minutes. Resection margins were clear in all patients (Table 6.1).

All patients tolerated the early introduction of oral fluids and diet. The median time (i.q.r.) to cessation of intravenous fluids was the first postoperative day (1-2 days). Patients received a median volume of 3000mls (2500–4000mls) of intravenous fluid on the day of theatre, with 2000mls (1000–2500mls) and 500mls (0–1500mls) on days 1 and 2 respectively. The median intravenous sodium load was 459mmols (343-496mmols), 77mmols (45-154mmols) and 75mmols (0-87mmol) on day 0, day 1 and day 2 respectively. One patient required a postoperative blood transfusion on the day of theatre. The median dose of morphine received was 12mg (5-23mg) on day 0, 16mg (4-23mg) on day 1 and 0mg (0-2mg) on day 2.

Data on time to first bowel motion was available for 10 patients with a median time of 4 (3-5) days to first bowel motion. The median duration of hospital stay was 4 (3-5) days.

1 epileptic patient developed carbamazepine toxicity following liver resection due to reduced enzymatic breakdown of the drug, delaying their discharge. A further 2 patients developed right upper quadrant fluid collections postoperatively requiring no

intervention. 1 patient was re-admitted with wound pain which settled after 48 hours with simple analgesia. There were no postoperative mortalities during the study period. We did not notice any significant alteration in renal function or in the recovery of synthetic liver function during the series (Table 6.2).

Table 6.1 Baseline Characteristics for patients in fast-track liver resection series

		Liver resection
N		12
Age (years)		60 (55 - 66)
Sex	Male	8
	Female	4
ASA Grade	1	4
	2	7
	3	1
	4	0
Mean operating time (mins)		130
Operation		1 Lobectomy
		2 Trisegmentectomy
		3 Bisegmentectomy
		6 Segmentectomy

Values are median (interquartile range)

Table 6.2 Blood parameters for patients in fast-track liver resection series

	Pre-op	Day 1	Day 2	Day 3
Hb	13.2 (12.3-13.9)	10.5 (10.1-12.4)	11.0 (9.1-11.7)	9.8 (8.8-10.9)
Urea	4.5 (4.0-5.0)	5.5 (3.8-6.3)	4.0 (2.8-5.3)	4.2 (3.3-5.1)
Cr	87 (74-100)	83 (68-93)	82 (63-101)	76 (59-100)
Alb	44 (41-46)	32 (26-34)	33 (32-35)	35 (30-35)
AST	23 (21-33)	354 (201-530)	233 (115-457)	122 (89-205)
ALT	21 (16-22)	351 (204-579)	351 (178-918)	260 (149-628)
Bil	11 (9-14)	17 (12-30)	22 (10-32)	23 (13-34)

Values are median (interquartile range)

6.4 Discussion

Liver resection is currently the treatment of choice for colorectal liver metastases. With increased experience in liver resection as well as recent technical advances, surgery is becoming safer for a larger proportion of patients²⁶⁶. Advances in postoperative care with the introduction of multi-modal rehabilitation programmes may offer a further benefit to those already being realised. The opportunity to get patients home quicker after surgery has implications not only for provision of healthcare services but also for a patient group where quality of life, and especially time spent out of hospital, is particularly important.

Recovery protocols have already been used to good effect in other major abdominal procedures and liver surgery may also benefit from their introduction. Our short series of patients shows that rapid discharge from hospital following liver resection is both safe and achievable. Our results compare favourably to other series in the literature in terms of hospital stay, including laparoscopic series. It also compares favourably to historical controls with hospital stays of between 7 and 9 days prior to the introduction of fast-track recovery. It is however only a small number of patients and caution must be used in comparing it to much larger series including more extensive resections.

There have been a number of recent articles in the medical literature regarding the role of fluid and sodium restriction and the effects on postoperative recovery. In our series it was evident that patients tolerated the early introduction of oral fluids and diet. Furthermore the administration of intravenous fluid was limited to the first postoperative day. While

we attempted to restrict the amount of intravenous fluid and sodium that patients received as part of the protocol it is evident from the volumes infused that this was only partly successful. On the day of operation patients received a median of 3L of fluid containing a median of 459mmol of sodium. This was more than the targets set out in the protocol but was less than the 5-6L of fluid often infused in this patient group during operation. We did not encounter any renal complications with the fluid regime employed. While we found that limiting intravenous fluid and sodium in the perioperative period was potentially achievable, this small series does not give further information regarding its efficacy.

Further research is required to validate the individual elements of 'fast-track' protocols and the role of fluid optimisation and the effect on recovery in this particular patient group. There are also challenges brought about by the more rapid discharge of patients. From our initial experience with fast-track recovery it is clear that follow-up arrangements and access to surgical services have to be closely considered to ensure that patient care is not sacrificed in the drive for ever quicker turnover.

CHAPTER 7

THE EFFECT OF COLONIC RESECTION ON RECOVERY OF GASTROINTESTINAL FUNCTION FOLLOWING MAJOR ABDOMINAL SURGERY

7.1 Introduction

The first mention of postoperative ileus as a clinical entity was by Pal in 1890¹⁵¹. Ileus can be described as ‘the transient impairment of bowel motility after abdominal surgery or other injury²⁷⁷. It is a significant cause of postoperative morbidity, causing nausea, vomiting and abdominal pain as well as delaying the institution of oral diet, early mobilisation and ultimately discharge from hospital. The causes of ileus have again come under scrutiny in the medical literature with the introduction of fast-track surgery as ileus is one of the main barriers in colorectal surgery to discharging patients early.

The pathophysiology of ileus is multifactorial although the relative influence of individual factors as well as their hierarchical order is still a matter for debate. Inhibitory reflex arcs with afferents from somatic, visceral and parietal fibres are thought to play a part. Important also is the interplay between the sympathetic and parasympathetic nervous system as well as the intrinsic nervous system of the gastrointestinal tract. The parietal peritoneum has been shown to play a major role in the process with inflammatory mediators, endogenous and exogenous opioids also exerting an influence.

Studies into extent, location and duration of ileus have been largely contradictory. We do know from both animal and human studies that ileus resolves quickly in the stomach and small intestine but that the left colon is the most functionally depressed and contributes significantly to duration of postoperative ileus^{137, 138, 152, 278}. It is also clear from studying the return of myoelectrical activity to the left colon following surgery that there is good

correlation between the resolution of ileus and the passage of the first bowel motion which is used as a clinical endpoint¹³⁷.

It has been a traditionally held view that intestinal manipulation and operation time have a significant effect on the duration of postoperative ileus. However there has been little evidence to support this. A number of in vitro studies have proposed a local inflammatory role¹⁵⁴⁻¹⁵⁹. It has been suggested that the trauma provoked by handling of the bowel causes an increased inflammatory cell infiltrate in the muscular layer along with an increase in mucosal permeability. This local inflammation may interfere with myoelectrical activity causing postoperative ileus. It is also claimed that the increased mucosal permeability leads to bacterial translocation and further postoperative morbidity. While these experimental findings seem to support the traditional surgical viewpoint they have not been supported by clinical studies in humans. It has already been shown that the left colon is the rate limiting step in the resolution of gastrointestinal function. The studies suggesting a local inflammatory process induced by manipulation were carried out on animal small bowel which may explain the conflicting results.

Controversy over the effect of intestinal manipulation during surgery still remains and linked to this the effect of the colonic resection itself on the return of gastrointestinal function has not been widely researched. The aim of this study was to investigate the effect of intestinal manipulation and colonic resection on the return of gastrointestinal function following major abdominal surgery.

7.2 Patients and Methods

We carried out a prospective study of 10 consecutive patients undergoing colorectal resection and 10 consecutive patients undergoing liver resection in one surgical centre and operated on by a single surgeon. In this way we compared 2 groups of patients each undergoing major abdominal surgery, one with colonic resection and mobilisation, the other with minimal gastrointestinal manipulation and no colonic resection. Liver resections were carried out through a large right sub-costal incision with full mobilisation of the liver. Colonic resections were carried out through a mid-line laparotomy. In both groups an identical recovery protocol was instituted.

As part of the recovery protocol no nasogastric tubes or abdominal drains were used. Early oral feeding was offered to all patients consisting of oral fluids immediately after surgery and light diet from the morning after surgery. Due to the lack of ward facilities available to manage epidurals the postoperative analgesic regime was based around PCA morphine. Patients were also prescribed regular non-opioid analgesics in the form of Ibuprofen and Paracetamol to try to minimise opioid use. All other medications with an effect on gastrointestinal motility were stopped prior to surgery. All patients were managed with a restricted intravenous fluid regimen aiming at 2 litres of intravenous fluid over the first 24 hours alone. The intravenous fluid used was 4% dextrose/ 0.18% saline to deliver the recommended daily requirement of sodium. Patients underwent an intensive physiotherapy regime to encourage early mobilisation.

Data was collected on sodium and fluid intake, opioid intake, blood parameters, time to first bowel movement and hospital stay. Results were analysed with Student's t test. A P-value less than 0.05 was considered to be statistically significant.

7.3 Results

The median (i.q.r.) age of patients undergoing colorectal resection was 73 years (67-77) compared with a median age of 61 years (56-66 years) for patients undergoing liver resection. The male to female ratio, ASA grades and mean operating time between the two groups were not significantly different (Table 7.1).

The colonic resection group required significantly more opioid analgesia on the first postoperative day with 31mg (7-42mg) *versus* 16mg (5-28mg) (p=0.01). There were no significant differences in the use of other analgesics during the postoperative period. The liver resection group received significantly more intravenous fluid on the day of theatre with a median of 3 (2.5-4) litres *versus* 2 (2-2.2) litres (p<0.01) (Table 7.2).

Despite the intravenous fluid restriction regime and use of non-steroidal anti-inflammatory analgesics we did not encounter any adverse effect on renal function. Liver transaminases were raised postoperatively in the group undergoing liver resection but quickly returned to normal levels. 2 patients undergoing liver resection required a postoperative blood transfusion compared with no patients undergoing colonic resection (Table 7.3).

The median time to first bowel motion for patients undergoing colorectal resection was 4.5 (4-5) days compared with 4 (3-5) days for patients undergoing liver resection (p=0.22). The median hospital stay was 4.5 (4-6) days for patients undergoing colorectal

resection compared with 4 (3-6) days for patients undergoing liver resection ($p=0.43$) (Figure 7.1).

2 patients undergoing liver resection developed small postoperative fluid collections which did not require treatment. 1 liver resection patient was re-admitted on postoperative day 7 with wound pain which settled with analgesia. There were no complications in the colonic resection group.

Table 7.1 Baseline Characteristics for patients undergoing colonic/ liver resection

		Colon resection	Liver resection
N		10	10
Age (years)		74 (61 - 83)	61 (56 - 66)
Sex	Male	5	6
	Female	5	4
ASA Grade	1	1	3
	2	7	6
	3	2	1
	4	0	0
Mean operating time (mins)		120	130
Operation	5 Right Hemicolectomy		1 Lobectomy
			1 Trisegmentectomy
	5 Left Hemicolectomy		3 Bisegmentectomy
			5 Segmentectomy

Values are median (interquartile range)

Table 7.2 Opioid and intravenous fluid intake for colon/ liver resection patients

	Colon resection (n=10)	Liver resection (n=10)	
Morphine Day 0 (mg)	31 (7-42)	16 (5-28)	P=0.01
Morphine Day 1 (mg)	31 (21-43)	21 (9-34)	P=0.13
IV Fluid Day 0 (mls)	2000 (2000-2200)	3000 (2500-4000)	P<0.01
IV Fluid Day 1 (mls)	2000 (1500-2000)	2250 (1000-2500)	P=0.36

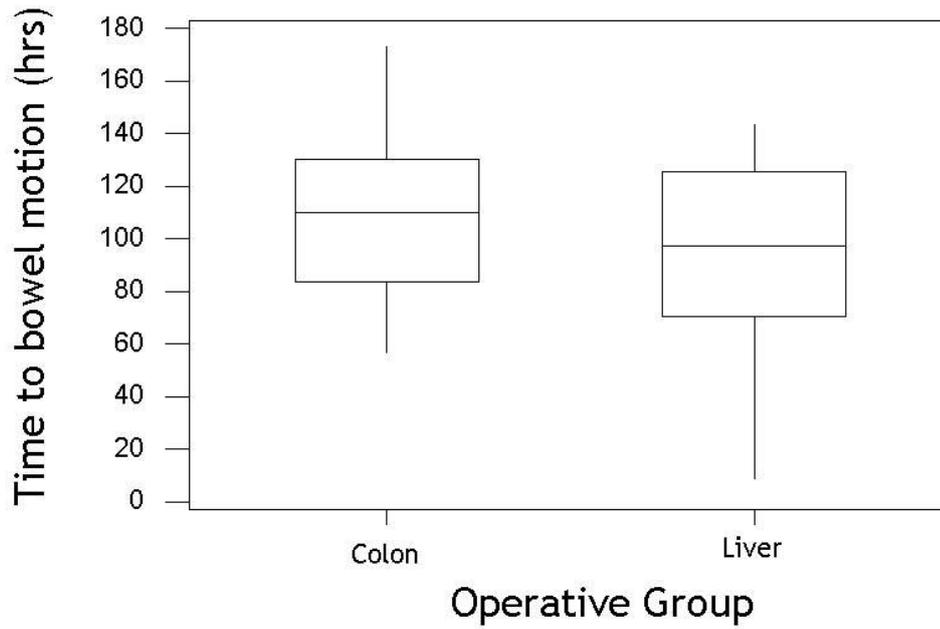
Values are median (interquartile range)

