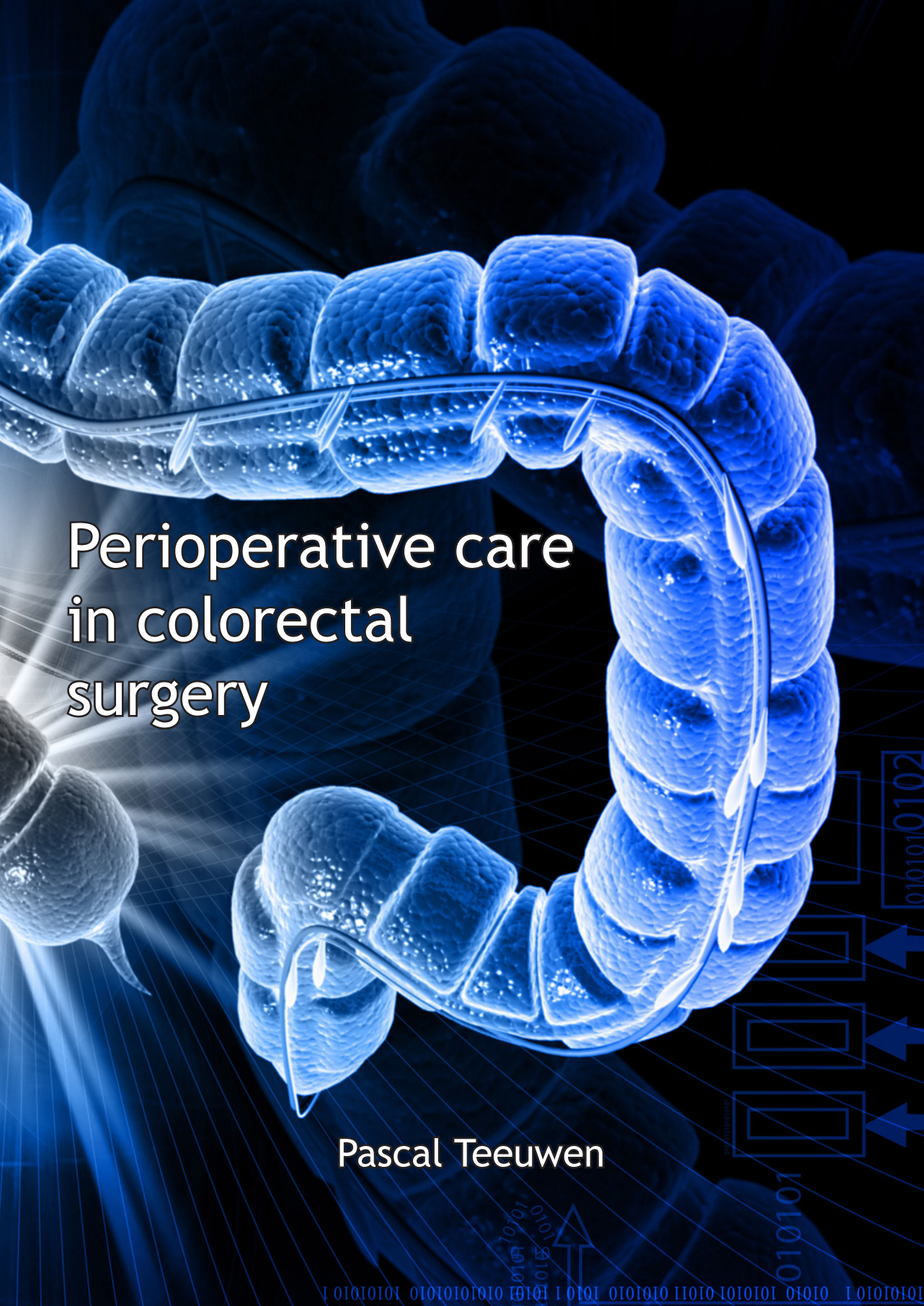
Perioperative care
in colorectal
surgery
Pascal Teeuwen

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Chapter 1

Introduction, aim and outline of the thesis

Enhanced Recovery After Surgery

After studying several aspects of postoperative recovery in the mid-eighties and nineties, Hendrik Kehlet proposed a multimodal approach to improve postoperative recovery in 1997, nowadays known as Enhanced Recovery After Surgery (ERAS).(1) The program aims to reduce the surgical stress response with subsequent increased demands on organ function.

All elements in the program have shown to improve patient outcome separately. Preoperative information about postoperative care reduces anxiety and improves patient participation. Preoperative carbohydrate loading diminishes insulin resistance and results in a better gastrointestinal function.(2,3) Avoidance of bowel preparation results in less discomfort and electrolyte disturbance.(4-8) Epidural anaesthesia provides adequate reduction of postoperative pain, without the need of systemic opioids that hamper the central nervous system, respiratory and gastrointestinal function. (9-11) Restricted intraoperative fluid therapy reduces morbidity, the time to recovery of gastrointestinal function and hospital stay.(12,13)
Early start of enteral feeding diminishes mortality, morbidity and hospital stay, (14) whereas early mobilization prevents pulmonary complications.(10)
All elements are implemented in a multimodal strategy aiming at enhancing recovery and reducing the stress response after surgery.

In 2006, the enhanced recovery program was introduced in the Department of Surgery of the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The effects of this program are evaluated in this thesis. In order to assess the influence of an enhanced recovery program and to compare the results with conventional treatment regimens, it is of utmost importance to adequately define patient groups. Before starting the evaluation of the ERAS program a study was done to evaluate different scoring systems to assess patient's risk of complications or death. The Physiological and Operative Severity Score for the eNumeration of Mortality and morbidity (POSSUM) scoring systems was developed in 1991.(15) In 1998 the Portsmouth POSSUM was found to have a higher predictive value than the initial model. In 2003, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) developed its own scoring system for surgical patients with colorectal cancer. The inaccuracies of the previous POSSUM scores led to the introduction of the specialty-specific ColoRectal POSSUM score in 2004.(16) In **Chapter 2**, the value of POSSUM and ACPGBI risk prediction in surgery is assessed in a retrospective case-control study including patients with colorectal cancer and benign colorectal diseases.

Enhanced recovery after surgery protocols aim at reducing the surgical stress response and optimizing recovery, thus reducing the length of hospital stay. However, there have been concerns regarding protocol compliance, high readmission rates and the true impact on morbidity.
In **Chapter 3**,the mortality, morbidity and in-hospital stay after colorectal surgery

of patients treated following the ERAS protocol is compared with a cohort of carefully matched patients who received conventional postoperative care.
Rectal surgery differs from colonic surgery and is associated with higher complication rates and a longer hospital stay.(17) In **Chapter 4** the impact of Enhanced Recovery after Surgery on postoperative recovery in rectal surgery is described in a case-matched cohort study.
Although the separate elements of Enhanced Recovery After Surgery have proven to be helpful in the recovery of patients and the evidence on the beneficial effects of the ERAS package is accumulating, it is not clear which elements have most impact on early recovery. (18-23) The clinical impact of individual elements of the fast track program is evaluated in **Chapter 5**. Especially the role of early feeding, mobilization, epidural anaesthesia and restricted fluid therapy is elaborated. As a consequence of our findings, a systemic review and meta-analysis was performed to determine if intraoperative fluid management by the use of oesophageal Doppler could improve the outcome of patients undergoing colorectal surgery (**Chapter 6**).

One of the consequences of the implementation of an enhanced recovery program is a shorter hospital stay. Anastomotic leakage is one of the most serious adverse events after colorectal surgery. Its reported incidence varies from 1-25%.(24) Diagnosing leaks relies on the clinical and radiographic findings. Early diagnosis and prompt treatment are essential since delay is associated with increased mortality and morbidity.(25,26) Radiological diagnosis by means of e.g. contrast radiography or computer tomography are often advised when anastomotic dehiscence is suspected. However, sensitivity of both contrast radiography and computer tomography for diagnosing anastomotic dehiscence are rather low, being 65% and 54% respectively. Interobserver variability may be as high as 10 %.(27,28) Since leakage of bowel contents elicits at least a local inflammatory response, F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) may be a promising imaging technique to improve the detection of anastomotic bowel leak, at an early stage when granulocytes and macrophages migrate to the inflammatory process.(29-31) A first condition for such an application would be that the signal remains low during undisturbed healing. **Chapter 7** describes postoperative FDG uptake in colonic and colorectal anastomosis in patients without evidence of active infection or anastomotic leakage.

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Chapter 2

Predictive value of POSSUM and ACPGBI scoring in mortality and morbidity of colorectal resection: a case-control study

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Abstract

Background

Preoperative risk prediction to assess mortality and morbidity may be helpful to surgical decision-making. The aim of this study was to compare mortality and morbidity of colorectal resections performed in a tertiary referral center with mortality and morbidity as predicted with Physiological and Operative Score for enUmeration of Mortality and morbidity (POSSUM), Portsmouth-POSSUM and Colorectal-POSSUM. The second aim of this study was to analyze the accuracy of different POSSUM-scores in surgery performed for malignancy, inflammatory bowel diseases and diverticulitis. POSSUM scoring was also evaluated in colorectal resection in acute versus elective setting. In procedures performed for malignancy, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) score was assessed in the same way for comparison.

Methods

POSSUM, P-POSSUM and CR-POSSUM predictor equations for mortality were applied in a retrospective case control study to 734 patients who had undergone colorectal resection. The total group was assessed first. Second, the predictive value of outcome after surgery was assessed for malignancy (n=386), inflammatory bowel diseases (n=113), diverticulitis (n=91) and other indications, e.g. trauma, endometriosis, volvulus or ischemia (n=144). Third, all subgroups were assessed in relation to the setting in which surgery was performed: acute or elective. In patients with malignancy, the ACPGBI score was calculated as well. In all groups, Receiver Operating Characteristic (ROC) curves were constructed.

Results

POSSUM, P-POSSUM and CR-POSSUM have a significant predictive value for outcome after colorectal surgery. Within the total population as well as in all four subgroups, there is no difference in the area under the curve between the POSSUM, P-POSSUM and CR-POSSUM scores. In the subgroup analysis, smallest areas under the ROC curve are seen in operations performed for malignancy, which is significantly worse than for diverticulitis and in operations performed for other indications. For elective procedures, P-POSSUM and CR-POSSUM predict outcome significantly worse in patients operated for carcinoma than in patients with diverticulitis. In acute surgical interventions, CR-POSSUM predicts mortality better in diverticulitis than in patients operated for other indications. The ACPGBI score has a larger area under the curve than any of the POSSUM scores. Morbidity as predicted by POSSUM is most accurate in procedures for diverticulitis and worst when the indication is malignancy.

Conclusion

The POSSUM scores predict outcome significantly better than can be expected by chance alone. Regarding the indication for surgery, each POSSUM score predicts outcome in patients operated for diverticulitis or other indications more accurately than for malignancy. The ACPGBI score is found to be superior to the various POSSUM scores in patients who have (elective) resection of colorectal malignancy.

Introduction

A large number of scoring systems to assess patient's risks of complications or death have been developed. The Physiological and Operative Score for enUmeration of Mortality and morbidity (POSSUM) was reported to be the most appropriate of the scores currently available for general surgical practice.(1) It uses 12 physiological and 6 operative variables to give a calculated risk of morbidity and death. POSSUM was intended to be used in a comparative surgical audit. It was applied to a number of surgical procedures, including vascular (V-POSSUM)(2), oesophagogastric (O-POSSUM)(3) or colorectal (CR-POSSUM)(4) surgery. Since the introduction of POSSUM in 1991 by Copeland et al. (5) Several studies have shown the POSSUM score to overestimate the mortality risk.(6-8) The Portsmouth POSSUM was proposed to improve the predictive value of the initial model and has been primarily validated on patients undergoing vascular surgery.(9-11) In 2003, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) developed its own scoring system for surgical patients with colorectal cancer. The ACPGBI score is supposed to be easier to use than the three POSSUM models.(12;13)

The first aim of this study was to assess the role of POSSUM in surgical audit. For this purpose, observed mortality and morbidity of colorectal resections performed in a tertiary referral center were compared with mortality and morbidity as predicted with POSSUM, P-POSSUM and CR-POSSUM scores and the ACPGBI score for patients operated on colorectal cancer. The second aim of this study was to examine the accuracy of the various POSSUM-scores for individual risk prediction in surgery performed for malignancy, inflammatory bowel diseases and diverticulitis.

Methods

Inclusion

A retrospective case control study was performed of all patients older than 15 years undergoing colorectal resection between January 2003 and January 2008 in the Radboud University Nijmegen Medical Centre. Surgical interventions were performed in an elective or acute setting. Acute operation was defined as surgical interventions after emergency admission. All other operations were classified as elective.