Table 7.3 Blood parameters for patients undergoing colonic/ liver resection

Colon patients	Pre-op	Day 1	Day 2	Day 3
Hb	12.3 (11.3-13.5)	12.3 (11.6-13.1)	11.5 (10.2-11.8)	11.8 (10.3-12.7)
Urea	5.4 (4.7-7.2)	5.2 (4.7-6.9)	5.5 (3.8-7.1)	5.0 (4.1-8.8)
Cr	97 (87-108)	91 (85-129)	93 (86-110)	97 (92-105)
Alb	42 (41-43)	37 (36-39)	36 (36-38)	36 (34-41)
Liver Patients	Pre-op	Day 1	Day 2	Day 3
Hb	13.2 (12.3-13.9)	10.5 (10.1-12.4)	11.0 (9.1-11.7)	9.8 (8.8-10.9)
Urea	4.5 (4.0-5.0)	5.5 (3.8-6.3)	4.0 (2.8-5.3)	4.2 (3.3-5.1)
Cr	87 (74-100)	83 (68-93)	82 (63-101)	76 (59-100)
Alb	44 (41-46)	32 (26-34)	33 (32-35)	35 (30-35)
AST	23 (21-33)	354 (201-530)	233 (115-457)	122 (89-205)
ALT	21 (16-22)	351 (204-579)	351 (178-918)	260 (149-628)

Values are median (interquartile range)

Figure 7.1 Time to return of gastrointestinal function: boxes show median and interquartile range; whiskers give range by study group for patients undergoing colon/ liver resection



7.4 Discussion

The results of the study suggest that the colonic resection itself has little effect on the duration of ileus after major abdominal surgery. The colonic resection group did receive significantly more opioid analgesia postoperatively which should have had the effect of delaying the return of gastrointestinal function in this group. We would have expected this to exaggerate the difference between the groups however this was not borne out by our results. The liver resection group received more intravenous fluid in the postoperative period but the effect that this may have had on duration of ileus is not yet clear from clinical trials. It is also worth noting that all of the liver patients had undergone previous colectomy for removal of the primary tumour. We could have expected this to reduce transit times and possibly exaggerate the difference between the groups but this was not borne out by the results.

It is difficult to identify the perfect control group for the comparison of colonic resection in a clinical setting. There may be inherent differences between the two groups that we are unaware of which may affect the duration of ileus. However we did not see any clinically relevant difference relating to colonic resection and the return of gastrointestinal function.

While the number of patients in the study is small the results would be in line with previous animal studies relating to the site and extent of operative dissection and the duration of postoperative ileus^{137, 138, 152, 278}. Our results would however contradict in vitro studies suggesting impairment of muscle function from leucocytic infiltration secondary

to manipulation of the bowel^{154, 156}. Larger studies would be required to further validate the results of our study.

The study also demonstrates the effects of a fast-track protocol on recovery and hospital stay following major abdominal surgery. In both the liver resection and the colonic resection patients, median discharge was on the fourth postoperative day with only 1 subsequent readmission.

CHAPTER 8

CONCLUSIONS

Some of the major recent advances in the development of modern surgery have been concerned with perioperative care and recovery of the patient following surgery. Interest in recovery has focused on both the efficacy of individual interventions as well as processes and pathways to improve outcome. Improvements in perioperative recovery have allowed for many surgical procedures to be carried out on an outpatient or 'day-surgery' basis which in the past would have required an in-patient stay. This has benefits not only for the patient who has a faster recovery but for healthcare systems and society in general as costly inpatient beds are reduced and patients return to work more quickly. As experience has grown in this area the principles of rapid recovery have been applied to an increasing number of procedures. It is on this background that the idea of 'fast-track' surgery has become popular over the last decade.

Fast-track surgery refers to an approach proposed by Professor Henrik Kehlet. The idea is that through a multidisciplinary, protocol-driven approach and using evidence-based recovery techniques the stress response to surgery can be modified to reduce end-organ dysfunction and promote a more rapid recovery. Using such an approach Kehlet's group have reported hospital stay following colorectal resection of around 2-3 days^{174, 213, 263}. Further applying his ideas to orthopaedic²⁷⁹, gynaecological²⁵³ and vascular surgery²⁵², similar improvements in recovery have been suggested. These initial findings have so far been limited to case series carried out by enthusiasts and have not been widely adopted into clinical practice. They have also drawn criticism regarding the safety of such rapid discharge from hospital and the burden placed on primary care and the wider community.

To investigate the effects of both individual interventions and the use of fast-track recovery protocols we carried out a review of the recent medical literature. Following this we were able to draw certain conclusions regarding the efficacy of different aspects of perioperative clinical practice. In particular we focused on recovery following major abdominal surgery including colorectal resection. It is clear from reviewing the evidence that many of the interventions that are still made are based on traditions of care passed on through an apprenticeship model of training with little basis in clinical science.

The use of nasogastric tubes has until recently been routine practice suggested to reduce postoperative ileus, nausea and vomiting. It has also been claimed to reduce aspiration, wound dehiscence and anastomotic leakage. There is however no evidence to support these claims with significant patient discomfort and increased respiratory complications a likely side-effect. The use of nasogastric tubes also delays the introduction of oral diet.

Providing oral diet for patients after gastrointestinal surgery is another area where practice is slowly changing. It is now clear from the literature that the majority of patients will tolerate diet and oral fluids immediately after surgery with no detrimental effects. Concerns over disruption of anastomoses or an increased incidence of aspiration have not been borne out although improvements in overall outcome have been difficult to prove.

Intra-peritoneal drains date back to the very earliest pioneers of surgery and for almost as long there has been controversy over their use. Placing drains after elective gastrointestinal surgery is not supported by current evidence. The drain is rapidly encapsulated

and does not drain the general peritoneal cavity, provoking its own foreign body response and serous exudate. Furthermore, there is no evidence to suggest that drains reduce or control the effect of an anastomotic leak.

Mechanical bowel preparation is yet another area that has been steeped in surgical dogma. Its use dates to around the Second World War when surgeons recognised that infective complications following gastrointestinal surgery were common due to the high bacterial count of colonic content. Since its widespread acceptance into clinical practice there have been a number of important developments not least the overwhelming evidence for antibiotic prophylaxis in colorectal surgery. Despite this the efficacy of bowel preparation has not been fully re-examined. The evidence that is available suggests that at the very least there is no difference in complication rate when avoiding the use of bowel preparation and this approach may even carry a reduced rate of anastomotic leakage.

With a change in practice away from the use of nasogastric tubes and toward early feeding of patients postoperatively, the problem of postoperative ileus has come under close scrutiny. Ileus has a multifactorial pathophysiology and is not clearly understood. It is also a major source of morbidity following abdominal surgery. Many factors influencing the duration of ileus have been investigated including the extent, location and duration of surgery, the effect of minimally invasive surgery and also opioid analgesics and other pharmacological agents. Up to this point the most significant single intervention has been that of thoracic epidural analgesia which is thought to work by

blocking the spinal reflex arc partly responsible for the delay in return of gastrointestinal function. These results have led to thoracic epidural analgesia becoming the gold standard for elective colorectal surgery and allowing opioid sparing with further benefits in terms of reducing postoperative ileus.

During the course of our scientific work ileus has been a significant focus. We investigated further the effect of bowel manipulation and resection by comparing a group of patients undergoing colonic resection and a group of patients undergoing liver resection. The patients in the liver resection group had no bowel handling during major abdominal surgery of similar duration to the colonic group. The same recovery pathway was used in each group. We found no difference in the duration of ileus between the two groups (median 4.5 (i.q.r. 4-5) *versus* 4 (3-5) days) suggesting that bowel handling and the act of colonic resection have little clinically relevant effect on the duration of ileus.

The use of minimally invasive techniques or laparoscopic surgery is an increasingly popular topic within abdominal surgery. After a rapid early uptake of the technique in the early 1990's it fell out of favour after reports of compromise to the oncological clearance of colorectal cancer. It has taken over a decade to recover and now its equivalence to open surgery in terms of oncological outcome is in little doubt. The advantages proposed for laparoscopic surgery have been based on more rapid short-term recovery and reduced postoperative complications. While improvements in recovery have certainly been proven it is not clear whether these relate to the technique itself or to the differences in recovery pathways used postoperatively. Laparoscopic surgeons have tended to be among the more

progressive encouraging early feeding and mobilisation and it may be this that has led to the reductions in hospital stay. It has been suggested that applying the same recovery pathways to open surgery in the form of 'fast-track' surgery can lead to comparable results.

To investigate this further we studied a prospective group of patients undergoing elective colorectal resection using either open or laparoscopic-assisted surgery. We applied the same fast-track recovery protocol to both groups of patients. We found that when patients were aggressively rehabilitated there was no difference in pain (global $p=0.24-0.74$), return of gastrointestinal function (median 5.3 (i.q.r. 4.1-6.2) *versus* 4.2 (3.1, 5.8) days; $p=0.70$) or hospital stay (5.8 (4.1-7.8) *versus* 5.9 (4.1-7.8) days; $p=0.99$) between the two groups. There were no obvious differences in postoperative complications although the study was not powered to look at this endpoint. The study suggests that before laparoscopic surgery is introduced more widely there needs to be further research carried out to define the potential advantages. The technique is significantly more expensive than open surgery therefore unless there are benefits with respect to long-term complications its cost-effectiveness remains in doubt.

It is clear that a number of areas regarding laparoscopic surgery and the effect on recovery require further study. While certain procedures can be carried out entirely laparoscopically others such as colorectal resection require a limited laparotomy either for the purposes of anastomosis or specimen retrieval (laparoscopically-assisted). The overall effect of incision size on recovery following abdominal surgery has never been

clearly defined. With the introduction of laparoscopic cholecystectomy the benefits in terms of reduced analgesic requirement, hospital stay and convalescence were clear when compared with conventional cholecystectomy²⁸⁰. However when compared with mini-laparotomy cholecystectomy through a 6cm incision the benefits in short-term recovery disappear^{281, 282, 115}. Colorectal resection can feasibly be carried out through incisions comparable to the size of retrieval wounds used during laparoscopically-assisted procedures²⁸³. It may be that below a critical incision length there is little difference in recovery between open and laparoscopic surgery. Further randomised trials in this area are required to clearly define the role of incision length in postoperative recovery.

Following on from the perceived benefits of laparoscopic surgery is the introduction of the idea of “no scar surgery”. With the advances in flexible endoscopy there has been interest in the feasibility of natural orifice trans-luminal endoscopic surgery (N.O.T.E.S.). This new concept involves gaining access to the peritoneal cavity via a transgastric, transcolonic, transvesical or transvaginal route by creating an intentional perforation. The theoretical advantages of this approach include reduced abdominal wall pain due to the absence of an incision, with a reduction in wound infection, hernia formation and adhesions. Until recently experiments have been limited to the animal model. A wide variety of procedures have been reported from liver biopsy and cholecystectomy to splenectomy and gastrojejunostomy²⁸⁴⁻²⁸⁷. The first human procedure was reported by Rao and Reddy in India who carried out a transgastric appendicectomy on a patient with severe abdominal wall burns (oral/ video confirmation only). This was followed in April 2007 by a cholecystectomy via the transvaginal route carried out in Strasbourg by

Professor Marescaux. While in an early stage of its development a number of technical challenges have arisen including closure techniques, instrument limitations, methods of retraction and dealing with complications. There is also little evidence thus far as to whether the theoretical benefits in terms of recovery and morbidity will actually be realised. Further trials in this exciting area will be required before the role of natural orifice surgery can be determined.

The use of intravenous fluids during the perioperative period is commonplace but despite this, evidence regarding its effect on patient recovery has been limited. In 2002 Lobo et al. published a trial in the *Lancet* suggesting that following a regime of restricted intravenous fluid and sodium could reduce both duration of ileus and hospital stay²³². The study suffered from limited numbers and the lack of blinding and so we decided to carry out a large randomised controlled trial to test the hypothesis. Our findings suggest that using a restricted intraoperative fluid protocol, postoperative fluid and sodium restriction has no effect on return of gastrointestinal function or hospital stay. There is apparent contradiction between the findings of our trial and the Lobo trial however on closer examination of the results clear conclusions can be reached. Following the Lobo trial and a further study by Brandstrup²³³ reporting reduced complications with a restricted fluid regime it was felt unethical to use the volumes of intravenous fluid reported in these studies. The previous studies had given up to 6 litres of fluid on the day of theatre which at the time was not excessive when compared with retrospective reviews of practice. This large difference in fluid volumes is the likely reason for the differences seen in postoperative outcome. Despite a large cumulative difference in intravenous fluid and

sodium in our trial we limited the control arm to around 3 litres of fluid on the day of operation. By comparing the results from the three trials it is clear that the most important period for fluid balance is the immediate perioperative phase, at the height of the metabolic-endocrine response. During the first 24 hours the body retains any excess fluid causing tissue oedema, which can lead to increased complications, duration of ileus and in turn hospital stay. After the immediate perioperative phase the body's own homeostatic mechanisms are more able to cope with any fluid excess.

The wider interest in fluid therapy around the time of surgery has increased over the period of our studies. New techniques have developed particularly relating to the monitoring of fluids and intravascular volume. Studies regarding the use of oesophageal Doppler monitoring suggest that particularly where large fluid shifts are likely or significant co-morbidity is present that goal-directed therapy may improve outcome²³⁷⁻²³⁹. Even newer techniques are now available allowing cardiac output to be measured from a peripheral arterial-line catheter. This will mean that guided therapy will be possible in awake patients during the postoperative period rather than solely ventilated patients (Lithium Dilution Cardiac Output (LiDCO monitors)). Further studies are required to determine the effect of goal-directed fluids on recovery and whether it is beneficial when compared to a protocol-driven approach such as the one used in the present study. The role of new technology will also require additional research to compare different types of monitoring, which patients derive most benefit and the duration for which monitoring is required.

While much of the recent interest has focussed on the volume of intravenous fluid administered in the perioperative period, conclusions can also be reached about the optimal type of fluid. Evidence suggests that large volume administration of salt containing fluids, particularly normal saline, may be detrimental to patient recovery. Balanced fluids such as Hartmann's solution reduce the incidence of hyperchloraemic acidosis and the resulting reduction in gastric mucosal perfusion when compared to saline-based fluids²²⁵. Hyperchloraemia has also been shown to lead to reduced renal blood flow and increased nausea, vomiting and abdominal pain^{223, 225, 288}.

While it is true that crystalloid and sodium restriction does seem to improve postoperative outcome, some of the benefit attributed to the approach may be due to the difference in the relative administration of colloid. This is particularly clear in the goal-directed fluid trials where patients in the monitored arm received early administration of approximately 500mls of extra colloid compared to the control group. It may be that as suggested in our own trial the timing as well as type of fluid is important for recovery. Even in the trials of crystalloid restriction, colloids were used predominantly to treat clinically apparent hypovolaemia and this may have had an influence on patient outcome. Further randomised trials will be required to determine the relative importance of these different facets. Current advice should include the use of balanced fluids, relative crystalloid restriction for maintenance requirements and the early use of colloids guided where possible by monitoring of secondary circulatory variables.

While we have concentrated on certain individual interventions during the period of study we have also gained in experience using fast-track recovery techniques. By applying fast-track principles to an area of surgery where it has not previously been reported we were able to show significant reductions in hospital stay following liver resection when compared to data in the medical literature. We looked at patients undergoing elective colorectal resection both before and during the running of the randomised controlled trial and found that in our practice the recovery protocol used led to a reduction in postoperative stay of around 2 days (5.8 (4.1-7.8) *versus* 7.5 (6.0-9.0) days). This has significant implications both for patients and for healthcare systems. While the length of stay for patients in our trial is longer than that reported by Kehlet's group (day 3 *versus* 5) we did not find the high rates of re-admission experienced in their practice. We found the technique to be safe with no adverse effects directly attributable to rapid discharge.

Advances in postoperative recovery continue to make surgery safer for the majority of patients. Recovery protocols draw together evidence-based practice applying individual interventions for a synergistic effect. Further research is necessary particularly in the areas of intravenous fluid management and minimally invasive surgery so that these benefits can be realised still further.

APPENDIX I

UNIVERSITY DEPARTMENT OF SURGERY

and

ROBERTSON CENTRE FOR BIOSTATISTICS

PATIENT INFORMATION SHEET (Version 1.0)



UNIVERSITY
of
GLASGOW

Effect of intravenous fluid restriction on patient recovery following major abdominal surgery (A single blind pragmatic randomised clinical trial).

Dear Patient

Thank you for taking the time to read this information sheet. Your general practitioner has referred you to this hospital because you need an operation on your bowel. We would like to invite you to participate in a study whose aim is to compare recovery between traditional fluid administration versus restricted fluid administration post-operatively.

What is the purpose of the study

It has been normal surgical practice to rest the bowel after abdominal surgery. While this is happening fluids are administered through a drip in your arm. Oral fluids are commenced 2-3 days after your operation, progressing to light diet – soups and puddings – and then on to a normal diet. The fluids given through the drip contain water, salt and glucose. Some recent studies suggest that these fluids increase your weight and slow your recovery. In addition we now know that your bowel heals much faster than previously thought and will tolerate liquids *and possibly a light diet* within a few hours of operation.

What do I have to do?

Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. If you agree to participate in the study the decision on who receives traditional fluids through the arm and who receives restricted fluids will be made randomly by a computer which has no information about the individual. Patients in each group then have a different treatment and these are compared. In this trial you will not know which treatment group you are in, nor will the Consultant assessing your recovery. All the other doctors and nurses

APPENDIX I (continued)

involved in your care will know what fluids you are receiving in case a change in your treatment is required.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. It should be noted that your participation in this study may not be of direct benefit to you, but could help in the development of treatment for future patients. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Will my taking part in this study be kept confidential?

All information, which is collected, about you during the course of the research will be kept strictly confidential. Your own GP will be notified of your participation in the trial, as will any other medical practitioner involved in your care, and by participating in the study you will be agreeing to this..

Contact for Further Information

If you have any questions you would like to ask about the study, or your involvement in the study, please contact _____ during normal office hours.

Finally, we would remind you that taking part in this study is entirely voluntary, and if you decide to join, you can stop at any time without giving a reason. Take time to make your decision, and to discuss the study with your family. Rest assured that whatever decision you make, your surgeon, the nurses, and your GP will continue to give you their best possible care and attention.

Signed.....

APPENDIX II

WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project :

Effect of intravenous fluids and sodium restriction on patient recovery following major abdominal surgery.

A single blind pragmatic randomised clinical trial.

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

f.....

give my consent to the research procedures above, the nature, purpose and possible consequences of which have been described to me

by.....

Patient's signature.....Date.....

Doctor's signature.....

APPENDIX IV

FLUID RESTRICTION STUDY PATIENT

NAME

RESTRICTED	<input type="checkbox"/>	STANDARD	<input type="checkbox"/>
------------	--------------------------	----------	--------------------------

PRE-OP: Allow diet until 6 hours pre-op
Encourage clear fluids until 2 hours pre-op

FLUIDS: Restricted - 2 L 4% Dextrose/ 0.18% Saline daily
- Stop IV fluids after 24hrs
Standard - 1L N. Saline + 2L 5% Dextrose daily
- No restriction on fluid intake
- IV fluids to stop day 3

(for further information refer to the guidelines in the Junior Doctors Room)

ANALGESIA:

Morphine by PCA IV

Paracetamol 1G qid either PR or PO

NSAIDs allowed after 48hrs

Tramadol 50mg prn 6hrly only after PCA optimised

Patients to have Fortisip drinks twice daily from Day 1.

BOWELS

Time of first flatus Time of first motion

WEIGHT

.....
Pre-op	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

HEIGHT

.....

Please remind patients to fill in their pain and nausea scores at 8am and 8pm each day

APPENDIX V

FLUID RESTRICTION STUDY GUIDELINES

We aim to include most patients having major elective abdominal surgery. Patients with significant co-morbidity will not be included. Furthermore patients having operations involving pelvic dissection will not be included

Patients will have a sheet in their observations folder indicating if they are included in the study.

Pre-op:

- Patient's will have their **weight** measured.
- They should all be prescribed **Clexane 20 mg subcut. at 8pm** for DVT prophylaxis and wear **TED stockings** until mobile.
- They can take diet until 6 hours pre-op and **clear fluids until 2 hours pre-op.**

Bowel preparation:

- Patients for right colon resections do not require bowel prep.
- Patients for left colon resection should have **1 Phosphate enema the evening before and 1 Phosphate enema on the day of surgery.**

IV Fluids:

Restricted

- **2 L 4% Dextrose/ 0.18% Saline per day.**
- Encourage oral fluids from day 1 and stop IV fluids at midnight on day 1.
- **Fluid deficit will be judged by urine output (<1.5ml/kg over past 4 hrs) or hypotension (<85-90 mmHg systolic) and replaced as colloid. Fluid challenges of Gelofusine or blood (depending on Hb) in 250ml boluses at 15min intervals until urine output and/or BP improved and CVP normalised**
Remember that the patient can drink so encourage oral fluids
- Remove urinary catheter at midnight on day 1.

Standard

- **1 L N. Saline + 2 L 5% Dextrose per day.**
- Resuscitate as clinically indicated with the fluid of your choice. No restriction to fluid regime. Fluids to stop when clinicians feel it is safe after day 3.

APPENDIX V (continued)

Oral intake:

- **Encourage oral fluids immediately** postoperatively
- **Two Fortisip drinks daily** until discharge.
- Diet to be introduced as soon as patient will tolerate.

Bloods:

- Patients should have **FBC, U+E, Albumin daily** including pre-operatively and **the evening of theatre**.
Other blood tests should be taken as clinically indicated.

Analgesia:

- **Paracetamol** 1g q.i.d. for every patient
- **Ibuprofen** 600mg orally either as required or regularly only after **48hrs post-op**.
If patient gives a history of previous peptic ulcer disease/ dyspeptic symptoms the prescribe with Losec 40mg.
If patient gives a history of current ulcer or renal impairment **DO NOT PRESCRIBE**
- **PCA Morphine** will be used in most cases but this should be stopped by midnight of day 2
- **Tramadol** 100mg prn 6hrly IV/IM for breakthrough pain
Do not prescribe any other analgesic agents and try to avoid opiate or codeine based medication as much as possible.

Monitoring:

A record will be kept of:

- **IV and oral fluid intake**
- **Urine output hourly while catheter in-situ**
- **Analgesic and antiemetic requirement**
- **Blood results daily**
- **Height and daily weights**
- **Pain and nausea scores twice daily** (*please remind the patient to fill in form*)
- **Time of first flatus and bowel motion**
- **Complications**

Follow up

Patients will be phoned daily by the research nurse daily for 2 weeks and should be seen at the outpatient clinic 1 week after discharge.