Data extraction

The following data were extracted from the medical records: demographics, Body Mass Index, coexistent morbidity, use of immunosuppressive medication, ASA (American Society of Anesthesiology) grade, indication and type of surgery, type of anastomosis, surgical re-intervention (laparotomy, not radiological drainage), hospital stay, POSSUM, Portsmouth-POSSUM, colorectal-POSSUM, morbidity predicted by POSSUM, postoperative mortality and morbidity. Morbidity was defined as an

unexpected event within 30 days after surgery, which was harmful for the patient's health and required a change of therapeutic strategy. Complications were classified as defined by POSSUM (http://www.sfar.org/scores2/possum2.html). Mortality was defined as any death within 30 days after surgical intervention. ACPGBI scores were calculated in patients who had colorectal resection for histological proven cancer.

POSSUM and ACPGBI

The POSSUM-score comprises a physiological and an operative component. The physiological score is based on 12 variables to be assessed in different grades. The operative severity score uses 6 variables. The definitive POSSUM-score is calculated with the physiological as well as the operative severity score. (http://www.sfar.org/scores2/possum2.html, http://www.riskprediction.org.uk/) According to the literature on POSSUM, a normal grade was used if a variable was not available. The ACPGBI score, developed for oncologic resections, uses multifactorial logistic regression analysis to adjust for multiple risk factors, their interactions, and the clustering of adverse outcome. It is the result of a nationwide attempt in the UK to provide accurate risk adjusted outcomes involving over 8.000 patients from 77 centers. The ACPGBI score assesses 5 operative variables: age, cancer resection, ASA (American Society of Anesthesiology) grade, Dukes' stage and operative urgency (http://www.riskprediction.org.uk/).

Outcome

The (P-, CR-) POSSUM predicted mortality and morbidity was compared with the observed mortality and morbidity. Subgroup analysis was made for operations performed for carcinoma, inflammatory bowel disease, diverticulitis and other indications, e.g. trauma, endometriosis, volvulus or ischemia.
Primary outcome was mortality. Secondary outcome measures were morbidity, (POSSUM-) complications and hospital stay.

Statistical analysis

Receiver Operating Characteristic (ROC) curves were constructed of each group analyzed in order to examine sensitivity and specificity of each POSSUM score. Areas under the curves were compared within and between subgroups. Analysis of ROC curves is a widely accepted method to investigate the properties of a diagnostic test. The Area under the curve (AUC) measures the ability of the test to correctly classify those with and without a disease. Comparing the AUC in several subgroups and for different POSSUM scores therefore is the most appropriate manner to distinguish the diagnostic abilities between certain POSSUM scores in a specific subgroup or between subgroups for a specific POSSUM score.

Results

From January 2003 to January 2008, colorectal resection was performed in 734 patients: 385 females (52.5%) and 349 men (47.5%). The mean age was 58.4 years (+ 16.8; range: 16-96y). In 386 (52.5%) patients the indication for surgery was malignancy, in 113 (15.4%) inflammatory disease and 91 (12.4%) diverticulitis. 144 (19.6%) patients underwent colorectal surgery for other reasons: intestinal ischemia, volvulus, trauma, endometriosis or carcinoma of urogenital or gynecologic origin. The most frequent surgical procedures were resection of the sigmoid (23.2%) and right hemicolectomy (19.8%; Table 1).

Table 1. Demographics and performed procedures in the different subgroups.

	Malignancy		Inflammatory bowel disease		Diverticulitis		Other		Total
Type of surgery	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	
n	335	51	93	20	50	41	77	67	734
Male	177	25	40	5	21	21	24	34	349
Female	158	26	53	15	29	20	53	33	385
Age (y)	65.4	64.7	40.3	42.3	58.2	58.7	49.4	58.5	58.4
	(12.8)*	(15.6)	(14.3)	(16.0)	(12.0)	(15.9)	(15.1)	(17.9)	(16.8)
Body Mass Index	25.2	24.7	23.5	21.7	26.3	25.3	25.9	23.7	24.8
(kg/m^2)	(4.3)	(3.7)	(4.3)	(3.5)	(4.4)	(4.0)	(4.9)	(2.8)	(4.2)
ASA	2.1	2.2	1.9	2.2	2.0	1.9	2.1	2.7	2.1
	(0.7)	(0.7)	(0.5)	(0.8)	(0.8)	(0.8)	(0.8)	(1.0)	(0.7)
Right hemicolectomy	99	16	5	0	0	5	7	13	145
Left hemicolectomy	25	6	3	1	4	0	21	5	65
Transversum resection	11	3	2	1	2	0	5	9	33
Ileocecal resection	19	5	55	15	4	5	7	11	121
Sigmoid resection	52	12	4	2	35	30	15	21	171
(Sub-) Total colectomy	35	4	17	1	1	0	6	5	69
Rectosigmoid resection	94	5	7	0	4	1	16	3	130

* Number in brackets is standard deviation.

Elective operations were performed in 555 patients (74.9%), 179 (25.1%) were operated in an acute setting. The number of patients who had one or more surgical re-interventions was 152 (20.7%) (Table 2).

Table 2. POSSUM scores, observed mortality and morbidity, re-intervention rate and hospital stay in the different subgroups.

	Malignancy		Inflammatory bowel disease		Diverticulitis		Other		Total		
Type of surgery	*Elective*	*Acute*	*Elective*	*Acute*	*Elective*	Acute	*Elective*	*Acute*	*Elective*	*Acute*	Total
n	335	51	93	20	50	41	77	67	555	179	734
Predicted mortality POSSUM (%) P-POSSUM CR-POSSUM	 14.5 5.4 3.9	 24.6 12.2 8.7	 6.7 2.3 1.3	 17.3 5.7 3.0	 8.8 2.8 2.1	 22.0 10.8 8.4	 9.3 2.9 1.6	 25.5 12.4 7.9	 10.7 3.7 2.5	 24.4 11.2 7.7	 17.0 5.9 4.0
Observed mortality (%)	27 (8.1)	7 (13.5)	1 (1.1)	1 (5.0)	3 (6.0)	6 (14.6)	4 (5.2)	16 (23.9)	35 (6.3)	30 (16.7)	65 (8.9)
Predictive mortality (%)	50.7	64.1	29.6	45.2	35.9	58.8	35.7	64.7	40.1	61.0	46.0
Observed mortality (%)	130 (38.8)	18 (35.3)	32 (34.4)	10 (50.0)	18 (36.0)	16 (39.0)	32 (41.6)	33 (49.3)	212 (38.2)	77 (43.0)	289 (39.4)
Wound haemorrhage	2								2		2
Deep haemorrhage	6	3	1		1		1	1	9	4	13
Chest infection	14	6	5	2	2	1	5	3	26	12	38
Wound infection	19	7	8	1	7	4	4	7	38	19	57
Urinary infection	17	6	3		1	1	3	3	24	10	34
Deep infection	15	2	6		4	4	8	8	33	14	47
Septicaemia	9	8	1		1	3	1	4	12	17	29
Pyrexia of unknown origin			1						1		1
Wound dehiscence	9	1	2	2		1		4	11	8	19
Deep venous thrombosis and pulmonary embolus	6		1				1		8		8
Cardiac failure	8	2		4	1	2		2	9	10	19
Impaired renal function	3	1		1		1		1	3	4	7
Hypotension	2			1		1			2	2	4
Respiratory failure	2	3	1	1	1	2	2	4	6	10	16
Anastomotic leakage	29	5	8	1	4	2	4	9	45	17	62
Total complications	***141***	***44***	***37***	***15***	***22***	22	***29***	***46***	***229***	***127***	***356***
Re-intervention	56	11	16	5	9	10	20	25	101	51	152
Hospital stay (median days) (range)	10 (2-127)	11 (2-150)	8 (1-55)	7 (1-64)	9 (3-57)	8 (3-61)	12 (1-59)	15 (5-132)	10 (1-127)	12 (1-150)	10 (1-150)

Morbidity was 289 / 734 (39.4%). The total number of complications amounted 356; so the mean number of complications per patient is 1.7. Amongst electively operated patients, 212 (38.2%) had one or more complications. 77 (43.0%) patients, operated on in an acute setting, had an unfavorable postoperative course. The most common complications were anastomotic leakage, surgical site infection, and pulmonary and urinary infections. Mean morbidity as predicted by POSSUM was 46.0% (Table 2). Sixty-five patients (8.9%) died within 30 days after surgery (Table 2,3).

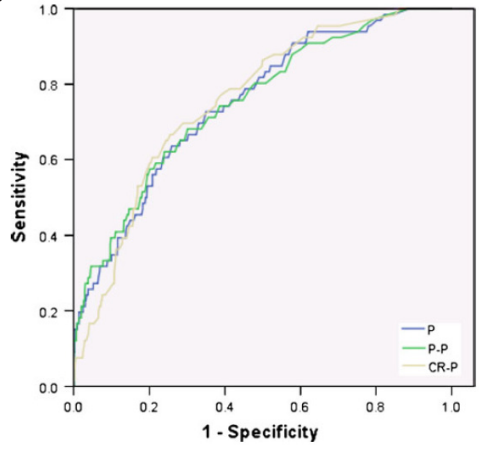
Table 3. Causes of mortality.

	Malignancy		Inflammatory bowel disease		Diverticulitis		Other		Total		
Type of surgery	*Elective*	*Acute*	*Elective*	*Acute*	*Elective*	*Acute*	*Elective*	*Acute*	*Elective*	*Acute*	*Total*
Observed mortality	27	7	1	1	3	6	4	16	35	30	65
Respiratory insufficiency	2	2				2	1	5	3	9	12
Cardiac failure	3		1						4		4
Abdominal sepsis											
leakage	5	2		1	1			3	6	6	12
disease		1			1	2		2	2	5	7
ischemia	2					1		2	2	3	5
Change of treatment strategy*	7	2				1	1	3	8	6	14
Unknown	5						1		6		6
Cerebrovascular accident	1							1	1	1	2
Bleeding	1					1			2		2
Transfusion reaction	1								1		1

* Due to metastasis, progressive haematological malignancy, loss of perspective.

The predicted mortality by POSSUM was 17.0%, Portsmouth-POSSUM 5.9% and ColoRectal-POSSUM 4.0%. In the total population as well as the subgroups (except the group with patients operated for inflammatory bowel diseases) POSSUM, P-POSSUM and CR-POSSUM had a significant larger predictive value for outcome after (elective and acute) colorectal surgery than can be expected by chance alone ($P<0.001$) (Figure 1).

Figure 1. ROC total group.



Within the total population as well as in all four subgroups, there is no difference in the area under the curve between the POSSUM, P-POSSUM and CR-POSSUM scores. In the subgroup analysis, smallest areas under the ROC curve are seen in operations performed for malignancy (0.65; 0.65; 0.65) (Figure 2a, 2b, 2c, 2d).

Figure 2a. Subgroup analysis; malignancy.

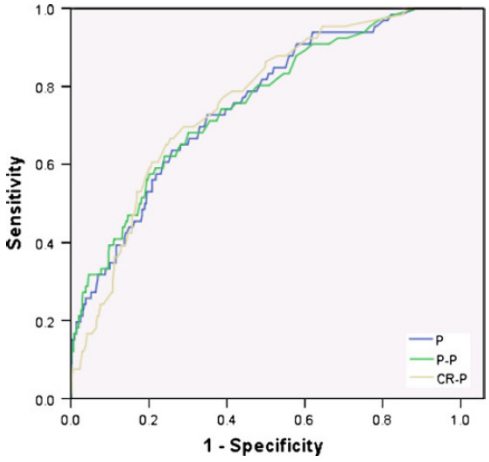


Figure 2b. Subgroup analysis; inflammatory bowel disease.

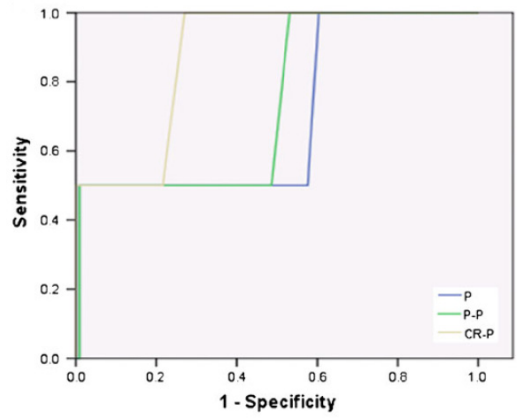


Figure 2c. Subgroup analysis; diverticulitis.