APPENDIX VII

Fluid and Sodium Restriction Study

Version 1.0

Page 1

Centre <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <small>02</small>	Initials <input type="text"/> <small>03</small>	Date of Visit <input type="text"/> <input type="text"/> <input type="text"/> <small>D D M M Y Y⁰⁴</small>
---	--	---	--

A. DETAILS

1. Operation: _____
2. Indication: Cancer ¹ Diverticulae ² Polyp ³ Other ⁴ specify _____ ⁰⁷
3. Theatre date:
D D M M Y Y⁰⁵
4. Height:
(cm) ⁰⁹
5. Weight:
(kg) ¹⁰
6. Anaesthetic Score
(range 1-5): ¹¹

B. FLUID

1. Regime: Standard ¹ Restricted ²
2. Intake:
- | | 4% Dex./0.18% Sal. | N. Saline | 5% Dextrose | Oral | Other | Other specify |
|-------|---|---|---|---|---|---------------------|
| Day 0 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹⁵ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹⁶ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹⁷ | _____ ¹⁸ |
| Day 1 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ¹⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁰ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²¹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²³ | _____ ²⁴ |
| Day 2 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁵ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁶ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ²⁹ | _____ ³⁰ |
| Day 3 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³¹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³⁵ | _____ ³⁶ |
| Day 4 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ³⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁰ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴¹ | _____ ⁴² |
| Day 5 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁵ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁶ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁷ | _____ ⁴⁸ |
| Day 6 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁴⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁰ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵¹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵³ | _____ ⁵⁴ |
| Day 7 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁵ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁶ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>ml</small> ⁵⁹ | _____ ⁶⁰ |

C. ANALGESIA

1. Epidural in-situ: Day 0 ⁶¹ Day 1 ⁶² Day 2 ⁶³
2. 24 hr PCA requirement: Day 0
mg ⁶⁴ Day 1
mg ⁶⁵ Day 2
mg ⁶⁶
3. Additional Requirement:
- | | Paracetamol | Ibuprofen | Morphine | Other | Other specify |
|-------|--|--|--|--|----------------------|
| Day 0 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁶⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁶⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁶⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁰ | _____ ⁷¹ |
| Day 1 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁵ | _____ ⁷⁶ |
| Day 2 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁷⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁰ | _____ ⁸¹ |
| Day 3 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁵ | _____ ⁸⁶ |
| Day 4 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁸⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁰ | _____ ⁹¹ |
| Day 5 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁵ | _____ ⁹⁶ |
| Day 6 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁷ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁸ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ⁹⁹ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ¹⁰⁰ | _____ ¹⁰¹ |
| Day 7 | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ¹⁰² | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ¹⁰³ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ¹⁰⁴ | <input type="text"/> <input type="text"/> <input type="text"/>
<small>mg</small> ¹⁰⁵ | _____ ¹⁰⁶ |

APPENDIX VII (continued)

Fluid and Sodium Restriction Study

Version 1.0

Page 2

Centre <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <small>02</small>	Initials <input type="text"/> <small>03</small>	Date of Visit <input type="text"/> <small>D D M M Y Y⁰⁴</small>
---	--	---	--

A. ANTIEMETIC

1. Requirement:

	Metoclopramide	Prochlorperazine	Ondansetron
Day 0	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>05</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>06</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>07</small>
Day 1	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>08</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>09</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>10</small>
Day 2	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>11</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>12</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>13</small>
Day 3	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>14</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>15</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>16</small>
Day 4	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>17</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>18</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>19</small>
Day 5	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>20</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>21</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>22</small>
Day 6	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>23</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>24</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>25</small>
Day 7	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>26</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>27</small>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> mg <small>28</small>

B. WEIGHT, PAIN AND NAUSEA SCORES

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
1. Weight (kg)	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>29</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>30</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>31</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>32</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>33</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>34</small>	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <small>35</small>
2. VAS at rest	<input type="text"/> <input type="text"/> am <small>36</small>	<input type="text"/> <input type="text"/> am <small>37</small>	<input type="text"/> <input type="text"/> am <small>38</small>	<input type="text"/> <input type="text"/> am <small>39</small>	<input type="text"/> <input type="text"/> am <small>40</small>	<input type="text"/> <input type="text"/> am <small>41</small>	<input type="text"/> <input type="text"/> am <small>42</small>
	<input type="text"/> <input type="text"/> pm <small>43</small>	<input type="text"/> <input type="text"/> pm <small>44</small>	<input type="text"/> <input type="text"/> pm <small>45</small>	<input type="text"/> <input type="text"/> pm <small>46</small>	<input type="text"/> <input type="text"/> pm <small>47</small>	<input type="text"/> <input type="text"/> pm <small>48</small>	<input type="text"/> <input type="text"/> pm <small>49</small>
3. VAS move	<input type="text"/> <input type="text"/> am <small>50</small>	<input type="text"/> <input type="text"/> am <small>51</small>	<input type="text"/> <input type="text"/> am <small>52</small>	<input type="text"/> <input type="text"/> am <small>53</small>	<input type="text"/> <input type="text"/> am <small>54</small>	<input type="text"/> <input type="text"/> am <small>55</small>	<input type="text"/> <input type="text"/> am <small>56</small>
	<input type="text"/> <input type="text"/> pm <small>57</small>	<input type="text"/> <input type="text"/> pm <small>58</small>	<input type="text"/> <input type="text"/> pm <small>59</small>	<input type="text"/> <input type="text"/> pm <small>60</small>	<input type="text"/> <input type="text"/> pm <small>61</small>	<input type="text"/> <input type="text"/> pm <small>62</small>	<input type="text"/> <input type="text"/> pm <small>63</small>
4. Nausea score	<input type="text"/> am <small>64</small>	<input type="text"/> am <small>65</small>	<input type="text"/> am <small>66</small>	<input type="text"/> am <small>67</small>	<input type="text"/> am <small>68</small>	<input type="text"/> am <small>69</small>	<input type="text"/> am <small>70</small>
	<input type="text"/> pm <small>71</small>	<input type="text"/> pm <small>72</small>	<input type="text"/> pm <small>73</small>	<input type="text"/> pm <small>74</small>	<input type="text"/> pm <small>75</small>	<input type="text"/> pm <small>76</small>	<input type="text"/> pm <small>77</small>

C. BLOOD RESULTS

	Pre-op	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. Na (mmol)	<input type="text"/> <input type="text"/> <input type="text"/> <small>78</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>79</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>80</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>81</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>82</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>83</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>84</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>85</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>86</small>
2. K ⁺ (mmol)	<input type="text"/> <input type="text"/> <input type="text"/> <small>87</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>88</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>89</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>90</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>91</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>92</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>93</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>94</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>95</small>
3. Urea (mmol)	<input type="text"/> <input type="text"/> <input type="text"/> <small>96</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>97</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>98</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>99</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>100</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>101</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>102</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>103</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>104</small>
4. Cr (μmol)	<input type="text"/> <input type="text"/> <input type="text"/> <small>105</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>106</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>107</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>108</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>109</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>110</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>111</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>112</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>113</small>
5. Hb (g)	<input type="text"/> <input type="text"/> <input type="text"/> <small>114</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>115</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>116</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>117</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>118</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>119</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>120</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>121</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>122</small>
6. Hct. (%)	<input type="text"/> <input type="text"/> <input type="text"/> <small>123</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>124</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>125</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>126</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>127</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>128</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>129</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>130</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>131</small>
7. WCC (10 ⁹ /l)	<input type="text"/> <input type="text"/> <input type="text"/> <small>132</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>133</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>134</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>135</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>136</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>137</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>138</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>139</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>140</small>
8. Albumin (g)	<input type="text"/> <input type="text"/> <input type="text"/> <small>141</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>142</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>143</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>144</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>145</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>146</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>147</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>148</small>	<input type="text"/> <input type="text"/> <input type="text"/> <small>149</small>

APPENDIX VII (continued)

Fluid and Sodium Restriction Study

Version 1.0

Visual Analogue Pain Scores, Page 1

Centre <input type="text"/> <input type="text"/> <input type="text"/> 01	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> 02	Name of Patient _____	Date of Visit <input type="text"/> <input type="text"/> <input type="text"/> D D M M Y Y 03
--	--	--------------------------	--

1. (Day 1)

8am Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8am Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

2. (Day 2)

8am Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8am Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

3. (Day 3)

8am Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8am Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

4. (Day 4)

8am Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8am Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 _____ 5 _____ 10
No Pain Moderate Worst Pain imaginable

APPENDIX VII (continued)

Fluid and Sodium Restriction Study

Version 1.0

Visual Analogue Pain Scores, Page 2

Centre <input type="text"/> <input type="text"/> <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>02</small>	Name of Patient _____	Date of Visit <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <small>D D M M Y Y⁰⁴</small>
---	---	--------------------------	---

5. (Day 5)

8am Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8am Move 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 5 10
No Pain Moderate Worst Pain imaginable

6. (Day 6)

8am Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8am Move 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 5 10
No Pain Moderate Worst Pain imaginable

7. (Day 7)

8am Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8am Move 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Rest 0 5 10
No Pain Moderate Worst Pain imaginable

8pm Move 0 5 10
No Pain Moderate Worst Pain imaginable

APPENDIX VII (continued)

Fluid and Sodium Restriction Study

Version 1.0

Nausea Scores

Centre <input type="text"/> <input type="text"/> <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>02</small>	Name of Patient _____	Date of Visit <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>D D M M Y Y⁹⁴</small>
---	---	--------------------------	---

B. NAUSEA SCORES

0 = no nausea

1 = mild nausea, no treatment

2 = moderate nausea, response to treatment

3 = moderate nausea, no response to treatment

4 = severe nausea

1. (Day 1)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
2. (Day 2)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
3. (Day 3)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
4. (Day 4)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
5. (Day 5)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
6. (Day 6)	8am	0	1	2	3	4
	8pm	0	1	2	3	4
7. (Day 7)	8am	0	1	2	3	4
	8pm	0	1	2	3	4

APPENDIX VIII

Fluid and Sodium Restriction Study

SF36, Page 1

Draft 02

Centre <input type="text"/> <input type="text"/> <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>02</small>	Initials <input type="text"/> <input type="text"/> <input type="text"/> <small>03</small>	Date of Visit <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <small>D D M M Y Y⁰⁴</small>
---	---	---	---

Thank you for completing this booklet. Please follow the instructions.

Confidentiality: Your name and address do not appear anywhere on this booklet. The information that you give will not be used in any way that could identify you personally.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

GENERAL HEALTH

For questions 1 and 2, please **circle the number** that best describes your health.

- | | | | | | |
|---|------------------------|------------------------|------------------------|------------------------|------------------------|
| | Excellent | Very good | Good | Fair | Poor |
| 1. In general, would you say your health is: | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 |
| | | | | | <small>05</small> |
| | Much better | Somewhat better | About the same | Somewhat worse | Much worse |
| 2. Compared to one year ago, how would you rate your health in general now? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 |
| | | | | | <small>06</small> |

HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do in a typical day. Does your health limit you in these activities? If so, how much? **Please circle one number on each line.**

- | | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|------------------------|------------------------|------------------------|
| a) Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>07</small> |
| b) Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>08</small> |
| c) Lifting or carrying groceries. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>09</small> |
| d) Climbing several flights of stairs | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>10</small> |
| e) Climbing one flight of stairs. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>11</small> |
| f) Bending, kneeling or stooping. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>12</small> |
| g) Walking more than a mile . | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>13</small> |
| h) Walking half a mile . | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>14</small> |
| i) Walking 100 yards . | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>15</small> |
| j) Bathing or dressing yourself. | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 |
| | | | <small>16</small> |

4. During the **past 4 weeks**, have you had any of the following problems with your work or other daily activities **as a result of your physical health?**

Please **circle 1 for Yes or 2 for No** on each line.

- | | Yes | No |
|--|------------------------|------------------------|
| a) Cut down on the amount of time you spend on work or other activities | <input type="text"/> 1 | <input type="text"/> 2 |
| | | <small>17</small> |
| b) Accomplished less than you would have liked. | <input type="text"/> 1 | <input type="text"/> 2 |
| | | <small>18</small> |
| c) Were limited in the kind of work or other activities. | <input type="text"/> 1 | <input type="text"/> 2 |
| | | <small>19</small> |
| d) Had difficulty performing the work or other activities (for example, it took extra effort). | <input type="text"/> 1 | <input type="text"/> 2 |
| | | <small>20</small> |

APPENDIX VIII (continued)

Fluid and Sodium Restriction Study

SF36, Page 2

Draft 02

Centre <input type="text"/> <input type="text"/> <input type="text"/> <small>01</small>	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>02</small>	Initials <input type="text"/> <input type="text"/> <input type="text"/> <small>03</small>	Date of Visit <input type="text"/> <input type="text"/> <input type="text"/> <small>D D M M Y Y⁰⁴</small>
---	---	---	--

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Please circle 1 for Yes or 2 for No on each line.

- | | Yes | No |
|---|------------------------|--------------------------------------|
| a) Cut down on the amount of time you spend on work or other activities | <input type="text"/> 1 | <input type="text"/> 2 ₀₀ |
| b) Accomplished less than you would have liked. | <input type="text"/> 1 | <input type="text"/> 2 ₀₀ |
| c) Did not do work or other activities as carefully as usual. | <input type="text"/> 1 | <input type="text"/> 2 ₀₇ |

For questions 6, 7 & 8, please circle the number that best describes you and your health.

- | | Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| 6. During the past 4 weeks , to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or other groups? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 ₀₀ |

- | | None | Very Mild | Mild | Moderate | Severe | Very Severe |
|---|------------------------|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| 7. How much bodily pain have you had over the past 4 weeks ? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₀₀ |

- | | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| 8. During the past 4 weeks , how much did pain interfere with your normal work (including both work outside the home and housework)? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 ₁₀ |

YOUR FEELINGS

9. The following questions are about how you feel and how things have been with you during the last month. For each question, please circle the number that best describes the way you have been feeling.

Make sure that you circle one number on each line.

- | | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|------------------------|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| How much time during the past month : | | | | | | |
| a) Did you feel full of life? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₁ |
| b) Have you been a very nervous person? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₂ |
| c) Have you felt so down in the dumps that nothing could cheer you up? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₃ |
| d) Have you felt calm and peaceful? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₄ |
| e) Did you have a lot of energy? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₅ |
| f) Have you felt downhearted and low? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₆ |
| g) Did you feel worn out? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₈ |
| h) Have you been a happy person? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₇ |
| i) Did you feel tired? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₁₉ |
| j) Has your health limited your social activities (like visiting friends or close relatives)? | <input type="text"/> 1 | <input type="text"/> 2 | <input type="text"/> 3 | <input type="text"/> 4 | <input type="text"/> 5 | <input type="text"/> 6 ₂₀ |

APPENDIX VIII (continued)

Fluid and Sodium Restriction Study

SF36, Page 3

Draft 02

Centre <input type="text"/> <input type="text"/> <input type="text"/> ₀₁	Patient No. <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> ₀₂	Initials <input type="text"/> <input type="text"/> ₀₃	Date of Visit <input type="text"/> _D <input type="text"/> _D / <input type="text"/> _M <input type="text"/> _M / <input type="text"/> _Y <input type="text"/> _{Y04}
--	--	---	--

HEALTH GENERAL

10. Please choose the answer that **best** describes how **true** or **false** each of the following statements is for you.

Please circle one number on each line.

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
a) I seem to get ill more easily than other people.	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>	<input type="text" value="5"/>
b) I am as healthy as anyone I know.	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>	<input type="text" value="5"/>
c) I expect my health to get worse.	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>	<input type="text" value="5"/>
d) My health is excellent.	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>	<input type="text" value="5"/>

<hr style="border: none; border-top: 1px solid black; margin-bottom: 5px;"/> <i>Investigators Name</i>	<hr style="border: none; border-top: 1px solid black; margin-bottom: 5px;"/> <i>Investigators Signature</i>	<hr style="border: none; border-top: 1px solid black; margin-bottom: 5px;"/> <i>Date</i>
--	---	--

APPENDIX IX

Fluid and Sodium Restriction Study

*Mr Phil Duffy
Research Office
Western Infirmary
Glasgow
G11 6NT
0141 211 2425*

Dear

It is now three months since you agreed to participate in the above study. To enable us to record your progress I would be obliged if you could complete the enclosed questionnaire and return it in the pre-paid envelope provided.

We would be very interested to know if you were aware of which side of the study you were allocated to. I would therefore be grateful if you could tick the appropriate box on the enclosed sheet and return it along with your questionnaire.

I trust you are having no problems and would like to remind you that I can be contacted on the above number should you require any advice or information.

Thank you for your continued support of this project.

Kind regards

Phil Duffy
Project Manager

APPENDIX IX (continued)

Fluid and Sodium Restriction Study

*Mr Phil Duffy
Research Office
Western Infirmary
Glasgow
G11 6NT
0141 211 2425*

Name _____

Study No: _____

Restricted fluids

Standard fluids

Don't know

REFERENCES

1. Egbert LG, Bant GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patient. *N Engl J Med* 1964; 207: 824-827.
2. Kieholt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. *Am Psychol* 1998; 53: 1209-1218.
3. Wilmore D. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg* 2002; 236(5):643-648.
4. Palmer JF. *Complete Works of John Hunter*. Philadelphia: Haswell, Barrington, Haswell 1935: 622.
5. Kussmaul CA. Heilung von Ileus durch Magenausspülung. *Berl Klin Wschr* 1884; 21: 669-685.
6. Levin AI. A new gastroduodenal catheter. *JAMA* 1921; 76: 1007-9.
7. Wangenstein OH. The early diagnosis of acute intestinal obstruction with comments on pathology and treatment: with a report of successful decompression of three cases of mechanical bowel obstruction by nasal catheter suction siphonage. *West J Surg Obstet Gynaecol* 1932; 40: 1-17.
8. Gerber A, Rogers FA, Smith LL. The treatment of paralytic ileus without the use of gastrointestinal suction. *Surg Gynaecol Obstet* 1958; 107: 247-250.
9. Gerber A. an appraisal of paralytic ileus and the necessity of postoperative gastrointestinal suction. *Surg Gynaecol Obstet* 1963; 117: 294.
10. Shibata Y, Toyoda S, Nimura Y, Miyati M. Patterns of intestinal motility recovery during the early stage following abdominal surgery: Clinical and manometric study. *World J Surg* 1997; 21: 806-810.
11. McIver MA, Benedict EB, Cline JW. Postoperative gaseous distension of the abdomen. *Arch Surg* 1926; 155: 1197-1199.
12. Reasbeck PG, Rice ML, Herbison GP. Nasogastric intubation after intestinal resection. *Surg Gynaecol Obstet* 1984; 158: 354-358.
13. Herrington JL, Edwards WH, Sawyers JL. Elimination of routine use of gastric decompression following operations for gastroduodenal ulcer. *Ann Surg* 1964; 159: 807-818.

14. Meltvedt R Jr, Knecht B, Gibbons G, Stahler C, Stojowski A, Johansen K. Is nasogastric suction necessary after elective colon resection? *Am J Surg* 1985; 149: 620-622.
15. Bauer JJ, Gerlernt IM, Salky BA, Kreel I. Is routine postoperative nasogastric decompression really necessary? *Ann Surg* 1985; 201: 233-236.
16. Argov S, Goldstein I, Barzilai A. Is routine use of nasogastric tube justified in upper abdominal surgery? *Am J Surg* 1980; 139: 849-850.
17. Colvin DB, Lee W, Eisenstat TE, Rubin RJ, Salvati EP. The role of nasointestinal intubation in elective colonic surgery. *Dis Colon Rectum* 1986; 29(5): 295-299.
18. Racette DL, Chang FC, Trekell ME, Farha GJ. Is nasogastric intubation necessary in colon operations? *Am J Surg* 1987; 154: 640-642.
19. Cheadle WG, Vitale GC, MacKie CR, Cuschieri A. Prophylactic postoperative nasogastric decompression. *Ann Surg* 1985; 202(3): 361-366.
20. Nathan BN, Pain JA. Nasogastric suction after elective abdominal surgery: a randomised study. *Ann R Coll Surg Engl* 1991; 73: 291-294.
21. Wolff BG, Pemberton JH, van Heerden JA et al. Elective colon and rectal surgery without nasogastric decompression: a prospective, randomised trial. *Ann Surg* 1989; 209(6): 670-673.
22. Sagar M, Kruegener G, MacFie J. Nasogastric intubation and elective abdominal surgery. *Br J Surg* 1992; 79(11): 1127-1131.
23. Otchy DP, Wolff BG, van Heerden JA, Ilstrup DM, Weaver AL, Winter LD. Does the avoidance of nasogastric decompression following elective abdominal colorectal surgery affect the incidence of incisional hernia? *Dis Colon Rectum* 1995; 38(6): 604-608.
24. Hak Yoo C, Ho Son B, Kon Han W, Kil Pae W. Nasogastric decompression is not necessary in operations for gastric cancer: prospective randomised trial. *Eur J Surg* 2002; 168: 379-383.
25. Akbaba S, Kayaalp C, Savkilioqlu M. Nasogastric decompression after total gastrectomy. *Hepatogastroenterology* 2004; 51(60): 1881-5.
26. Miller DF, Mason JR, McArthur J, Gordon I. A randomised prospective trial comparing three established methods of gastric decompression after vagotomy. *Br J Surg* 1972; 59(8): 605-608.

27. Petrelli NJ, Stulc JP, Rodriguez-Bigas M, Blumenson L. Nasogastric decompression following elective colorectal surgery: a prospective randomised trial. *Am Surg* 1993; 59(10): 632-5.
28. Cunningham J, Temple WJ, Langevin JM, Kortbeek J. A prospective randomised trial of routine postoperative nasogastric decompression in patients with bowel anastomoses. *Canadian J Surg* 1992; 35(6): 629-632.
29. Huerta S, Arteaga JR, Sawicki MP, Liu CD, Livingston EH. Assessment of routine elimination of postoperative nasogastric decompression after Roux-en-Y gastric bypass. *Surgery* 2002; 132(5): 844-848.
30. Friedman SG, Sowerby SA, Del Pin CA, Scher LA, Tortolani AJ. A prospective randomised study of abdominal aortic surgery without postoperative nasogastric decompression. *Cardio Surg* 1996; 4(4): 492-494.
31. Pearl ML, Valea FA, Fischer M, Chalas E. A randomised trial of postoperative nasogastric tube decompression in gynaecologic oncology patients undergoing intra-abdominal surgery. *Obs & Gyn* 1996; 88(3): 399-402.
32. Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. *Ann Surg* 1995; 221(5): 469-478.
33. Nelson R, Tse B, Edwards S. Systematic review of prophylactic nasogastric decompression after abdominal operations. *Br J Surg* 2005; 92: 673-680.
34. Golub RW, Cirocco WC, Golub R. Current trends gastric decompression: a survey of the American Society of Colon and Rectal Surgeons. *Dis Colon Rectum* 1994; 37: 48-51.
35. Billroth T. *Clinical Surgery*. London: The New Sydenham Society, 1881: 307-308.
36. Von Ott. Die Drainage nach Laparotomyie experimentelle untersuchung *Medicinsky Westnick* No: 1878. *Zentralbl Gynakol* 1879; 3: 86-7.
37. Delbert P. Recherches experimentelle sur la lavage au peritoneum. *Ann Gynecol Obstet* 1889; 32: 165-197.
38. Robinson JO. Surgical drainage: an historical perspective. *Br J Surg* 1986; 73: 422-426.
39. Smith SRG, Connolly PW, Crane PW, Gilmore OJA. The effect of surgical drainage materials on colonic healing. *Br J Surg* 1982; 69: 153-155.

40. Yates JL. An experimental study of the local effects of peritoneal drainage. *Surg Gynaecol Obstet* 1905; 1: 473-92
41. Lennox MS. Prophylactic drainage of colonic anastomoses. *Br J Surg* 1984; 71: 10, 11.
42. Canalis F, Ravitch MM. Study of healing of inverting and everting intestinal anastomoses. *Surg Gynecol Obstet* 1968; 126: 109-14.
43. Ellis H. The aetiology of postoperative abdominal adhesions: an experimental study. *Br J Surg* 1962; 219: 10-16.
44. Berliner SD, Burson LC, Lear P. Use and abuse of intraperitoneal drains in colon surgery. *Arch Surg* 1964; 89: 686-690.
45. Manz CW, LaTendresse C, Sako Y. The detrimental effects of drains on colonic anastomoses: an experimental study. *Dis Colon Rectum* 1970; 13: 17-25.
46. Nora PF. Prophylactic abdominal drains. *Arch Surg* 1972; 105: 173-176.
47. Crowson WN, Wilson CS. An experimental study of the effects of drains on colon anastomoses. *Am Surg* 1973; 39: 597-601.
48. Urbach DR, Kennedy ED, Cohen MM. Colon and rectal anastomoses do not require routine drainage: A systematic review and meta-analysis. *Ann Surg* 1999; 229: 174-180.
49. Sehapayak S, McNatt M, Carter HG, Bailey W, Baldwin A. Continuous sump-suction drainage of the pelvis after low anterior resection: A reappraisal. *Dis Colon Rectum* 1973; 16: 485-489.
50. Collins CD, Talbot CH. Pelvic drainage after anterior resection of the rectum. *Arch Surg* 1969; 99: 391.
51. Allen-Mersh TG, Sprague DB, Mann CV, Turner MJ. Pelvic drainage after anterior resection of the rectum. *Dis Colon Rectum* 1989; 32:223-226.
52. Galandiuk S, Fazio VW. Postoperative irrigation-suction drainage after pelvic colonic surgery: A randomised trial. *Dis Colon Rectum* 1991; 34: 223-228.
53. Sagar PM, Hartley MN, MacFie J, Mancey-Jones B, Sedman P, May J. Randomised trial of pelvic drainage after rectal resection. *Dis Colon Rectum* 1995; 38: 254-258.
54. Sagar PM, Couse N, Kerin M, May J, MacFie J. Randomised trial of drainage of colorectal anastomosis. *Br J Surg* 1993; 80: 769-771.