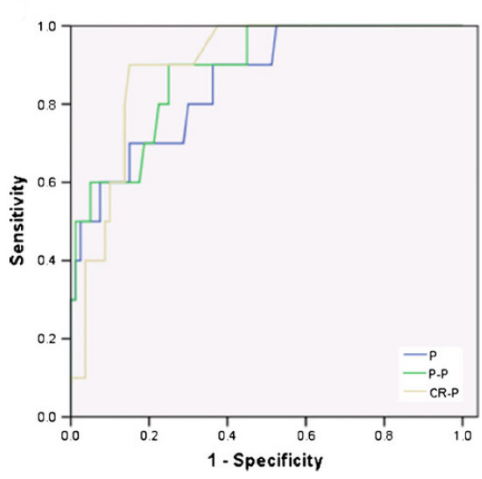
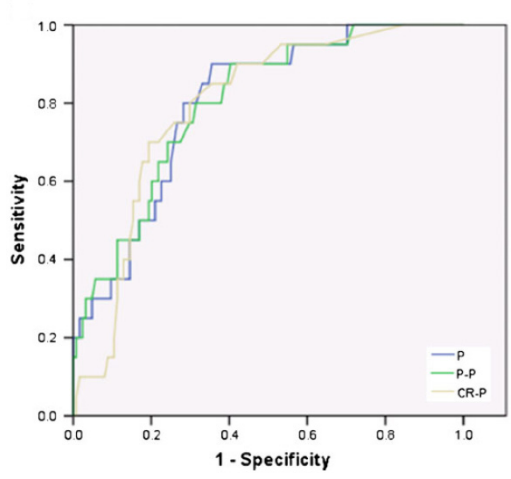


Figure 2d. Subgroup analysis; other.



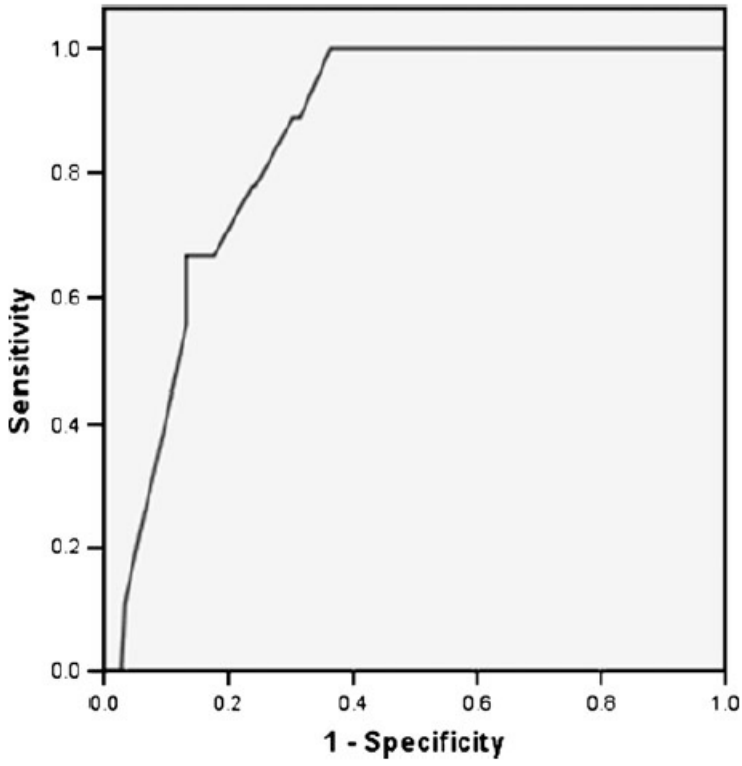
This is significant worse than in the diverticulitis group (0.86, P=0.01; 0.88, P<0.001 and 0.89, P=0.02; respectively) and in operations performed for other indications (0.80, P=0.03; 0.80, P=0.03 and 0.79, P=0.03; respectively). For elective procedures, P-POSSUM and CR-POSSUM predictions are significantly worse in patients operated for carcinoma than in patients with diverticulitis (0.61 vs. 0.85; P=0.02 and 0.63 vs.0.89; P<0.001; respectively). For acute surgical interventions, CR-POSSUM predicts mortality better in diverticulitis than in patients operated for other indications (0.89 vs. 0.66; P=0.02). Within the group operated on carcinoma, 190 patients had a known histology and the ACPGBI score was calculated (Table 4).

Table 4. ACPGBI score in 190 patients with carcinoma.

Carcinoma	
N	190
Male : Female	108 : 82
Age (mean ± SD, range)	66 ± 12.2 (33-89)
Effective: acute	163 : 27
ASA (mean ± SD)	2.11 ± 0.73
Observed mortality (%)	9 (4.7)
Observed morbidity (%)	58 (30.5)
ACPGBI score (mean ± SD)	5.55 ± 4.48

The observed mortality in this group was 4.7%, morbidity 30.5%. The ACPGBI score predicted a mortality rate of 5.55% (+ 4.48).
27 of the 190 performed procedures were in an acute setting (Figure 3).

Figure 3. Predictive value of ACPGBI score on outcome after colorectal resection for malignancy.



The ACPGBI score, designed for oncologic colorectal resections, has a larger area under the curve than any of the POSSUM scores (0.854; P<0.001). The same applies to oncologic resections performed in the elective setting (P<0.001). ACPGBI was found not to be superior to POSSUM (P=0.83), P-POSSUM (P=0.56) and CR-POSSUM (P=0.84) in acute oncologic surgery. 14 out of 65 patients (21.5%) died after a change in treatment policy due to extensive oncological disease (n=11) or the lack of perspective on an acceptable outcome (n=3). Morbidity as predicted by POSSUM is most accurate in procedures for diverticulitis (0.757) and worst when the indication is malignancy (0.532).

Discussion

When POSSUM is applied for individual risk prediction in patients undergoing colorectal resections for malignancy, inflammatory bowel diseases or diverticulitis, the most accurate mortality predictions with any of the POSSUM scores was in patients with diverticulitis. The ACPGBI score is found to be superior to POSSUM scoring in patients who had (elective) resections of colorectal cancers.

POSSUM and surgical audit

One of the main concerns in POSSUM scoring is its overestimation of mortality. The mortality rate predicted by POSSUM (17.0%) was double the observed mortality in our total study population (8.9%). The drawbacks of the original POSSUM score led to the development of Portsmouth POSSUM and Colorectal POSSUM. In our study, both scores underestimated the mortality risk (5.9% and 4.0% respectively). Several reasons can be pointed out. First, the primary studies on POSSUM extend their analyses back to the early 1990s and are less likely to represent current practice.(14) Better understanding of diseases, improvements in diagnostic and therapeutic techniques have lowered mortality rates. Regarding surgical practice, developments such as laparoscopic intervention and enhanced recovery programs have caused a decrease in mortality.(15) Hence, mathematical prediction models may be outdated. Law et al.(16) reported over-prediction of the POSSUM scores for laparoscopic colorectal resections. In converted controls however, POSSUM scoring was reliable which implies a discrepancy in predictive value due to operative technique. Second, POSSUM was originally developed with patients in the United Kingdom. However, outcomes may vary with other countries or high volume, specialized centers.(17;18) Third, surgery got more and more specialized over time. The original POSSUM score was designed for the general surgical patient. The accuracy of these models is under discussion due to the use of mixed patient populations. More recently, several studies specify risk prediction for different subgroups.(14) In our opinion, the main argument against the use of POSSUM in surgical audit is found in the validation as a risk prediction model. Nearly all reports on POSSUM scoring validate the score on their own series, which leads to different conclusions of reports regarding to over- or under predicting of the scores. Patient selection, local facilities and skills may be confounding factors. This is illustrated by a broad range of observed vs. expected ratios in the literature (Table 5).

Table 5. Observed: expected ratios in the literature.

Author	POSSUM		P-POSSUM		CR-POSSUM		ACPGBI	Mortality
	POSSUM	*O:E**	*P-POSSUM*	*O:E*	*CR-POSSUM*	*O:E*		
Malignancy								
Oomen (33)	10.6	0.16	3.8	0.45	3.8	0.45		1.7
Slim (7)	13.3	0.28	5.5	0.67				3.7
Ferjani (20)	12.7	0.80	4.4	2.32	9.6	1.06	8.1	10.2
Ren (42)	5.6	0.18	2.8	0.35	4.8	0.20		1.0
Horzic (43)			6.7	1.24	7.5	1.11		8.3
Ugolini (44)			7.9	0.79	9.14	0.68	19.4	6.3
Menon (9)			15.6	0.56				8.7
Tez (30)			9.0	0.77	7.8	0.88		6.9
Bromage (28)	1.9	3.37		1.59		1.25		6.5
Ibister (45)	6.7	0.21	3.5	0.40				1.4
Poon (46)			15.0	0.75				11.3
Tan (47)					11.2	0.14	5.4	1.6
Ugolini (48)			11.2	0.92	13.1	0.79		10.3
Can (49)	13.4	0.27	5.2	0.69				3.6
Diverticulitis								
Oomen (33)	6.3	0.52	2.2	1.50	2.3	1.43		3.3
Slim (7)	6.9	0.38	2.8	0.93				2.6
Oomen (50)	7.7	0.74						5.7
Constatinides (32)	21.9	0.49	10.5	1.03	10.0	1.08		10.8

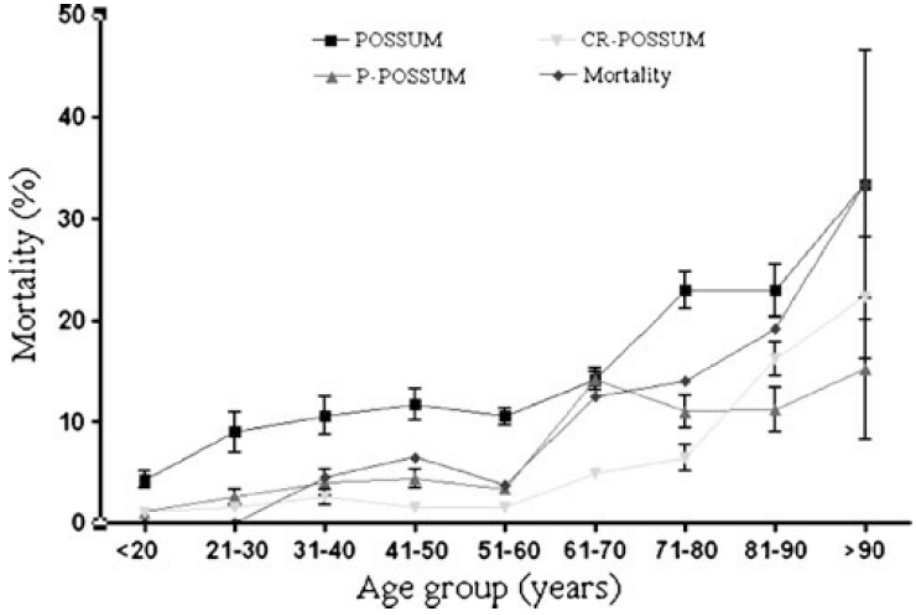
In our opinion, risk prediction models need to be validated to a 'gold standard' in order to allow comparative audit. Since reports on surgical outcome differ and definitions of adverse outcome may vary, this desired standard may be unrealistic. Russell(19) and Ferjani(20) have stated that a system with standard definitions is mandatory before clinical performance can be compared between health care systems and institutions. A proper and uniform definition of mortality is essential in risk prediction. Most studies on POSSUM describe mortality as primary outcome only. As Brooks et al.(6) pointed out, the majority of surgical procedures carry a low risk of death. However, along with decreasing mortality rates, the relevance of predicting morbidity is increasing. POSSUM also predicts the chance that a patient develops one or more complications with only moderate accuracy (area under the curve 0.53- 0.76). Cumulative Sum Techniques (CUSUM), described in 1954 by Page and its first introduction in surgical practice in 1994, might encounter the drawbacks mentioned above. This technique allows one to judge whether an observed variation in performance is acceptable (i.e. probably due to chance) or whether the variation is greater than what could be expected from

random variation and thus may be a cause for concern. However, acceptable and unacceptable outcome rate as Type I and II error rate has to be defined first. CUSUM is helpful in the evaluation of a clinical procedure before its implementation without the drawbacks of a randomized clinical trial. Plotting of cumulative sum has proved valuable for examining sequential measures, detecting changes over time and is applied as a means of assessing surgical skills of trainees. Continued surveillance using the CUSUM allows early detection of factors that lead to an increased failure rate. Quality control and objective and quantified recording of the findings meet the recommended criteria for medical audit.(21-25)

POSSUM and individual risk prediction

By tailoring POSSUM to patient- and procedure-specific assessment, it becomes a tool that can help to inform the individual patient on a certain procedure and the risk on adverse outcome. Several studies reported the value of POSSUM in surgery for colorectal cancer.(9; 26-30) Tekkis et al.(31) developed the colorectal POSSUM and differentiated for elective or acute procedures and procedures performed for malignancy or no malignancy. Constantinides et al.(32) studied the value of POSSUM scoring in patients with complicated diverticulitis and concluded that CR-POSSUM was more accurate to predict outcome than (P-) POSSUM. Oomen et al.(33) retrospectively compared the different POSSUM scores in 241 patients undergoing elective resection of the sigmoid for carcinoma or diverticular disease. Although patients with diverticular disease had a higher score than patients with malignancy, mortality rate did not differ. It was concluded that none of the POSSUM scores was predictive of disease-specific mortality. However, we found significant differences in POSSUM scoring related to the indication of surgery. All POSSUM scores predicted outcome more accurately in patients with diverticular disease than in patients operated on colorectal cancer. Within the subgroup of patients with diverticular disease, we could not define a superior POSSUM score. POSSUM, P- and CR-POSSUM scores also predicted equally in patients with colorectal cancer. In our opinion, disease-specific patient and operative variables should be included to improve the scores. Furthermore, patients are getting older and pre-existent morbidity is likely to increase. In our series, a larger variation of the various POSSUM scores is found in octogenarians (Figure 4). This is in accordance with Slim et al.(6), who studied risk prediction by POSSUM and the AFC index (Association Française de Chirurgie). It is unclear whether the introduction of more extensive cardiac and pulmonary risk indexes might further improve predictive accuracy of POSSUM scoring. It may further complicate POSSUM scoring. The AFC index is a simpler instrument without any mathematical formulas. It uses only 4 independent preoperative factors and is found to be as predictive as P-POSSUM.