55. Johnson CD, Lamont PM, Orr N, Lennox M. Is a drain necessary after colonic anastomosis? *J R Soc Med* 1989; 82: 661-4.
56. Hoffmann J, Shokouh-Amiri MH, Damm P, Jensen R. A prospective controlled study of prophylactic drainage after colonic anastomoses. *Dis Colon Rectum* 1987; 30: 449-452.
57. Merad F, Yahchouchi E, Hay JM, Fingerhut A, Laborde Y, Langlois-Zantain O. Prophylactic abdominal drainage after elective colonic resection and suprapromitory anastomosis: A multi-center study controlled by randomization. *Arch Surg* 1998; 133: 309-314.
58. Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: Multivariate analysis of 707 patients. *World J Surg* 2002; 26: 499-502.
59. Yeh CY, Changchien CR, Wang JY et al. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. *Ann Surg* 2005; 241: 9-13.
60. Plumley PF. A simple regime for preparation of colon before large-bowel surgery. *Br J Surg* 1966; 53: 413-414.
61. Irvin TT, Giligher JC. Aetiology of disruption of intestinal anastomoses. *Br J Surg* 1973; 60: 461-464.
62. Beck DE, Harford FJ, DiPalma JA. Comparison of cleansing methods in preparation for colonic surgery. *Dis Colon Rectum* 1985; 28: 491-495.
63. Fleites RA, Marshall JB, Eckauuser ML, Mansour EG, Imbembo AL, McCullough AJ. The efficacy of polyethylene glycol electrolyte lavage solution versus traditional mechanical bowel preparation for elective colonic surgery: a randomised, prospective, blinded clinical trial. *Surgery* 1985; 98: 708-717.
64. Beck DE, Fazio VW, Jagelman DG. Comparison of oral lavage methods for preoperative colonic cleansing. *Dis Colon Rectum* 1986; 29: 699-703.
65. Crapp AR, Tillotson P, Powis SJ, Cooke WT, Alexander-Williams J. Preparation of the bowel by whole-gut irrigation. *Lancet* 1975; 2: 1239-1240.
66. Irving AD, Scrimgeour D. Mechanical bowel preparation for colonic resection and anastomosis. *Br J Surg* 1987; 74: 580-581.

67. Mansvelt B, Arrigo E, Passelecq E, Gavelli A, Harb J, Huguet C. Minimal intestinal preparation before colectomy for cancer: experience of 189 cases. *Ann Chir* 1992; 46: 592-595.
68. van Geldere D, Fa-Si-Oen PR, Noach LA, Rietra PJ, Perterse JL, Boom RP. Complications after colorectal surgery without mechanical bowel preparation. *J Am Coll Surg* 2002; 194: 40-47.
69. Brownson P, Jenkins S, Nott D, Ellenbogen S. Mechanical bowel preparation before colorectal surgery: results of a randomised trial. *Br J Surg* 1992; 79: 461-462.
70. Schein M, Assalia A, Eldar S, et al. Is mechanical bowel preparation necessary before primary colonic anastomosis? An experimental study. *Dis Colon Rectum* 1995; 38: 749-752.
71. Nichols RL, Condon RE. Preoperative preparation of the colon. *Surg Gynecol Obstet* 1971; 132: 323-337.
72. Nichols RL, Sherwood L, Gorbach SL, Condon RE. Alteration of intestinal microflora following preoperative mechanical preparation of the colon. *Dis Colon Rectum* 1971; 14:123-127.
73. Gorbach SL, Neale G, Levitan R, Hepner GW. Alterations in human intestinal microflora during experimental diarrhea. *Gut* 1970; 11: 1-6.
74. O'Dwyer PJ, Conway W, McDermott EW, et al. Effect of mechanical bowel preparation on anastomotic integrity following low anterior resection in dogs. *Br J Surg* 1989; 76: 756-758.
75. Burkitt DS, Donovan IA. Intraluminal pressure adjacent to left colonic anastomoses. *Br J Surg* 1990; 77: 1288-1290.
76. Solla JA, Rothenberger DA. Preoperative bowel preparation: A survey of colon and rectal surgeons. *Dis Colon Rectum* 1990; 33(2): 154-159.
77. Beloosesky Y, Grinblat J, Weiss A, Grosman B, Gafter U, Chagnac A. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med* 2003; 163: 803-808.
78. Holte K, Nielsen KG, Madsen JL, Kehlet H. Physiologic effects of bowel preparation. *Dis Colon Rectum* 2004; 47(8): 1397-1402.
79. Sanders G, Mercer SJ, Saeb-Parsey K, Akhavan MA, Hosie KB, Lambert AW. Randomised clinical trial of intravenous fluid replacement during bowel preparation for surgery. *Br J Surg* 2001; 88: 1363-5.

80. Santos JC Jr, Batista J, Sirimarco MT, Guimaraes AS, Levy CE. Prospective randomised trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. *Br J Surg* 1994; 81: 1673–1676.
81. Burke P, Mealy K, Gillen P, Joyce W, Traynor O, Hyland J. Requirement for bowel preparation in colorectal surgery. *Br J Surg* 1994; 81: 907–910.
82. Zmora O, Mahajna A, Bar-Zakai B et al. Colon and rectal surgery without mechanical preparation: A randomised prospective trial. *Ann Surg* 2003; 237(3): 363–367.
83. Miettinen RP, Laitinen ST, Makela JT, Paakkonen ME. Bowel preparation with oral polyethylene glycol electrolyte solution versus no preparation in elective open colorectal surgery: prospective, randomised study. *Dis Colon Rectum* 2000; 43: 669–675.
84. Fa-Si-Oen P, Roumen R, Buitenweg J et al. Mechanical Bowel Preparation or Not? Outcome of a Multicenter, Randomised Trial in Elective Open Colon Surgery. *Dis Colon Rectum* 2005; 48(8): 1509.
85. Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomised study. *Arch Surg* 2005; 140: 285–288.
86. Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P. Randomised clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. *Br J Surg* 2005; 92: 409–414.
87. Bucher P, Mermillod B, Morel P, Soravia C. Does mechanical bowel preparation have a role in preventing postoperative complications in elective colorectal surgery? *Swiss Medical Weekly* 2004; 134(5-6): 69–74.
88. Bucher P, Mermillod B, Gervaz P, Morel P. Mechanical bowel preparation for elective colorectal surgery: A meta-analysis. *Arch Surg* 2004; 139: 1359–1364.
89. Guenaga, K, Atallah, AN, Castro, AA, Matos D, Wille-Jorgensen, P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database of Systematic Reviews* Vol (1), 2006.
90. Wille-Jorgenson P, Guenaga KF, Matos D, Castro AA. Preoperative mechanical bowel cleansing or not? An updated meta-analysis. *Colorectal Dis* 2005; 7: 304–310.
91. Scottish Intercollegiate Guidelines Network. Management of colorectal cancer: a national clinical guideline. Edinburgh: SIGN, 2003; 67.

92. Garlock J, Seley G. The use of sulphonamide in surgery of the colon and rectum; preliminary report. *Surgery* 1939; 5:787-790.
93. Page CP, Bohnen JMA, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH. Antimicrobial prophylaxis for surgical wounds: Guidelines for clinical care. *Arch Surg* 1993; 128: 79-88.
94. Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JB. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. *Am J Med* 1981; 70: 51-58.
95. Stone HH, Hooper CA, Kolb LD, Geheber CE, Dawkins EJ. Antibiotic prophylaxis in gastric, biliary and colonic surgery. *Ann Surg* 1976; 184: 443-452.
96. Coppa GF, Eng K. Factors involved in antibiotic selection in elective colon and rectal surgery. *Surgery* 1988; 104: 853-8.
97. Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H, Fagerstrom RM. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls. *N Engl J Med* 1981; 305: 795-799.
98. Bartlett SP, Burton RC. Effects of prophylactic antibiotics on wound infection after elective colon and rectal surgery: 1960 to 1980. *Am J Surg* 1983; 145: 300-309.
99. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. *Br J Surg* 1998; 85: 1232-41.
100. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. 1992; 326: 281-286.
101. Silver A, Eichorn A, Kral J et al. Timeliness and use of antibiotic prophylaxis in selected inpatient surgical procedures. *Am J Surg* 1996; 171: 548-552.
102. Bratzler DW, Houck PM, Richards C et al. Use of antimicrobial prophylaxis for major surgery: Baseline results from the national surgical infection prevention project. *Arch Surg* 2005; 140: 174-182.
103. DiPiro JT, Vallner JJ, Bowden TA, Clark BA, Sisley JF. Intraoperative serum and tissue activity of cefazolin and cefoxitin. *Arch Surg* 1985; 120: 829-832.
104. Jensen LS, Andersen A, Fristrup SC et al. Comparison of one dose versus three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elective colorectal surgery. *Br J Surg* 1990; 77: 513-518.

105. Rowe-Jones DC, Peel ALG, Kingston RD, Shaw JFL, Teasdale C, Cole DS. Single dose cefotaxime plus metronidazole versus three dose cefuroxime plus metronidazole as prophylaxis against wound infection in colorectal surgery: a multicentre prospective randomised study. *BMJ* 1990; 300: 18-22.
106. McDonald M, Grabsch E, Marshall C, Forbes A. Single- versus multiple- dose antimicrobial prophylaxis for major surgery: a systematic review. *ANZ J Surg* 1998; 68 (6); 388-395.
107. Platell C, Hall JC. The prevention of wound infection in patients undergoing colorectal surgery. *J Hosp Infec* 2001; 49: 233-238.
108. Lau WY, Chu KW, Poon GP, Ho KK. Prophylactic antibiotics in elective colorectal surgery. *Br J Surg* 1988; 75: 782-785.
109. Becquemin J-P, Piquet J, Becquemin M-H, Melliere D, Harf A. Pulmonary function after transverse or midline incision in patients with obstructive pulmonary disease. *Intensive Care Med* 1985; 11: 247±51.
110. Garcia-Valdecasas JC, Almenara R, Cabrer C et al. Subcostal incision versus midline laparotomy in gallstone surgery: a prospective trial. *Br J Surg* 1988; 75: 473-5.
111. Lindgren PG, Nordgren SR, Oresland T, Hulten L. Midline or transverse abdominal incision for right-sided colon cancer—a randomised trial. *Colorectal Dis* 2001; 3: 46-50.
112. Armstrong PJ, Burgess RW. Choice of incision and pain following gallbladder surgery. *Br J Surg* 1990; 77(7): 746-8.
113. Halasz NA. Vertical vs horizontal laparotomies. *Arch Surg* 1964; 88: 911-914.
114. Brown SR, Goodfellow PB. Transverse verses midline incisions for abdominal surgery. *The Cochrane Database of Systematic Reviews* 2005(4).
115. O'Dwyer PJ, McGregor JR, McDermott EWM, Murphy JJ, O'Higgins NJ. Patient recovery following cholecystectomy through a 6cm or 15cm transverse subcostal incision: a prospective randomised clinical trial. *Postgrad Med J* 1992; 68(804): 817-9.
116. Greenall MJ, Evans M, Pollock AV. Midline or transverse laparotomy? A random controlled clinical trial. Part 1: Influence on healing. *Br J Surg* 1980; 67: 188-190.
117. Grantcharov TP, Rosenberg J. Vertical compared with transverse incisions in abdominal surgery. *Eur J Surg* 2001; 167: 260-267.

118. Sethia KK, Selkon JB, Berry AR, Turner CM, Kettlewell MG, Gough MH. Prospective randomised controlled trial of urethral versus suprapubic catheterization. *Br J Surg* 1987; 74: 624–5.
119. Basse L, Werner M, Kehlet H. Is urinary drainage necessary during continuous epidural analgesia after colonic resection? *Reg Anesth Pain Med* 2000; 25: 498-501.
120. Christensen BP, Kronborg O. Suprapubic bladder drainage in colorectal surgery. *Br J Surg* 1981; 68: 348–9.
121. Klaaborg KE, Kronborg O. Suprapubic bladder drainage in elective colorectal surgery. *Dis Colon Rectum* 1986; 29: 260–2.
122. Perrin LC, Penfold C, McLeish A. A prospective randomised controlled trial comparing suprapubic with urethral catheterization in rectal surgery. *ANZ J Surg* 1997; 67: 554-556.
123. O’Kelly TJ, Mathew A, Ross S, Munro A. Optimum method for urinary drainage in major abdominal surgery: a prospective randomised trial of suprapubic versus urethral catheterization. *Br J Surg* 1995; 82:1367–8.
124. Ratnaval CD, Renwick P, Farouk R, Monson JR, Lee PW. Suprapubic versus transurethral catheterisation of males undergoing pelvic colorectal surgery. *Int J Colo Dis* 1996; 11: 177-9.
125. Perrin LC, Benoist S, Panis Y et al. Optimal duration of urinary drainage after rectal resection: A randomised controlled trial. *Surgery* 1999; 125: 135-141.
126. Mullen JL, Gertner MH, Buzby GP, Goodhart MH, Rosato EF. Implications of malnutrition in the surgical patient. *Arch. Surg* 1979; 114: 121.
127. Wilmore DW. Metabolic response to severe surgical illness: overview. *World J Surg* 2000; 24: 705.
128. MacFie J. Enteral versus parenteral nutrition: the significance of bacterial translocation and gut-barrier function. *Nutrition* 2000; 16: 606.
129. Smedley F, Bowling T, James M et al. Randomised clinical trial of the effects of preoperative and postoperative nutritional supplements on clinical course and cost of care. *Br J Surg* 2004; 91: 983-990.
130. VA TPN Cooperative Study: Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; 325: 525-532.

131. Bellantone R, Dopglio G, Bossola M et al. Preoperative parenteral nutrition in the high risk surgical patients. *J Parenter Enteral Nutr* 1998; 12: 195.
132. Meguid M, Curtas M, Meguid V, Debonis D, Terz JJ. Effects of pre-operative TPN on surgical risk: preliminary status report. *Br J Clin Pract* 1998; 42(Suppl.): 53.
133. Muller J, Keller H, Brenner U, Walter M, Holzmuller W. Indications and effects of preoperative parenteral nutrition. *World J Surg* 1986; 10: 53.
134. Moghissi K, Hornshaw J, Teasdale P, Dawes EA. Parenteral nutrition in carcinoma of the oesophagus treated by surgery: nitrogen balance and clinical studies. *Br J Surg* 1977; 64: 125.
135. Von Meyenfeldt M, Meijerink W, Rouflart M. Perioperative nutritional support: a randomised clinical trial. *Clin Nutr* 1992; 11: 180.
136. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet* 2001; 358: 1487-1492.
137. Woods JH, Erickson LW, Condon RE, Schulte WJ, Sillin LF. Postoperative ileus: a colonic problem? *Surgery* 1978; 84: 527-533.
138. Condon RE, Cowles VE, Schulte WJ, Frantzides CT, Mahoney JL, Sarna SK. Resolution of postoperative ileus in humans. *Ann Surg* 1986; 203: 574-580.
139. Wilson JP. Postoperative motility of the large intestine in man. *Gut* 1975; 16: 689-692.
140. Han-Geurts IJM, Jeekel J, Tilanus HW, Brouwer KJ. Randomised clinical trial of patient-controlled versus fixed regimen feeding after elective abdominal surgery. *Br J Surg* 2001; 88: 1578-1582.
141. Feo CV, Romanini B, Sortini D et al. Early oral feeding after colorectal resection: A randomised controlled study. *ANZ J Surg* 2004; 74: 298-301.
142. Heslin MJ, Latkany L, Leung D, et al. A prospective, randomised trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg* 1997; 226: 567-580.
143. Reissman P, Teoh TA, Cohen SM, et al. Is early oral feeding safe after elective colorectal surgery: a prospective randomised trial. *Ann Surg* 1995; 222: 73-77.
144. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus 'nil by mouth' after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001; 323: 773.

145. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomised, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* 2003; 46(7): 851-859.
146. Gatt M, Anderson ADG, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomised clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005; 92: 1354-1362.
147. Basse L, Madsen JL, Kehlet H. Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative. *Br J Surg* 2001; 88:1498–1500.
148. Anderson ADG, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomised clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; 90(12): 1497-1504.
149. Baig MK, Wexner SD. Postoperative ileus: a review. *Dis Colon Rectum* 2004; 47: 516-526.
150. Bayliss WM, Starling EH. The movements and innervations of the small intestine. *J Physiol (Lond)* 1899; 24:99–143.
151. Pal J. Über den Einfluss des Bauchschnittes auf die Darmbewegung. *Zentralbl Physiol* 1890; 4: 338.
152. Graber JN, Schulte WJ, Condon RE, Cowles VE. Relationship of duration of postoperative ileus to extent and site of operative dissection. *Surgery* 1982; 92: 87-92.
153. Lindquist B. Propulsive gastrointestinal motility related to retroperitoneal irritation: An experimental study in the rat. *Acta Chir Scand* 1968; supp 384: 44-53.
154. Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. *Ann Surg* 1998; 228: 652-663.
155. Bueno L, Ferre JP, Ruckebusch Y. Effects of anesthesia and surgical procedures on intestinal myoelectric activity in rats. *Digest Dis Sci* 1978; 23: 690-695.
156. Schwarz NT, Beer-Stolz D, Simmons R, Bauer A. Pathogenesis of paralytic ileus: Intestinal manipulation opens a transient pathway between the intestinal lumen and the leukocytic infiltrate of the jejunal muscularis. *Ann Surg* 2002; 235: 31-40.
157. Deitch EA. Simple intestinal obstruction causes bacterial translocation in man. *Arch Surg* 1989; 124: 699–701.

158. Van Leeuwen PA, Boermeester MA, Houdijk AP. Clinical significance of translocation. *Gut* 1994; 35: S28–S34.
159. Eskandari MK, Kalff JC, Billiar TR, et al. Lipopolysaccharide activates the muscularis macrophage network and suppresses circular smooth muscle activity. *Am J Physiol* 1997; 273: 727–734.
160. Pappagallo M. Incidence, prevalence and management of opioid bowel dysfunction. *Am J Surg* 2001; 182: 11-18.
161. Manara L, Bianchetti A. The central and peripheral influences of opioids on gastrointestinal propulsion. *Annu Rev Pharmacol Toxicol* 1985; 25: 249-273.
162. Frantzides CT, Cowles V, Salaymeh B, et al. Morphine effects on human colonic myoelectric activity in the postoperative period. *Am J Surg* 1992; 163: 144–148.
163. Wallin G, Cassuto J, Hogstrom S, Rimback G, Faxen A, Tolleson PO. Failure of epidural anesthesia to prevent postoperative paralytic ileus. *Anesthesiology* 1986; 65: 292-297.
164. Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. *Acta Anaesthesiol Scand* 1987; 31: 161-164.
165. Ahn H, Bronge A, Johansson K, Ygge H, Lindhagen J. Effect of continuous postoperative epidural analgesia on intestinal motility. *Br J Surg* 1988; 75: 1176-8.
166. Wattwil M, Thoren T, Hennerdal S, Garvill JE. Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. *Anesth Analg* 1989; 68: 353-8.
167. Bredtmann RD, Herden HN, Teichmann W et al. Epidural analgesia in colonic surgery: results of a randomised prospective study. *Br J Surg* 1990; 77: 638-642.
168. Riwar A, Schar B, Grotzinger U. Effect of continuous postoperative analgesia with peridural bupivacaine on intestinal motility following colorectal resection. *Helv Chir Acta* 1991; 58: 729-33.
169. Liu SS, Carpenter RL, Mackey DC, Thirlby RC, Rupp SM, Shine TS et al. Effects of perioperative analgesic technique on rate of recovery after colon surgery. *Anesthesiology* 1995; 83: 757-765.
170. Neudecker J, Schwenk W, Junghans T, Pietsch S, Bohm B, Muller JM. Randomised controlled trial to examine the influence of thoracic epidural analgesia

- on postoperative ileus after laparoscopic sigmoid resection. *Br J Surg* 1999; 86: 1292-5.
171. Bohm B, Milsom JW, Fazio VW. Postoperative intestinal motility following conventional and laparoscopic intestinal surgery. *Arch Surg* 1995; 130: 415-419.
 172. Davies W, Kollmorgen CF, Tu QM et al. Laparoscopic colectomy shortens postoperative ileus in a canine model. *Surgery* 1997; 121: 550-555.
 173. Basse L, Madsen JL, Billesbolle P, Bardram L, Kehlet H. Gastrointestinal transit after laparoscopic vs open colonic resection. *Surg Endosc* 2003; 17: 1919-1922.
 174. Basse L, Jakobsen DH, Bardram L et al. Functional recovery after open versus laparoscopic colonic resection: A randomised blinded study. *Ann Surg* 2005; 241: 416-423.
 175. Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: a prospective randomised trial. *ANZ J Surg* 1998; 68: 125-8.
 176. Waldhausen JH, Schirmer BD. The effect of ambulation on recovery from postoperative ileus. *Ann Surg* 1990; 212: 671-7.
 177. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth*. 2002; 89: 622-632.
 178. Disbrow EA, Bennett HL, Owings JT. Effect of preoperative suggestion on postoperative gastrointestinal motility. *West J Med* 1993; 158: 488-92.
 179. Holte K, Kehlet H. Postoperative ileus: Progress towards effective management. *Drugs* 2002; 62: 2603-2615.
 180. Wolff BG, Michelassi F, Gerkin TM, Techner L, Gabriel K, Du W, Wallin BA. Alvimopan, a novel, peripherally acting γ -opioid antagonist. *Ann Surg* 2004; 240: 728-735.
 181. Tuffier TH. Anesthesie medullaire chirurgicale par injection sous-arachno lombaire de coca; technique et resultats. *La Semaine Medicale* 1900; 20: 167-169.
 182. Kehlet H. Surgical stress: the role of pain and analgesia. *Br J Anaesth* 1989; 63: 189-195.
 183. Carli F, Webster J, Pearson M, Pearson J, Bartlett S, Bannister P et al. Protein metabolism after abdominal surgery: effect of 24-hr extradural block with local anaesthetic. *Br J Anaesth* 1991; 67: 729-734.

184. Hosoda R, Hattori M, Shimada Y. Favorable effects of epidural analgesia on hemodynamics, oxygenation and metabolic variables in the immediate post-anesthetic period. *Acta Anaesthesiol Scand* 1993; 37: 469–474.
185. Kouraklis G, Glinavou A, Raftopoulos L, Alevisou V, Lagos G, Karatzas G. Epidural analgesia attenuates the systemic stress response to upper abdominal surgery: a randomised trial. *Int Surg* 2000; 85: 353–357.
186. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database of Systematic Reviews* 2005; 3.
187. Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomised trial. *Dis Colon Rectum* 2001; 44: 1083–1089.
188. Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgan JL. Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. *Anesthesiology* 1993; 78: 666–676.
189. Senagore AJ, Delaney CP, Mekhail N, Dugan A, Fazio VW. Randomised clinical trial comparing epidural anaesthesia and patient-controlled analgesia after laparoscopic segmental colectomy. *Br J Surg* 2003; 90: 1195-1199.
190. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; 290: 2455–2463.
191. Park WY, Thompson J, Lee KK. Effect of epidural anesthesia and analgesia on postoperative outcome: A randomised controlled veterans affairs co-operative study. *Ann Surg* 2001; 234: 560-571.
192. Rigg JRA, Jamrozik K, Myles PS et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; 359: 1276-1282.
193. Semm K. Endoscopic appendectomy. *Endoscopy* 1983; 15: 59-64.
194. Nenner RP, Imperato PJ, Alcorn CM. Serious complications of laparoscopic cholecystectomy in New York State. *N Y State J Med.* 1992; 92:179-81.
195. Cooperman AM, Katz V, Zimmon D, et al. Laparoscopic colon resection: a case report [abstract]. *J Laparoendosc Surg* 1991; 1: 221-224.
196. Fowler DL, White SA. Laparoscopy-assisted sigmoid resection [abstract]. *Surg Laparosc Endosc.* 1991; 1:183-188.

197. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection. *Surg Laparosc Endosc* 1991; 1(3): 155-150.
198. Falk PM, Beart RW Jr, Wexner SD et al. Laparoscopic colectomy: a critical appraisal. *Dis Colon Rectum* 1993; 36(1): 28-34.
199. Alexander RJT, Jaques BC, Mitchell KG. Laparoscopically assisted colectomy and wound recurrence. *Lancet* 1993; 341: 249-50 (Letter).
200. Nduka CC, Monson JRT, Menzies-Gow N, Darzi A. Abdominal wall metastases following laparoscopy. *Br J Surg* 1994; 81: 648-52.
201. Wexner SD, Cohen SM. Port site metastases after laparoscopic colorectal surgery for cure of malignancy. *Br J Surg* 1995; 82: 295-298.
202. Di Palo S, Vignali A, Tamburini A, Parolini D, Orsenigo E, Staudacher C. Colorectal laparoscopic surgery. Single center experience with 599 cancer patients. *Supplementi di Tumori* 2005; 4(3): S133-4.
203. Lacy AM, Garcia-Valdecasas JC, Delgado S et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002; 359: 2224-9.
204. Braga M, Frasson M, Vignali A, Zuliani W, Civelli V, Di Carlo V. Laparoscopic vs. open colectomy in cancer patients: Long term complications, quality of life, and survival. *Dis Colon Rectum* 2005; 48: 2217-2223.
205. Thaler K, Dinnewitzer A, Mascha E et al. Long-term outcome and health-related quality of life after laparoscopic and open colectomy for benign disease. *Surg Endosc* 2003; 17: 1404-8.
206. Leung KL, Kwok SPY, Lam SCW et al. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. *Lancet* 2004; 363: 1187-92.
207. The Clinical Outcomes of Surgical Therapy Study Group. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. *N Engl J Med* 2004; 350(20): 2050-2059.
208. Guillou PJ, Quirke P, Thorpe H et al for the MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multi-centre randomised controlled trial. *Lancet* 2005; 365: 1718-1726.
209. Reza MM, Blasco JA, Andradas E, Cantero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. *Br J Surg* 2006; 93: 921-928.