Figure 4. Observed and predicted mortality related to age group.



Malignant colorectal disease

All mean POSSUM scores were higher in the carcinoma group than in diverticulitis, whilst observed mortality rates were comparable. ACPGBI scoring was found to be superior in predicting mortality after resection of colorectal cancer both in elective and acute interventions, which is consistent with the literature.(20)(34) 37 out of 386 patients operated for colorectal malignancy (9.6%) had known metastasis. Mortality rate was 29.7% (11/37); all patients died as consequence of a change to tender loving care due to a lack of perspective on a reasonable outcome (Table 3). Mean POSSUM, P-POSSUM and CR-POSSUM score in the deceased group were lower than in patients who survived (respectively 11.7 vs. 21.1, P=0.02; 3.9 vs. 7.8, P=0.05 and 2.5 vs. 3.6, P=0.07). Although based on a small population, these results demonstrate the insufficient predictive value of POSSUM scoring in patients with extensive oncological disease. Patients with colorectal cancer are likely to be immunosuppressed due to elderly age, nutritional status and the colorectal cancer itself. (35;36) The Dukes' classification is too coarse to reflect today's pathologists' power to detect disease parameters in cancer.(33) Implementation of nutritional status in POSSUM might help to improve the area under the curve in malignancy. (4,7,28) Both suggestions for improving POSSUM scoring need further research. Question remains whether or not these patients have to be taken into account in validating risk prediction models. Well-informed patients with advanced cancers may trade off a short-term risk in exchange for cancer cure. In this population, the risks of resectional surgery may outweigh the benefits of a simpler and possibly safer palliative operation, but this requires reliable risk estimations.(13)

Inflammatory bowel diseases

No previous studies evaluated POSSUM scoring in patients with inflammatory bowel disease. Due to the view of the physiological variables included in POSSUM, the younger, relatively healthy patient with inflammatory bowel disease is likely to have a different score than the elderly with an extensive medical history operated for colorectal carcinoma. Patients with colitis often have an increased white blood cell count and low levels of hemoglobin or albumin, reflecting disease activity. Furthermore, these patients often use immunosuppressive medication and have a poor nutritional status, which is found to increase adverse outcome after surgery.(37) We found lowest POSSUM scores in this subgroup for mortality, which corresponded with the observed death rate. However, POSSUM underestimated morbidity. Younger age and the absence of cardiopulmonary comorbidity may explain the capability to overcome postoperative complications. POSSUM scoring for IBD may require a more prominent role of age, use of medication, nutritional status, level of hemoglobin, albumin and white blood cell count. (28) Calibration of POSSUM for patients with inflammatory bowel disease may be hard, since recent review showed an improved outcome of surgery to be highly dependent on accurate timing of the surgery and better perioperative care. (38)

Diverticular disease

The most reliable predictions as demonstrated by the highest areas under the curve were found for patients with diverticulitis. The observed mortality was considerably higher than in patients operated for inflammatory bowel diseases and almost similar to patients with carcinomas. Patients with diverticulitis had the highest body mass indexes and were operated urgently more often, both associated with an increased complication rate.(39-41) Left sided resections were more frequent performed in patients with diverticular disease (81.3%) than in malignancy (50.3%) and inflammatory bowel diseases (15%). Left sided resections are known to cause more complications.(37) Another explanation may be patient selection. High-risk patients with diverticular disease may be withheld from surgery, whereas a malignant indication for surgery will not allow a conservative treatment strategy. Accurate definition of high-risk patients is essential. Body mass index, operative urgency and degree of peritoneal contamination may be important variables in order to calibrate POSSUM scoring for diverticulitis.

This study questions the role of POSSUM for comparison of clinical performance between health care institutes. Poor definitions of surgical outcome and problematic validation of this risk prediction model are the main objections to use POSSUM for surgical audit. In its present form, POSSUM scoring should not be used for medical decision making in individual patients either. Future investigation needs to point out if further calibration of POSSUM is feasible, or that alternative risk prediction models need to be developed. One solution may be for models to be more disease specific.

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Chapter 3

Enhanced recovery after surgery (ERAS) versus conventional postoperative care in colorectal surgery

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Abstract

Background

Enhanced Recovery After Surgery (ERAS) programs are associated with reduced hospital, morbidity and mortality. The aim of the present study was to evaluate whether the introduction of ERAS care improved the adverse events in colorectal surgery. In a cohort study mortality, morbidity and length of stay were compared between ERAS patients and carefully matched historical controls.

Methods

Patients were matched for their type of disease, the type of surgery, (P-, CR-) POSSUM score, gender and American Society of Anesthesiologists (ASA) grade. The primary outcome measures of this study were mortality and morbidity. Secondary outcome measures were fluid intake, length of hospital stay, the number of re-laparotomies and the number of readmissions within 30 days. Data on the ERAS patients were collected prospectively.

Results

Sixty-one patients treated according to the ERAS program were compared with 122 patients who received conventional postoperative care. The two groups were comparable with respect to age, ASA grade, (P-, CR-) POSSUM score, type of surgery, stoma formation, type of disease and gender. Morbidity was lower in the ERAS group compared to the control group (14.8 % versus 33.6% respectively; P=<0.01). Patients in the ERAS group received significantly less fluid and spent fewer days in the hospital (median 6 days; range 3-50 vs. median 9 days; range 3-138; P= 0.032). There was no difference between the ERAS and the control group for mortality (0 vs. 1.6%; P=0.55) and readmission rate (3.3 vs. 1.6%; P= 0.60).

Conclusion

Enhanced Recovery After Surgery program reduces morbidity and the length of hospital stay for patients undergoing elective colonic or rectal surgery.

Introduction

Colorectal resections are associated with an in-hospital stay of 6 to 11 days and a complication rate of 15% to 20%. 'Fast-track' or enhanced recovery programs are developed to improve perioperative care in these patients.(1-3) ERAS (Enhanced Recovery After Surgery) protocols aim at reducing the surgical stress response and optimizing recovery, thus reducing the length of hospital stay. All elements in ERAS separately have been shown to improve patient outcome. Preoperative education about the ERAS program diminishes anxiety and is associated with an earlier return of gastro-intestinal motility after surgery.(4) Pre-operative carbohydrate loading is associated with earlier return of gastro-intestinal motility and a significantly shorter hospital stay.(5) Colonic lavages are associated with patient discomfort and electrolyte disturbances and can safely be avoided in elective colonic surgery.(6-10) Epidural analgesia provides better treatment of postoperative pain and leads to an earlier gastro-intestinal motility.(11;12) Hypotension, a common physiologic side effect of epidural analgesia, can be treated safely with a vasopressor.(13) Post-operative pain relief is best managed without opioid analgesia because of the adverse effects it has on the central nervous system, respiratory function and gastrointestinal function.(14) Intraoperative fluid management aiming at a zero balance reduces the number of patients who experience morbidity and shortens the time to recovery of gastro-intestinal motility and reduces hospital stay.(15;16) Early post-operative enteral feeding shows a reduction in the risk of postoperative complications, hospital stay and mortality.(17) Bed rest after surgery is undesirable because it impairs pulmonary function, tissue oxygenation and predisposes to pulmonary complications.(18) To avoid this, mobilizing patients as soon as possible is an important factor in improving postoperative care. The aim of the present study was to compare mortality, morbidity and in-hospital stay in a cohort of carefully matched patients receiving conventional postoperative care and the ERAS program to evaluate the clinical relevance of the improved perioperative care.

Methods

Identification of patients

A cohort of consecutive patients that underwent elective open colonic or rectal resection following the ERAS regime was compared with a matched historical cohort who underwent colonic or rectal resection with conventional perioperative care. Between May 2006 and July 2008 patients, who were above 18 years of age and were scheduled for any colonic or rectal resection and had an American Society of Anesthesiologists (ASA) grade of 1-3, were treated according to an ERAS program. In all patients a colorectal resection was performed, with or without primary anastomosis. A loop ileostomy was created in any low rectal anastomosis and in patients with a high estimated risk to develop anastomotic leakage.

Running two protocols of postoperative care in one surgical ward would be prone to bias in a randomized trial. For this reason a matched cohort study was performed. Since all eligible patients operated in the time-span mentioned above received ERAS, a historical control group was used, composed of patients that would have been eligible for ERAS in the successive period. Patients in the control group were operated from January 2003 to May 2006. The latter group was obtained from a surgical database. The same team of surgeons performed all procedures. Each patient from the ERAS group was matched with two patients from the control group on age, gender, (P-, CR-) POSSUM score (Physiological and Operative Score for enUmeration of Mortality and morbidity), American Society of Anesthesiologists (ASA) grade, type of disease and surgical procedure.

Criteria of exclusion

Patients with an ASA grade 4-5 and younger than 18 years were excluded from analysis.

ERAS protocol

In the outpatient clinic, patients who were treated according to the ERAS protocol were informed about the operative procedure and rehabilitation program. Before surgery, patients were consulted by an anesthesiologist and if necessary by a dietitian. All patients were admitted the day before surgery and could eat until midnight, including four drinks of carbohydrate (PreOP®, Nutricia; Numico, Zoetermeer, the Netherlands). Patients could drink water freely until 2 hours before surgery. Two hours before surgery patients received two drinks of PreOP®. In the case of a planned left sided resection, a phosphate enema was given the evening before and on the day of surgery. Thrombotic prophylaxis (nadroparin 2850 IE) was started the day before surgery. Antibiotic prophylaxis (cefazolin 2 g and metronidazole 500 mg intravenously) was given 30 minutes before incision. A transverse incision was preferred, except in Crohn's disease and rectal surgery. In order to maintain a normothermic body temperature, the temperature in the operating theatre was increased to 22 degrees Celsius and a bair hugger and warmed intravenous fluids were applied. Anesthesia consisted of a combination of epidural analgesia and general anesthesia. Before the induction of anesthesia, an epidural catheter was inserted at level Th7/8. After the confirmation of proper placement by a test dose (Lignocaine 2% 3 ml), bolus infusion of 4 ml sufentanil produced sufficient analgesia for the first 30 minutes of surgery. Afterwards, repeated bolus infusion of 2-3 ml bupivacaine 0.5 % maintained the operative analgesia. No additional opioids were given intravenously. At the end of surgery, continuous epidural infusion of 6 ml/hour of ropivacain 0.2% with 1 microgram/ml sufentanil was started for postoperative analgesia. This infusion lasted for two days postoperatively. During and after surgery, hypotension was preferably treated with a vasopressor agent (ephedrine 5 mg or phenylefrine 0,1 mg) instead of intravenous fluid bolus in order to maintain a neutral fluid balance throughout the perioperative period. No drains were used except in rectal surgery and

the nasogastric tubes were removed immediately after surgery. To prevent post-operative nausea and vomiting 4 mg ondansetron was administered intravenously at the end of surgery. After surgery the patient was allowed to drink water and, if tolerated, patients received two drinks of PreOP®. On postoperative day 1, patients were offered a normal diet. Intravenous fluid administration aimed at a urine production of at least 0.5 ml/kg and the total fluid intake should not exceed 2 liter/24h. Fluid balances were recorded daily. A structured mobilization program was also included in the ERAS protocol. Patients were encouraged to sit out of bed on the day of surgery and to walk the length of the ward on the first postoperative day. The inserted urinary catheter was removed at the same time as the thoracic epidural catheter. Subsequently, pain was managed with paracetamol and nonsteroidal anti-inflammatory drugs. The use of oral opioid analgesics was limited to relieve breakthrough pain. Each protocol item and any deviation from the protocol were noted on a bedside checklist. Discharge criteria were: adequate pain relief on non-opioid oral analgesia, normal food intake and return to preoperative mobility level.