210. Abraham NS, Young JM, Solomon MJ. Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. *Br J Surg* 2004; 91: 1111-1124.
211. King PM, Blazeby JM, Ewings P et al. Randomised clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006; 93: 300-308.
212. Jansson M, Bjorholt I, Carlsson CP et al. Randomised clinical trial of the costs of open and laparoscopic surgery for colonic cancer. *Br J Surg* 2004; 91: 409-417.
213. Basse L, Thorbøl JE, Løssl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum* 2004; 47: 271-278.
214. Allison SP, Lobo DN. Fluid and electrolytes in the elderly. *Curr Opin Clin Nutr Metab Care* 2004; 7: 27-33.
215. Stoneham MD, Hill EL. Variability in post-operative fluid and electrolyte prescription. *Br J Clin Pract* 1997; 51: 82-84.
216. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ. Peri-operative fluid and electrolyte management: a survey of consultant surgeons in the UK. *Ann R Coll Surg Engl* 2002; 84: 156-60.
217. Lobo DN, Dube MG, Neal KR, Simpson J, Rowlands BJ, Allison SP. Problems with solutions: drowning in the brine of an inadequate knowledge base. *Clinical Nutrition* 2001; 20: 125-130.
218. Prien T, Backhaus N, Pelster F, et al. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *J Clin Anesth* 1990; 2: 317-23.
219. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomised phase III clinical trial—Hextend Study Group. *Anesth Analg* 1999; 88: 992-8.
220. Moretti EW, Robertson KM, El-Moalem H, Gan TJ. Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. *Anesth Analg* 2003; 96: 611-7.
221. Choi PT, Yip G, Quinonez LG et al. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; 27: 200-210.

222. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. Abnormal saline and physiological Hartmann's solution: a randomised double-blind crossover study. *Clinical Science* 2003; 104: 17-24.
223. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* 1999; 88: 999-1003.
224. Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clinical Science* 2001; 101: 173-9.
225. Wilkes NJ, Woolf R, Mutch M et al. The Effects of Balanced Versus Saline-Based Hetastarch and Crystalloid Solutions on Acid-Base and Electrolyte Status and Gastric Mucosal Perfusion in Elderly Surgical Patients. *Anesth Analg* 2001; 93: 811-816.
226. Tournadre JP, Allaouchiche B, Malbert CH, Chassard D. Metabolic acidosis and respiratory acidosis impair gastro-pyloric motility in anesthetized pigs. *Anesth Analg* 2000; 90:74-79.
227. Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. *World J Surg* 2004; 28: 1046-51.
228. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiological patterns in surviving and non-surviving shock patients: use of sequential cardiorespiratory parameters in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 1973; 106: 630-6.
229. Maharaj CH, Kallam SR, Malik A, Hassett P, Grady D, Laffey JG. Preoperative Intravenous Fluid Therapy Decreases Postoperative Nausea and Pain in High Risk Patients. *Anesth Analg* 2005; 100(3): 675-682.
230. Holte K, Kehlet H. Compensatory fluid administration for preoperative dehydration – does it improve outcome? *Acta Anesthesiol Scand* 2002; 46: 1089-1093.
231. Mecray PM, Barden RP, Ravdin IS. Nutritional edema: its effect on the gastric emptying time before and after gastric operations. *Surgery* 1937; 1: 53-64.
232. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; 359: 1812-18.

233. Brandstrup B, Tonnesen H, Beier-Holgersen R et al. Effects of intravenous fluid restriction on postoperative complications: Comparison of two perioperative regimens. *Ann Surg* 2003; 238: 641-648.
234. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* 2005; 103: 25-32.
235. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; 130: 423-9.
236. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; 315: 909-12.
237. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; 57: 845-849.
238. Gan TJ, Soppitt A, Maroof M et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002; 97: 820-6.
239. Wakeling HG, McFall MR, Jenkins CS et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; 95: 634-42.
240. Pritts TA, Nussbaum MS, Flesch LV, Fegelman EJ, Parikh AA, Fischer JE. Implementation of a clinical pathway decreases length of stay and cost for bowel resection. *Ann Surg* 1999; 230(5): 728.
241. Basse L, Hjort J, Dorthe RN, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000; 232(1): 51-57.
242. Proske JM, Raue W, Neudecker J, Muller JM, Schwenk W. Fast-track rehabilitation in colonic surgery: a prospective trial. *Ann de Chirurgie* 2005; 130: 152-156.
243. Kremer M, Ulrich A, Buchler MW, Uhl W. Fast-track surgery: the Heidelberg experience. *Recent Results in Cancer Res* 2005; 165: 14-20.
244. Susa A, Roveran A, Bocchi A, Carrer S, Tartari S. Fast-track approach to major colorectal surgery. *Chirurgia Italiana* 2004; 56(6): 817-824.

245. Smedh K, Strand E, Jansson P et al. Rapid recovery after colonic resection. *Lakartidningen* 2001; 98(21): 2568-74.
246. Basse L, Billesbolle P, Kehlet H. Early recovery after abdominal rectopexy with multimodal rehabilitation. *Dis Colon Rectum* 2002; 45: 195-199.
247. Andersen J, Kehlet H. Fast-track open ileo-colic resection for Crohn's disease. *Colorectal Dis* 2005; 7: 394-397.
248. Basse L, Jacobsen DH, Billesbolle P, Kehlet H. Colostomy closure after Hartmann's procedure with fast-track rehabilitation. *Dis Colon Rectum* 2002; 45(12): 1661-1664.
249. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH. Fast-track postoperative management protocol for patients with high comorbidity undergoing complex abdominal and pelvic colorectal surgery. *Br J Surg* 2001; 88(11): 1533-1538.
250. DiFronzo LA, Yamin N, Patel K, O'Connell TJ. Benefits of early feeding and early hospital discharge in elderly patients undergoing open colon resection. *Am Coll Surg* 2003; 197: 747-752.
251. Firoozfard B, Christensen T, Kristensen JK, Mogensen S, Kehlet H. Fast-track open transperitoneal nephrectomy. *Scand J Urol Nephrol* 2003; 37: 305-308.
252. Mukherjee D. Fast-track abdominal aortic aneurysm repair. *Vasc Surg* 2003; 37(5): 329-334.
253. Ottensen M, Sorensen M, Rasmussen Y, Smidt-Jensen S, Kehlet H, Ottesen B. Fast-track vaginal surgery. *Acta Obstet Gynaecol Scand* 2002; 81: 138-146.
254. Moller C, Kehlet H, Friland SG, Schouenborg LO, Lund C, Ottesen B. Fast-track hysterectomy. *Eur J Obstet Gynaecol Reprod Biol* 2001; 98: 18-22.
255. Basse L, Raskov HH, Jakobsen DH et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* 2002; 89: 446-453.
256. Hjort J, Sonne E, Basse L, Bisgaard T, Kehlet H. Convalescence after colonic resection with fast-track versus conventional care. *SJS* 2004; 93(1): 24-8.
257. Kehlet H, Wilmore DW. Fast-track surgery. *Br J Surg* 2005; 92: 3-4.

258. Zutshi M, Delaney CP, Senagore AJ, Mekhail N, Lewis B, Connor JT, Fazio VW. Randomised controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with pre-emptive epidural anaesthesia/analgesia after laparotomy and intestinal resection. *Am J Surg* 2005; 268-272.
259. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-483.
260. Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. *Intensive Care Medicine* 1994; 20 (3): 203-209.
261. Wichmann MW, Hüttl TP, Winter H et al. Immunological effects of laparoscopic vs open colorectal surgery: A prospective clinical study. *Arch Surg* 2005; 140: 692-697.
262. Baker RP, Titu LV, Hartley JE, Lee PWR, Monson JRT. A case control study of laparoscopic right hemicolectomy vs open right hemicolectomy. *Dis Colon Rectum* 2004; 47(10): 1675-1679.
263. Senagore AJ, Dupree HJ, Delaney CP, Brady KM, Fazio VW. Results of a standardized technique and postoperative care plan for laparoscopic sigmoid colectomy. *Dis Colon Rectum* 2003; 46(4): 503-509.
264. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343: 1405-1410.
265. Cromheecke M, de Jong KP, Hoekstra HJ. Current treatment for colorectal cancer metastatic to the liver. *Eur J Surg Oncol* 1999; 25: 451-463.
266. Ohlsson B, Stenrarn U, Tranberg KG. Resection of colorectal liver metastases: 25-year experience. *World J Surg* 1995; 19: 59-71.
267. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. *Br J Surg* 1997; 84: 1136-1140.
268. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; 77: 1241-1246.
269. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Postoperative complication rates after hepatic resection in Maryland hospitals. *Arch Surg* 2003; 138: 41-46.

270. Kooby DA, Stockman JR, Ben-Porat LM et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003; 237: 860-870.
271. Burt BM, Brown K, Jarnagin W et al. An audit of results of a no-drainage practice policy after hepatectomy. *Am J Surg* 2002; 184(5): 441-445.
272. Oshowo A, Gillams A, Harrison E et al. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. *Br J Surg* 2003; 90: 1240-1243.
273. Descottes B, Glineur D, Lachachi F et al. Laparoscopic liver resection of benign live tumors. *Surg Endosc* 2003; 17: 23-30.
274. Gigot J-F, Glineur D, Santiago Azagra J et al. Laparoscopic liver resection for malignant liver tumors: Preliminary results of a multicenter European study. *Ann Surg* 2002; 236: 90-97.
275. Huang MT, Lee WJ, Wang W, Wei PL, Chen RJ. Hand-assisted laparoscopic hepatectomy for solid tumor in the posterior portion of the right lobe: initial experience. *Ann Surg* 2003; 238: 674-679.
276. Mala T, Edwin B, Gladhaug I et al. A comparative study of the short term outcome following open and laparoscopic liver resection of colorectal metastases. *Surg Endosc* 2002; 16: 1059-1063.
277. Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg* 2000; 87(11): 1480-1493.
278. Baker LW, Webster DR. Postoperative intestinal motility: an experimental study on dogs. *Br J Surg* 1968; 55: 374-378.
279. Rasmussen S, Kristensen BB, Foldager S, Myhrmann L, Kehlet H. Accelerated recovery program after hip fracture surgery. *Ugeskrift for Laeger* 2002; 165 (1): 29-33.
280. Keus F, de Jong JAF, Gooszen HG, van Laarhoven CJHM. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database of Systematic Reviews* 2007; Vol 2.
281. Keus F, de Jong JAF, Gooszen HG, van Laarhoven CJHM. Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database of Systematic Reviews* 2007; Vol 2.
282. Basu S, Giri PS, Roy D. Feasibility of same day discharge after mini-laparotomy cholecystectomy – a simulation study in a rural teaching hospital. *Can J Rural Med* 2006; 11: 93-98.

283. Hsu, TC. Feasibility of colectomy with mini-incision. *Am J Surg* 2005; 190 (1): 48-50.
284. Ko CW, Kalloo AN. Per-oral transgastric abdominal surgery. *Chin J Dig Dis* 2006; 7: 67-70.
285. Kantsevoy SV, Hu B, Jagannath SB et al. Transgastric endoscopic splenectomy: is it possible? *Surg Endosc* 2006; 20: 522-525.
286. Bergstrom M, Ikeda K, Swain P, Park PO. Transgastric anastomosis by using flexible endoscopy in a porcine model. *Gastrointest Endosc* 2006; 63: 307-312.
287. Pai RD, Fong DG, Bundga ME, Odze RD, Rattner DW, Thompson CC. Transcolonic endoscopic cholecystectomy: a NOTES survival study in a porcine model. *Gastrointest Endosc* 2006; 64: 428-434.
288. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; 71: 726-35.
289. Contant CME, Hop WCJ, van't Sant HP et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007; 370 (9605): 2112-2117.
290. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; 93: 1069-1076.
291. Kariv Y, Delaney CP, Senagore AJ et al. Clinical outcomes and cost analysis of a 'fast-track' postoperative care pathway for ileal pouch-anal anastomosis. A case control study. *Dis Colon Rectum* 2007; 50 (2): 137-146.
292. Scharfenberg M, Raue W, Junghans T, Schwenk W. 'Fast-track' rehabilitation after colonic surgery in elderly patients – is it feasible? *Int J Color Dis* 2007; 22 (12): 1469-1474.
293. Wichmann MW, Eben R, Angele MK, Brandenburg F, Goetz AE, Jauch KW. Fast track rehabilitation in elective colorectal surgery patients: A prospective clinical and immunological single-centre study. *ANZ J Surg* 2007; 77: 502-507.