Conventional postoperative care protocol

The perioperative care, before the ERAS program was implemented, was according to the surgeon's preference. Thrombotic and antibiotic prophylaxis was given and the practice of bowel preparation was largely abandoned. Discharge criteria were identical to the ERAS-era.

Data extraction

After retrieving all reports and information from paper and electronic patient files, the following data were extracted: sex, age, indication for surgery, type of surgery, ASA grade, POSSUM score, P-POSSUM score, CR-POSSUM score, stoma formation, type of medication, oral and intravenous fluid intake, urinary output, stoma production, nasogastric tube production, length of stay in the hospital, number of readmissions, complication and mortality rate. In the ERAS group additional data were prospectively collected: first day of defecation, length of epidural analgesia, first day of mobilisation and the number of days that oral analgesia was used.

Outcome measures

The primary outcome measures were mortality and morbidity. Mortality was defined as death within 30 days after surgery. A complication was defined as an unfavorable postoperative course with the need for an intervention to prevent further harm, according to the definition of the Dutch Association of Surgeons. Individual complications were defined as stated in Table 1. Secondary outcome measures were fluid intake, reinsertion of nasogastric tubes, number of re-laparotomies, length of hospital stay and number of readmissions within 30 days.

Table 1. Definitions of separate complications.

Surgical complications	
Wound hemorrhage	local hematoma requiring evacuation
Deep haemorrhage	postoperative bleeding requiring re-exploration
Burst abdomen	deep wound breakdown, requiring surgical closure of the abdominal wall
Deep infection	the presence of an intra-abdominal collection confirmed clinically or radiologically
Anastomotic leak	discharge of bowel content via the drain, wound or abnormal orifice
Wound infection	wound cellulitis or the discharge of purulent exudate and the necessity of opening the wound
Medical complications	
Chest infection	production of purulent sputum with positive bacteriological cultures, with or without chest radiography changes or pyrexia, or consolidation seen on chest radiograph
Urinary infection	the presence of > 10^5 bacteria / ml with the presence of white cells in the urine, in previously clear urine
Septicaemia	positive blood culture
Pyrexia of unknown origin	any temperature above 37° C for more than 24 h occurring after the original pyrexia following surgery (if present) had settled, for which no obvious cause could be found
Deep venous thrombosis and pulmonary embolus	when suspected, confirmed radiologically by venography or ventilation / perfusion scanning or diagnosed at post mortem
Cardiac failure	symptoms or signs of left ventricular or congestive cardiac failure (alteration from preoperative measures)
Impaired renal function	symptoms or signs of left ventricular or congestive cardiac failure (alteration from preoperative measures)
Hypotension	a fall in systolic blood pressure below 90 mmHg for more than 2 hours as determined by sphygmomanometry or arterial pressure transducer measurement
Respiratory failure	respiratory difficulty requiring emergency ventilation

* Complications had to occur within 30 days after surgery.

Analysis

The analysis was by intention-to-treat principles. No patients were excluded for reasons of protocol violations. Statistical analyses were performed with SPSS® version 16.0 (SPSS, Inc., Chicago IL) for Windows® and STATS direct® (Altrinchem, UK). Medians and ranges or means and standard deviations are presented for all continuous outcome measures. Comparisons between the ERAS and conventional postoperative care group were made using the chi-square test for binary outcomes and the student's t-test was used for continuous outcomes. Non-parametric tests were carried out to calculate statistical differences in POSSUM scores.

Results

Sixty-one patients, treated according to the ERAS program, were matched with 122 historical controls that had conventional postoperative care. The two groups were similar with respect to age, ASA grade, (P-, CR-) POSSUM score, type of surgery, stoma formation and type of disease (Table 2).

Table 2. Patient characteristics and types of surgery.

	ERAS (%) (n=61)	*Control (%) (n=122)*	*P-Value*
Characteristic			
Male *	36.1 (n=22)	50.8 (n=62)	0.06
Female *	63.9 (n=39)	49.2 (n=60)	
Age (years) *	57 (17.6)	60 (17.4)	0.39
POSSUM **	7.50 (6.1)	8.37 (6.7)	0.37
P-POSSUM **	2.59 (2.9)	2.57 (2.8)	0.92
CR-POSSUM **	2.75 (3.2)	2.79 (3.2)	0.93
Stoma formation *	11.5 (n=7)	9.0 (n=11)	0.60
Type of surgery *			0.95 ***
Ileocecal resection	21.3 (n=13)	19.7 (n=24)	
Right hemicolectomy	37.7 (n=23)	39.3 (n=48)	
Left hemicolectomy/ resection of sigmoid	3.3 (n=2)	3.3 (n=4)	
(Low) anterior resection	24.6 (n=15)	24.6 (n=30)	
Subtotal colectomy	13.1 (n=8)	13.1 (n=16)	
Type of disease *			
Cancer	75.4 (n=46)	77.1 (n=94)	0.83 ***
IBD	23.0 (n=14)	21.3 (n=26)	
Diverticulitis	1.6 (n=1)		
ASA grade *			
1	29.5 (n=18)	25.4 (n=31)	0.1 ***
2	59.0 (n=36)	53.3 (n=65)	
3	11.5 (n=7)	21.3 (n=26)	

* The first number is the percentage and the number in between the brackets is the absolute number
** The first number is the mean and the number in between brackets is the standard deviation
*** These P-values represent the overall similarity of the two groups in these characteristics

Females were slightly overrepresented in the ERAS population (63.9 vs. 36.1%; P=0.06). 57 patients (93%) who were treated in the ERAS group had an epidural catheter until the second postoperative day (median; range:1-4). 4 patients in whom placing the epidural catheter could not be realized received a PCA-pump. Patients were mobilized out of bed on the first postoperative day (median; range: 0-3).

The stools were passed on day 3 (median; range: 0-11) versus 4 days (median; range 1-8) in the control group. NSAIDs were used until day 4 (median; range: 0-15). Paracetamol was used until day 6 (median; range: 0-40). In the control group 77 patients had epidural anesthesia (63%). The morbidity rate was higher in the control group than in the ERAS group (33.6 % vs. 14.8 %; P<0.01). Total number of complications amounted 63 in the control group versus 12 in the ERAS group (P=<0.01). Corrected for gender, the control group had a 3.4 times higher risk to develop an unfavorable postoperative course than the ERAS group. Individual complications were similar in both groups, except for urinary tract infections. None of the patients in the ERAS group developed a urinary tract infection versus 6.6% of the patients in the control group (P=0.05). Septicemia occurred in none of the patients in the ERAS group, the incidence was 3.3% in the control group (P=0.30). 4.9% of the patients in the ERAS group developed a wound infection versus 11.5% of the patients in the control group (P=0.18). In the control group, 6.6% of the patients developed a deep surgical site infection. For ERAS this amounted 1.6% (P=0.28). Anastomotic leakage occurred more often in patients who had conventional postoperative care (7.4% vs. 3.3% (P=0.34). A dehiscence of all layers of the abdominal wall was seen in 1.6% in the ERAS group and in 4.1% of the patients in the control group (P=0.67) (Table 3).

Table 3. Morbidity rates in the ERAS and control group.

	ERAS %; (n)	Standard care %; (n)	P-Value
Surgical complications*			
Wound hemorrhage	0	0	
Deep haemorrhage	4.9 (3)	0.8 (1)	0.11
Anastomotic leak	3.3 (2)	7.4 (9)	0.34
Wound infection	4.9 (3)	11.5 (14)	0.18
Deep infection	1.6 (1)	6.6 (8)	0.28
Burst abdomen	1.6 (1)	4.1 (5)	0.67
Medical complications*			
DVT / embolus	0	0	
Chest infection	1.6 (1)	4.1 (5)	0.67
Cardiac failure	0 (0)	2.5 (3)	0.55
Urinary infection	0 (0)	6.6 (8)	0.05
Septicaemia	0 (0)	3.3 (4)	0.30
Pyrexia of unknown origin	0 (0)	0 (0)	
Impaired renal function	0 (0)	2.5 (3)	0.55
Hypotension	0 (0)	0 (0)	
Respiratory failure	1.6 (1)	2.5 (3)	0.99
Total number of complications **	12	63	0.0001
Patients with complication(s)	14.8 (9)	33.6 (41)	0.008

* The first number is the percentage and the number in between the brackets is the absolute number
** Only the absolute number is shown

No patient died in the ERAS group within 30 days after surgery. Two patients in the control group died (1.6%; P=0.55). One patient developed congestive heart failure after fluid resuscitation for hypotension. Eight days later she became septicaemic, a laparotomy was carried out and bowel ischemia was found. The other patient also received an excess of fluid because of her low urine output and low fluid intake. Nevertheless, her renal function deteriorated. Four days later she also developed fatal heart failure. Patients receiving ERAS postoperative care, were administered significantly less intravenous fluid during (day of) surgery and day 1 till 5 postoperative (P<0.001). Oral intake was higher than in the control group on day of, first and second day postoperative (P< 0.001). This led to a larger urinary production on the first three postoperative days in the control group (P<0.05). Total fluid intake was higher in the second and third postoperative day (p<0.05) (Figure 1-4).

Figure 1. Intravenous fluid intake (ml/day).

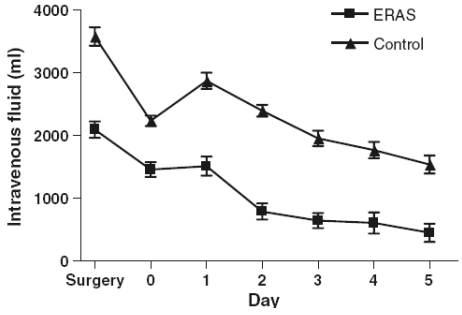


Figure 2. Oral fluid intake (ml/day).

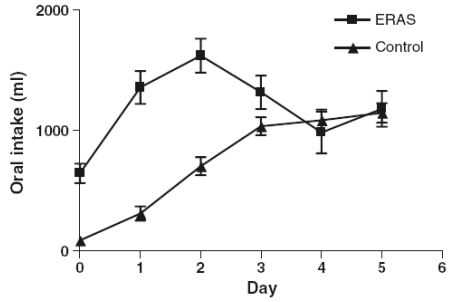


Figure 3. Total fluid intake (ml/day).

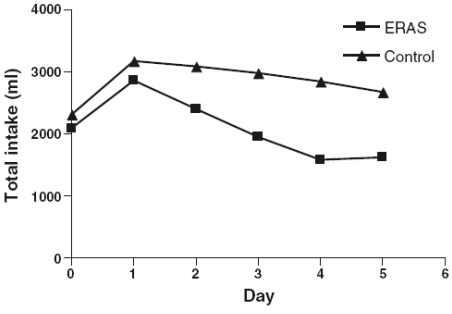
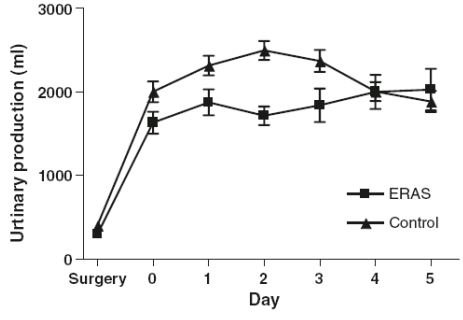


Figure 4. Urinary fluid intake (ml/day).



Reinsertion of nasogastric tubes was similar in both populations (P=0.85; Table 4). Patients treated according to the ERAS regime spent significantly fewer days in the hospital (median 6; range 3-50) than the control group (median 9; range 3-138; P= 0.032). The number of readmissions was similar in both groups (3.3% ERAS vs. 1.6% control; P=0.60) (Table 4).

Table 4. Mortality and secondary outcomes of the patients in the ERAS and control group.

	ERAS %; (n)	Standard care %; (n)	P-Value
Mortality*	0 (0)	1.6 (2)	0.55
Number of reinserted nasogastric tubes*	19.7 (12)	21.3 (26)	0.85
Time to first defecation (days)•	3 (0-11)	4 (1-8)	
Length of hospital stay (days)•	6 (3-50)	9 (3-138)	0.021
Number of readmissions*	3.3 (2)	1.6 (2)	0.60
Number of re-laparotomies*	14.8 (9)	17.2 (21)	0.83
Burst abdomen	1.6 (1)	4.1 (5)	0.67

* The first number is the percentage and the number in between the brackets is the absolute number
** The first number is median and the number in brackets in range

Two patients in the ERAS group were readmitted with surgical site infections. One developed a presacral abscess, which was drained transrectally. The other patient developed a wound abscess, which was incised and drained. One patient in the control group developed an intra-abdominal abscess, which was treated conservatively. The other patient had successful conservative treatment for a gastro paresis.

Discussion

The results of this study suggest that the Enhanced Recovery After Surgery program is superior to conventional postoperative care for patients undergoing elective colonic or rectal resection. Patients treated according to an ERAS program develop significantly less complications and are shorter hospitalized. This study is a historic cohort study with carefully matched controls. The control group was chosen from years prior to the introduction of the ERAS program. Because the discharge criteria were identical in both groups further reduction of bias was achieved. Observer bias was avoided, though awareness about early recovery may have influenced decisions on early discharge. On the other hand, data in the ERAS group were collected prospectively. The historic nature of the control group is likely to have caused the underreporting of complications, thus leading to an underestimation of the beneficial effect of ERAS. Since patients in both groups were operated by the same team of surgeons, selection bias is thought to be small. A randomized trial on ERAS is difficult to perform, because running traditional and ERAS care simultaneously carries the risk of mixing elements of both regimens. Blinding of nursing and medical staff would be impossible. To overcome these flaws, the design of such a study is challenging. In our study, patients were carefully matched. Females were slightly overrepresented in the ERAS group ($p=0.06$). Literature states male gender predisposes to an increased incidence of anastomotic leakage after colorectal surgery. One of the main theories is the higher levels of estrogens in females and anatomical differences of the pelvis.(19) Further analysis of the data excluded gender as a risk factor for the development of complications. There was less ASA 3 in the ERAS population (not significant). After excluding ASA 3 patients from analysis, significant differences in total number of complications and number of patients with one or more adverse events persisted. In this study, the targets of ERAS were met. All ERAS patients were informed in a standardized way in the outpatient clinic. They received a daily perioperative schedule. Patients knew what was expected and allowed. In the conventional group, it is likely information was not uniform due to variance in information between the individual surgeons. Second, all patients of ERAS received preoperative carbohydrate loading where none of the conventional treated patients had Pre-Op. Since it was policy not to apply colonic lavages before the ERAS era, there was no difference between both groups. Epidural use was good practice in the conventional group, however, in the ERAS protocol it was one of the key elements. This led to a higher epidural use in the ERAS population (93 vs. 63% respectively; $P<0.001$). Epidural analgesia, one of the main issues in fast track protocols, has been suggested to provide an optimal pain relief, thus reducing surgical stress response and may reduce postoperative morbidity and mortality.(3,12,20) Rodgers et al.(20) found a significant reduction in deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia, other infections and respiratory depression in patients with neuroaxial blockade. It is likely that this difference contributes to a reduced complication rate in ERAS. Patients in the ERAS group received less fluid intravenously and started drinking sooner after surgery.

Total fluid intake and urinary production was higher in the control group. In our findings, morbidity was higher in the control group. Excessive fluid administration is thought to contribute to an increased complication rate.(16,21-23) It is important to realize more elements than mentioned above may contribute to improved outcome: the use of short-acting and oral anaesthetics and prokinetics, lack of premedication and nasogastric tubes, early removal of catheters and drains, minimal length incisions, early mobilization and the preservation of normothermia.(3)
It is likely that the combination of elements in ERAS favoured uncomplicated outcome after colorectal surgery. Mortality did not differ between both groups. Two patients (83 and 85 years old) in the control group died because of cardiac complications. Patients in the control group had an almost three-fold risk to develop one or more complications. Individual complications failed to reach significance. Since data collection in the historic group could lead to underreporting of minor complications, this is less likely for major complications, e.g. anastomotic leakage, surgical site infections and burst abdomen failed significance. All, however, tend to be more frequent in the conventional care group. Although this ERAS program is evidence-based, some improvements can be made. Recent evidence suggests that perioperative supplemental oxygen administration reduces the incidence of surgical wound infections.(24) It exposes the patient to little or no risks, has little associated costs while it reduces the incidence of wound infections by half.(25) The addition of specialized nutritional products to the standard carbohydrate drinks, offered to patients in the used ERAS program, also shows promising results towards reducing complications after gastro-intestinal surgical procedures. The specialized nutritional products are the amino acids arginine and glutamine, omega-3 fatty acids and nucleotides in the form of RNA. Wound infections, anastomotic leakage, abdominal abscesses and pneumonia were significantly reduced. (26)
Patients who were treated according to the ERAS program spent significantly less time in the hospital. This did not result in more readmissions that reflect early recovery, probably due to a more favorable postoperative course. Besides, this implies benefit for the hospital resources because with the implementation of the ERAS program a higher level of cost-effectiveness can be reached.

This study demonstrates that the program as a whole is clearly beneficial and not flawed with unexpected negative effects. Epidural analgesia and a restricted fluid administration are thought to be the main contributing factors to a favorable outcome. More research is necessary to optimize perioperative care.

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Chapter 4

Enhanced recovery after surgery (ERAS) versus conventional perioperative care in rectal surgery

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Abstract

Background
Enhanced Recovery After Surgery programs have been developed to improve recovery, shorten hospital stay and reduce morbidity.

Objective
The aim of the current study is to examine the effects of the enhanced recovery program on the outcome of rectal surgery.

Design
A cohort of patients that underwent open rectal surgery following an enhanced recovery program was compared with a historical case matched control group receiving conventional perioperative care. Patients were matched for type of surgery, disease, comorbidity and demographic characteristics. Data regarding fast track targets, length of hospital stay, mortality, complications, re-laparotomies and readmissions were collected.

Results
Forty-one patients in the enhanced recovery group were compared with eighty-two case-matched patients receiving conventional care. The length of hospital stay (median 8 days versus 12 days, $P<0.005$) was reduced in the ERAS group. There were no significant differences in epidural use, mortality, morbidity and readmission rates.

Limitations
This study performed an intention to treat analysis for the multi-modal enhanced recovery program in rectal surgery. Specific elements of the program were not analyzed separately. The study used nonrandomized historic controls for comparison.

Conclusion
Enhanced recovery programs help to reduce hospital stay after rectal surgery.

Background

Traditionally, colorectal surgery has been associated with long recovery periods and a hospital stay of 1 to 2 weeks. Complication rates of 15-20% and up to 45-48% have been described.(1,2) Over the past decade, several traditional perioperative practices were shown to be outdated. Fast-track or Enhanced Recovery After Surgery (ERAS) programs have been designed to improve recovery, shorten hospital stay and reduce morbidity, without changing readmission rates and mortality. Moreover, ERAS has provided better control of postoperative pain, faster rehabilitation and return of gut function. (3-17) We confirmed these findings in our previous study concerning colorectal surgery in general.(18) Rectal surgery is associated with higher complication rates and longer hospital stay compared to colonic surgery.(16) Moreover, some items in the ERAS program, like the thoracic epidural, may need adjustment for rectal surgery, potentially eliciting different effects on recovery. Until this date, little is known about the value of enhanced recovery programs on rectal surgery.

The aim of the current study is to examine the effects of the Enhanced Recovery After Surgery program focusing exclusively on rectal surgery.

Materials and Methods

A consecutive series of patients from the Radboud University Nijmegen Medical Centre (Nijmegen, the Netherlands) that underwent open elective rectal surgery received perioperative care according to the ERAS protocol. The matched historical control group received conventional perioperative care. Patients aged 18 years or above, American Society of Anesthesiologists (ASA) grade I-III, who received this type of surgery between January 2008 and December 2009 were included. Cases undergoing multiorgan resections and emergency surgery were excluded. All patients were treated according to the ERAS protocol and underwent rectal surgery via laparotomy, with or without primary anastomosis. Like a previous study from this institution that examined ERAS care for general colonic resections(18), a matched cohort study was carried out. Matched controls were identified through an electronic database search for patients operated in our hospital between February 2000 and April 2006 (i.e. before the introduction of the ERAS program), who would have met the same in- and exclusion criteria for ERAS as mentioned above. Each patient from the ERAS group was carefully matched with two patients from the historical control group for age, gender, type of surgery, type of disease, ASA grade, age and Colorectal Physiologic and Operative Severity Score for the enUmeration of Mortality (CR-POSSUM) score. All procedures were performed according to the same technical operation protocols and operating team in the Radboud University Nijmegen Medical Centre, a tertiary referral center.

ERAS protocol

All patients in the ERAS group were cared for according to the enhanced recovery protocol as described previously(18), including preoperative patient teaching, carbohydrate supplements, thoracic epidural anesthesia and a restricted fluid regimen. Nasogastric tubes were removed directly after surgery. Peroperative intravenous fluid administration was based on calculated insensible loss aiming at a maximum fluid balance of + 500 mL. Suprapubic urinary drainage was standard in rectal resections since most patients had epidural anesthesia and urinary function may be impaired after rectal surgery and to prevent urinary tract infections. Oral fluid intake was resumed on the day of surgery and normal diet started as soon as tolerated. Normal diet was defined as: the eating of solid food in any desired quantity and without restrictions to the composition of the food or the way of preparation. Patients followed a mobilization program starting on the day of surgery. Sitting at the edge of the bed was encouraged on the day of operation and patients were stimulated walking on the corridor of the ward on the first postoperative day. In case of impaired mobility, regaining the preoperative mobility level was attempted on the first postoperative day. Postoperative analgesia was by patient controlled epidural infusion of Ropivacain (0.2%; 6 ml/h) and Sufentanyl (1 µg/ ml) for the first two days after the operation. Paracetamol and nonsteroidal anti-inflammatory drugs (Naproxen 2x 500 mg or Diclofenac 3x 50 mg) were given along with solid food. Opioid analgesics were used as escape analgesia only. Patients were considered fit for discharge when they had an adequate oral intake, had returned to their preoperative mobility level and were free of opioids or parenteral medication.

Conventional care protocol

Before the ERAS protocol was introduced in our hospital, patients received traditional perioperative care according to the surgeon's preference. Thrombotic and antibiotic prophylaxes were given and the practice of bowel preparation had already been abandoned. Discharge criteria were identical to the present ERAS protocol.

Data extraction

Data on ERAS patients were collected prospectively during admission. The doctor of the ward, responsible for daily visits and all patient examinations, collected data. Data were recorded on a case report form that was part of the daily notes in the patient file. The discharge letter was composed from this CRF in an automated fashion and used to extract data for further analysis in Excel and SPSS. Historical control group data were obtained from electronic and paper medical records. The collected variables are summarized in Table 1.

Table 1. Collected data*.

Surgical complications	*Pre-/intraoperative variables*	*Postoperative variables*
Low anterior resection	Sex	Complication
Abdominoperineal resection	Age	Length of hospital stay
	Indication for surgery	Re-laparotomies
	ASA grade	Readmissions
	CR-POSSUM score	In-hospital mortality
	Body mass index (BMI)	Compliance:
	Neoadjuvant therapy	- First day of mobilization; oral fluids; solid food defecation
	Medication use	- Day of stopping intravenous fluids; epidural analgesia
	Type of surgery	- Number of days oral analgesia was used
	Stoma and/or anastomosis formation	
	Level of epidural catheter	
	Intraoperative fluid balance	

* Data on ERAS patients were collected prospectively. Historical control group data were obtained from electronic and paper medical records.

Outcome measures

Outcome measures were length of hospital stay (LOS), mortality, complications, re-laparotomies and readmissions. Complications were classified as described before.(18) Complications and re-laparotomies were registered if taking place within 30 days after surgery or during (re-) hospitalization. Readmissions within 30 days after discharge were defined as surgery-related. Total LOS was classified as time hospitalized including days during any readmission.

Statistical analysis

Postoperative length of stay is an overall surrogate outcome measure reflecting recovery and the occurrence of complications. Based on previous data considering postoperative hospital stay after colorectal surgery in this institution, a sample size calculation showed that, using double controls, a minimum of 38 patients would be required in the ERAS group to demonstrate a significant reduction ($P<0.05$) in length of stay of 3 days with a power of 85 per cent.(18) Analysis was according to intention-to-treat principles. Results were analyzed using SPSS® (SPSS Inc, Chicago, Illinois) for Windows® version 16.0. Comparisons between the ERAS and control group were made using chi-square tests and Fisher's exact tests for all categorical variables, and Mann-Whitney U tests and t-tests for continuous variables. P values < 0.05 were considered statistically significant.

Results

Matching all patients in the ERAS group with historical cases resulted in similar patients in the study (n=41) and control (n=82) group. No significant differences were found regarding age, sex, ASA grade, BMI, CR-POSSUM score, operation indication and type of surgery (Table 2).

Table 2. Patient characteristics.

	ERAS (n=41)	Control (n=82)	P
Age (years) [1]	66.41 ± 11.62	63.39 ± 11.40	0.171 [3]
Sex [2]			
Male	65.9 (27)	59.8 (49)	0.5120 [4]
Female	34.1 (14)	40.2 (33)	
ASA [2]			
I	26.8 (11)	23.2 (19)	0.589 [4]
II	41.5 (17)	51.2 (42)	
III	31.7 (13)	25.6 (21)	
BMI [1]	25.55 ± 4.41	24.53 ± 3.61	0.173 [3]
CR-POSSUM (range 0.3-95.3) [1]	10.09 ± 10.82	8.42 ± 8.83	0.353 [3]
Physiology (range 6-16)	9.22 ± 2.56	8.55 ± 2.28	0.143 [3]
Operative severity (range 4-22)	11.41 ± 0.59	11.72 ± 0.59	0.008 [3]
Operation [2]			
Low anterior resection	53.7 (22)	53.7 (44)	1.000 [4]
diagnosis cancer	90.9 (20)	90.9 (40)	
Abdominoperineal resection	46.3 (19)	46.3 (38)	
diagnosis cancer	100 (19)	100 (38)	
First laparotomy [2]	70.7 (29)	59.8 (49)	0.234 [4]
Anastomosis [2]	41.5 (17)	45.1 (37)	0.700 [4]
Stoma formation [2]	87.8 (36)	74.4 (61)	0.086 [4]
Epidural anesthesia [2]	85.4 (35)	78.0 (64)	0.334 [4]
Neoadjuvant radiotherapy [2]			
5x5 Gy	34.1 (14)	29.6 (24)	0.583 [4]
25x2 Gy ± chemo	31.7 (13)	26.8 (22)	
None	34.1 (14)	43.9 (36)	

[1] Values are means ± standard deviation
[2] Percentages with absolute numbers in parenthesis
[3] t-test
[4] chi square test
ASA: American Society of Anesthesiologists; BMI: Body Mass Index; CR-POSSUM: Colorectal Physiologic and Operative Severity Score for the enUmeration of Mortality; IBD: Inflammatory Bowel Disease.

Stoma and anastomosis formation, prior laparotomies and type of anesthesia were similar in both groups. Most patients were operated on for cancer. There was no significant difference between the study group and the matched historic controls regarding use of neoadjuvant treatment in general and of chemo radiation in particular. The evaluation of adherence to the protocol showed a considerable shift of techniques applied. 80.5 percent of patients received epidural anesthesia. There was no difference in the use of epidural anesthesia between ERAS patients (85.4%) and controls (78.0%) (P=0.334). The epidural catheter was placed in the thoracic region in 73.2% of ERAS patients versus 50.0% in controls (P< 0.001). Lumbar epidural was used as an adjustment of technique to meet the anticipated needs of rectal surgery patients in 11.9% of ERAS patients versus 28.0% of historic controls (P<0.05). General anaesthesia without (adequate) epidural catheter was used in 14.6% of the ERAS patients vs. 22.0% in the control group (not significant). Peroperative fluid balances appeared to be less positive in ERAS (not significant). No significant difference was found between groups in the use of separate types of analgesics. Both opioids and non-steroidal anti-inflammatory drugs were used in similar percentages of patients with comparable periods of time.
Paracetamol use was comparable in both populations, but duration of use in the ERAS group was shorter. In the ERAS population, 70.7% had their nasogastric tubes removed and 61.0% started oral fluids on the day of surgery. The first postoperative day 70.7% of the patients mobilized out of bed and 48.8% resumed normal diet. Patients from the ERAS group stayed in hospital for a significantly shorter time than those in the conventional care group: median 8 days (interquartile range (i.q.r.) 6-18.5) versus 12 days (i.q.r. 9-17.5) (P<0.005; Table 3).

Table 3. Length of stay, readmissions, re-laparotomies and mortality .

	ERAS (n=41)	Control (n=82)	P
Median LOS (days) [1]	8 (6-18.5)	12 (9-17.5)	<0.005 [3]
LAR	8 (6-12)	10 (8-14)	0.035 [3]
APR	8 (7-22)	14.5 (10-24)	0.034 [3]
Median total LOS (days) [1]	9 (7-20.5)	13 (9-19)	0.040 [3]
Readmissions [2]	17.1 (7)	7.3 (6)	0.203 [4]
Re-laparotomies [2]	17.1 (7)	9.8 (8)	0.242 [4]
Mortality [2]	2.4 (1)	1.2 (1)	1.000 [5]

[1] Values are median (interquartile range)
[2] Percentages (absolute number)
[3] Mann-Whitney U test
[4] chi square test
[5] Fisher's Exact test.
LOS: postoperative length of stay. Total LOS: includes time in hospital during readmission.

Subgroup analysis revealed that patients undergoing LAR and APR both had a shorter length of stay. Although not significant, there was a trend towards more readmissions in the ERAS group. The total length of stay, however, was still shorter for ERAS patients: median 9 days (i.q.r. 7-20.5) versus 13 days (i.q.r. 9-19). The total number of complications did not differ in the control group compared to the ERAS group (68/82 vs. 31/41; P=0.334; Table 4).

Table 4. Morbidity rates in the ERAS and control group.

	ERAS (n=41)	Control (n=82)	P
Surgical complications	22.0 (9)	31.7 (26)	0.258 [2]
Wound hemorrhage	0	0	1.000 [3]
Deep hemorrhage	0	1.2 (1)	1.000 [3]
Anastomotic leak	4.9 (2)	3.7 (3)	1.000 [3]
Wound infection	9.8 (4)	20.7 (17)	0.127 [2]
Deep infection	9.8 (4)	6.1 (5)	0.479 [3]
Burst abdomen	2.4 (1)	1.2 (1)	1.000 [3]
Medical complications	34.1 (14)	37.8 (31)	0.691 [2]
DVT/embolus	0	0	1.000 [3]
Chest infection	14.6 (6)	7.3 (6)	0.212 [3]
Cardiac failure	0	2.4 (2)	0.552 [3]
Urinary infection	14.6 (6)	22.0 (18)	0.334 [2]
Septicemia	4.9 (2)	4.9 (4)	1.000 [3]
Pyrexia of unknown origin	0	2.4 (2)	0.552 [3]
Impaired renal function	7.3 (3)	2.4 (2)	0.332 [3]
Hypotension	4.9 (2)	6.1 (5)	1.000 [3]
Respiratory failure	2.4 (1)	2.4 (2)	1.000 [3]
Total number of complications [1]	31	68	0.334
Patients with complication(s)	39.0 (16)	56.1 (46)	0.074

Data are percentages with absolute numbers in parentheses, unless indicated otherwise.
[1] Absolute number
[2] chi square test
[3] Fisher's Exact test

39.0% of the ERAS patients had complications, compared to 56.1% in the conventional care group (P=0.07). Subgroup analysis of surgical complications, medical complications or each type of complication separately, failed to reach significance. Seven ERAS patients (17.1%) had complications which required re-laparotomy, against eight in the control group (9.8%); P=0.242. Reasons for re-laparotomy

in the ERAS group were perforated small intestine (1), anastomotic leakage (2), obstructive ileus (1), bowel necrosis (1), pelvic abscess (1) and burst abdomen (1). Control patients underwent re-laparotomy for anastomotic leakage (2), surgical site infection (1), burst abdomen (1), stoma necrosis (1), persistent ileus (1) and deep hemorrhage (1). In the ERAS group, one patient died on day 64 while hospitalized, due to multi organ failure and fecal peritonitis after a perforated small intestine. In the control group, one patient died on day 7 during admission, as a result of septicemia caused by generalized peritonitis after anastomotic leakage and re-laparotomy (P=1.000). Functional recovery was quicker in the ERAS group, as shown in Table 5.

Table 5. Functional recovery.

	ERAS (n=41)	Control (n=82)	P
Mobilization [1]	1 (1-1)	4 (2-5)	<0.001 [3]
Oral fluids [1]	0 (0-1)	2 (1-3)	<0.001 [3]
Solid food [1]	1 (1-3)	5 (4-8)	<0.001 [3]
Defecation [1]	2 (1-4)	4 (3-6)	<0.001 [3]
Nasogastric tube [2]	0 (0-1)	3 (2-6.75)	<0.001 [3]
IV fluids [2]	4 (2-8.75)	6 (4.75-12)	0.002 [3]
Epidural analgesia [2]	2 (2-2)	2 (1-2)	0.050 [3]
Opioids [2]	3 (2-4)	3 (1-5)	0.774 [3]
NSAID's [2]	6 (3-8)	6.5 (2-12)	0.643 [3]
Paracetamol [2]	7 (6-13.75)	10 (7.5-15)	0.006 [3]

Expressed as median number of days (i.q.r.).
[1] First postoperative day it was introduced
[2] Postoperative day it was stopped.
[3]cMann-Whitney U test

Mobilization and bowel movement started more rapidly, and oral fluids and normal diet were introduced at an earlier time after surgery (P<0.001). In the study population nasogastric tubes were removed on day 0 (i.q.r. 0-1) compared to day 3 (i.q.r. 2-7) in the conventional care group (P<0.001). Intravenous fluid administration was stopped 2 days earlier in the ERAS group (P=0.002).

Discussion

The present study shows that ERAS perioperative care reduces length of hospital stay after low anterior resection and abdominoperineal resection. The use of epidural anesthesia, readmission rates, mortality and morbidity did not change significantly. This report is a cohort study with carefully case-matched controls undergoing rectal surgery, resulting in two highly comparable groups. In contrast to several other articles, we also included multimorbid and senile patients without an age limit and those who had undergone previous abdominal surgery, thereby giving a valid image of the value of ERAS in these complex patients. This study however, has its drawbacks. A historical control group may give less reliable information about the parameters used and underestimate postoperative morbidity. Second, by non-randomizing the patients both groups may differ with regard to patient characteristics, primary diagnosis, co-morbidity and treatment. Too minimize this bias we performed a case matched controlled study. Discharge policies were identical in both groups, further reducing bias. While data on ERAS patients were collected prospectively, information on the control group was gathered retrospectively. This has likely led to an underreporting of complications in the historical group and thereby could have diminished the reported difference in complications between groups. The same applies to the effect of neoadjuvant treatment, more frequently and intensely applied in today's patients and rendering ERAS patients more prone to adverse events. Our data might therefore underestimate the beneficial effect of ERAS. In an enhanced recovery protocol, patients undergoing rectal resection have shown to have longer hospital stays than those getting colonic surgery.(19) In this study, ERAS showed to reduce LOS from a median of 12 days to 8 days in rectal surgery ($P<0.005$). This is in agreement with others reporting on the effects of ERAS in rectal surgery.(16,20,21) Delaney et al.(22) achieved mean (standard deviation) LOS of 4.6 (1.7) and 3.8(0.8) days following complex colorectal surgery with and without co-morbidity respectively. Patients however were much younger (mean age 44.4 years) and mostly had their surgery for inflammatory bowel disease (62%), and only 22% for (recurrent) cancer. Patients studied by Schwenk et al. were comparable regarding age and all had rectal surgery, but with the major difference that 56% of procedures were performed laparoscopic.(20) Laparoscopic surgery can cause less postoperative pain and quicker recovery and could therefore be a promising addition to enhanced recovery protocols.(23,24) Further trials are needed to make statements on possible beneficial effects of ERAS and laparoscopy. Since hospital stays have decreased in many centers over the past 10 years even without institution of specific ERAS protocols (due to changes in payment, practice, and surgeon and patient expectations), evaluating the influence of such protocols on length of stay remains worthwhile. In this study, total LOS (including days after readmission) was significantly shorter in het ERAS program ($P<0.05$). This shows much resemblance to the study of Nygren et al.(16), who reported a significant shorter total LOS despite increased readmission rates (ERAS: 19%, traditional: 4%) after rectal surgery.

Early discharge is likely to cause an increased readmission rate. Though, we noticed a trend towards more readmissions (ERAS: 17.1% vs. conventional: 7.3%, P=0.203) there was no significant difference in readmission rates between ERAS and control groups, a finding that is in accordance with a recent meta-analysis.(17) Proper use of adequate discharge criteria should prevent high readmission rates in fast-track surgical care.

In our ERAS group, 39.0% had one or more complications compared to 56.1% of the control group (not significant). Our complication rates may appear higher than many published articles on fast-track surgery and our previously published data but, like Hendry et al. showed in a large study, rectal surgery carries a higher risk of postoperative morbidity than colonic surgery.(18,21) Varying methods of reporting complications and differences between studied populations make the comparison of complication rates between studies difficult.(17) Compliance with the ERAS protocol was good. Postoperative variables are both markers of protocol compliance and markers of recovery. It is would be interesting to know which key element(s) of ERAS program is responsible for enhanced recovery. In this study, patients within ERAS mobilized faster, resumed normal diets sooner with quicker return of gastrointestinal function and duration of intravenous fluid administration was shorter (all highly significant). A reduction in morbidity was found in the ERAS patients, although this difference was not significant. Length of hospital stay was much shorter in ERAS. The use of epidural anesthesia was comparable within both populations. Therefore, the beneficial effect of the enhanced recovery program is more likely to be related to other factors than to epidural anesthesia. This is consistent with the findings of Zutshi et al.(25), who could not find an advantage of thoracic epidural anesthesia over patient controlled anesthesia after major gastrointestinal resection in a fast-track postoperative care plan. However, the population in this study involved patients undergoing segmental intestinal resection and does therefore not correlate with patients who had rectal surgery. Marret et al.(26) performed a meta-analysis on the effect of epidural anesthesia in colorectal surgery and could not find a significant reduction in hospital stay due to this key element. In conclusion, this study shows that ERAS helps to reduce hospital stay after low anterior and abdominoperineal resections. As in colonic surgery, enhanced recovery programs should be considered as standard care for rectal surgery.

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Submitted

Chapter 5

Failure of Enhanced Recovery After Surgery

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Abstract

Background
The reasons why patients fail the ERAS program and its impact are not known.

Objective
The aim of the study was to analyze the clinical courses of patients that deviate from the ERAS track and to evaluate subsequent morbidity.

Patients
104 consecutive patients underwent an open colorectal resection, 22 laparoscopic and 49 patients had rectal surgery according to the ERAS program.

Main outcome measures
All failures to reach one or more of the main protocol goals (epidural catheter use, early mobility and dietary intake), complications and hospital stay. Endpoints were analyzed separately for open and colonic and rectal surgery.

Results
Protocol compliance after colonic surgery was 73.4%. 53.8% of the patients failed on one or more goals. Solitary epidural failure occurred in 25% of the patients, mobility failure in 2% and 7.7% failed on dietary goals. Patients who failed epidural goals had a similar complication rate and hospital stay. In patients with impaired mobility hospital stay was prolonged (median 6 days vs. 8.5 days; $P<0.001$). Patients with problematic dietary intake had more Dindo 3-4 complications (7.9% vs. 28.6%; $P<0.05$) and were hospitalized longer (median 5.5 days vs. 8 days; $P<0.05$). After laparoscopic colonic surgery, 78.8% of the goals could be reached. 59.1% of the patients were able to meet ERAS goals. Solitary epidural failure occurred in 27.3% and 13.6% failed the dietary guidelines. Dindo 1-4 complications were similar in both populations. Patients who were able to follow the program were hospitalized shorter (median 5 days vs. 7 days; $P<0.05$).
Protocol compliance after rectal surgery was 69.4%. 40.8% patients succeeded the ERAS goals. 12.2% failed epidural anesthesia following protocol, 4% had impaired mobility and 18.4% did not resume normal diet as scheduled. Patients with epidural failure experienced more Dindo 3-4 complications (20% vs. 57.1%; $P<0.05$). For patients who failed the mobility goals, more Dindo 3-4 complication were found (18.4% vs. 72.7%; $P<0.01$) and hospital stay was prolonged (median 7 days vs. 22 days; $P<0.001$). Similar complication rate and hospital stay was found between patients who could and could not fulfill dietary ERAS goals after rectal surgery.

Limitations

This study analyzed not all elements of the ERAS program.

Conclusion

About 30% of the goals regarding epidural use, mobility and dietary intake are not reached in an ERAS program. Over half of the patients undergoing colonic and rectal resections do not meet one or more goals of the protocol. It is likely that the more severe complications interfere with protocol compliance, but other factors might contribute also.

Introduction

Enhanced Recovery After Surgery (ERAS) programs are associated with reduced hospital stay and a lower morbidity in patients undergoing colorectal resections when compared to traditional care.(1-7) The program aims to reduce the stress response by providing adequate pain relief and fluid restriction, facilitating recovery of gastro-intestinal function and early mobilization.
Still, a considerable proportions of patients does not reach these goals but protocol compliance has hardly been reported on.(5;8)
The aim of the study was to analyze how patients come to have clinical courses aberrant from the ERAS track and to evaluate the consequences in terms of complications and hospitalization.

Materials and methods

Patients

One hundred seventy-five consecutive adult patients that underwent a colorectal resection and who had an ASA score < 4 were included in the study. 104 patients had open colonic resection, 22 underwent laparoscopic colonic resection. Rectal resections were performed in 49 patients: 24 had a low anterior resection and 25 underwent abdominoperineal resection. In 4 patients with a low anterior resection, an end colostomy was constructed; the other had a diverting ileostomy. Of the patients operated for rectal carcinoma, 45.2% had preoperative radiotherapy 5x5 Gray, 50% received 25x2 Gray and 4.8% of the rectal carcinoma were not irradiated for several reasons. Patient characteristics, indication for surgery and performed procedures are listed in Table 1.

ERAS protocol

The ERAS protocol was described previously and compliance to the protocol was controlled and monitored with a checklist.(3;4) Patients were informed at the outpatient clinic about the operative procedure and the perioperative care, especially pain management, early mobilization and enteral feeding. The day before operation, a phosphate enema was given to all patients undergoing a left sided colon or rectal resection. No other bowel preparation was given. Oral carbohydrate loading was started at least 8 hours before surgery and was stopped 2 hours before induction of anesthesia. All patients received antibiotic and thromboembolic prophylaxis according to the local protocol. Surgery was done under a combination of general and epidural anesthesia via a thoracic epidural catheter. The same team of surgeons performed all procedures. In open procedures, a transverse laparotomy was preferred. In patients with inflammatory bowel disease, undergoing rectal resections or the creation of a stoma, a midline laparotomy was performed.

Table 1. Demography, indication for surgery and performed procedures.

	Open colonic surgery (n= 104)	Laparoscopic colonic surgery (n=22)	Rectal surgery (n=49)
Male: female	67:37	8:14	31:18
Age (mean/ SD)	54.9 (17.6)	45.5 (20.4)	63.5 (14.1)
Body Mass Index (mean/ SD)	25.6 (4.5)	23.6 (4.3)	25.3 (4.3)
Diabetes (%)	9.6	4.5	2.0
ASA (%)			
ASA 1	25	23.6	26.5
ASA 2	57.7	77.3	46.9
ASA 3	17.3	9.1	26.5
Indication (%)			
Malignancy	64.4	27.3	85.7
Inflammatory bowel disease	27.9	68.2	6.1
Diverticulitis	2.9	4.5	2.0
Other	4.8	-	6.1
Resection (%)			
Ileocecal	16.3	36.4	
Right hemicolon	31.7	4.5	
Transverse colon	1.9	4.5	
Left hemicolon	17.3	4.5	
Sigmoid	13.5	13.6	
Subtotal colon	19.2	36.4	
Low anterior			51
Abdominoperineal			49
Stoma formation			
Diverting ileostomy			38.8
End colostomy			59.2
Radiotherapy*			
None			4.8
5x5 Gy			45.2
25x2 Gy			50

* Percentage, corrected for patients operated for malignancy.

Nasogastric tubes and drains were avoided. Only in patients undergoing a rectal resection a presacral drain was placed during 24 hours postoperatively. All patients had a transurethral catheter until removal of the epidural catheter. Perioperative analgesia was given with a continuous infusion containing Ropivacain 0.2% (2 mg/ ml) and Sufentanil 1 microgram/ml at a rate of

6 ml/hour, via an epidural catheter (T 7-8). Pain was monitored with a visual analogue scale (VAS). If the VAS score remained greater than 5 in patients having a proper level of pain blockade, an epidural bolus with 3-4 ml Lidocain 2% was given. In case of persisting pain, patients also received Ketamin intravenously via a continuous infusion. If epidural analgesia failed, the epidural catheter was removed and intravenous morfinomimetics were administered via an on-demand patient controlled infusion system. Oral analgesics (Naproxen 2 dd 500 mg or Diclofenac 3 dd 50 mg) were started after starting oral feeding. Postoperative fluid intake was restricted to 2 liters per day, with allowance of a positive fluid balance of 500 ml. Oral fluid intake was started on the day of surgery and a normal diet was started as soon as tolerated. Normal diet was defined as the eating of solid food in any desired quantity and without restrictions to the composition of the food or the way of preparation. All patients received Magnesium oxide 2 dd 500 mg as laxative. Mobilization was started on the day of surgery. Sitting at the edge of the bed was encouraged on the day of operation and patients were stimulated to walk the corridor of the ward on the first postoperative day. In case of impaired mobility, regaining the preoperative mobility level was attempted on the first postoperative day. Discharge criteria were adequate pain relief (VAS score <5) on non-opioid oral analgesia, adequate oral food intake and return of preoperative mobility level. Bowel movement was not mandatory before discharge.

Definition of ERAS failure

Adequate epidural analgesia, early mobilization and oral intake are the cornerstones of the ERAS protocol. Each inability of the patient to reach the goals as set in the protocol was considered as **ERAS failure**. These goals were: (1) stress and pain relief by epidural anesthesia; (2) timely mobilization as scheduled; (3) early intake of solid foods according to schedule. **Epidural failure** was defined as insufficient pain relief by epidural analgesia (VAS >4) necessitating an epidural bolus or the use of intravenous/ subcutaneous opioids or the removal of the epidural catheter earlier than on the second or the morning of the third postoperative day. **Mobilization failure** was defined as mobilization more than one day behind schedule. Resuming a normal diet more than one day behind schedule was defined as a **diet failure**.

Data extraction and analysis

The following data were recorded: sex, age, indication for surgery, type of operation, ASA grade, daily intravenous and oral fluid intake, daily fluid balance, removal of the epidural catheter, first day of mobilization, length of postoperative hospital stay, number of readmissions, complications and mortality. All failures to adhere to the enhanced recovery protocol were recorded. Epidural anesthesia, early mobility and feeding were decided to be the main items

in the enhanced recovery program. Data related to these items were gathered prospectively. As stated above, failure regarding these goals was clearly defined. Outcomes for colonic (open versus laparoscopic) and rectal surgery were analyzed separately, since these procedures are known to have a different hospital stay and complication rate. Delayed discharge and the incidence of complications were not considered as ERAS failure but used as an outcome measure instead. Complications were classified according to Dindo et al.(9) Postoperative ileus requiring total parenteral nutrition, pulmonary or urinary infection, urinary retention, delirium were considered as Dindo grade I-II. Postoperative complications requiring surgical / radiological intervention or ICU admission were classified as Dindo grade III-IV (e.g. superficial and deep surgical site infection, bleeding, anastomotic leakage, iatrogenic injury, fascia dehiscence).

Statistical analysis

Comparisons were made using the chi-square test for binary outcomes and the student's t test was used for continuous outcomes.

Results

Open colonic surgery

Median hospital stay was 6 days (range 3-110 days). The readmission rate was 3/104 (2.9%). All patients readmitted within 30 days of discharge had experienced complications. The total number of ERAS goals that could have been fulfilled was 312. The population under study successfully reached 229 goals (73.4%). Of the 83 goals not reached, 40 regarded epidural anesthesia, 28 dietary and 15 mobility guidelines. 56 patients (53.8%) failed on one or more goals. Solitary epidural failure occurred in 25% of the patients, mobility failure in 2% and 7.7% failed on dietary goals only. 18.3% failed to reach two goals and 2.9% failed all three. The only demographic difference that could be identified between the ERAS success and failure population was a higher body mass index in the patients who could reach ERAS goals. The incidence of complications in the population who failed was 42.9%, which differs not significantly to the 25% complication rate of the patients who were able to meet ERAS goals. The number of Dindo 1-2 complications was 8 (in 8 patients; 16.7%) in the success group and 16 (in 15 patients; 26.8%) in the ERAS failures (not significant). For Dindo 3-4 complications, this amounted 7 (in 4 patients; 8.3%) and 20 (in 11 patients; 19.6%) respectively (not significant). The total number of complications was higher in patients who did not manage to reach ERAS goals (36 vs. 15; $P<0.01$). Patients able to fulfill ERAS goals were hospitalized shorter (median 5 days, range 3-35 vs. median 7, range 3-110; $P<0.05$). Readmission rate was similar (2.1% vs. 3.6%; not significant). Patients who failed epidural goals were compared with those who did not. There were no differences in Dindo complication rate and hospital stay. Patients who

failed to reach the mobility goals did not experience more complications, but hospital stay was prolonged (median 6 days, range 3-45 vs. median 8.5 days, range 6-110); P<0.001). Patients with difficulties to reach dietary goals experienced more Dindo 3-4 complications (7.9% vs. 28.6%; P<0.05) and were hospitalized longer (median 5.5 days, range 3-110 vs. median 8 days, range 4-50; P<0.05). Patients who failed the program experienced more blood loss and received more intravenous fluids intraoperatively than patients who succeeded to reach ERAS goals (mean 644 mL vs. mean 405 mL; P<0.05 and mean 2465 mL vs. 1925 mL; P<0.05, respectively). Patients who succeeded had less intravenous fluids on postoperative day 2 (mean 867 mL vs. mean 1333 mL; P<0.05) and drank more during the first two postoperative days (day 1: mean 1660 mL vs. mean 970 mL; P<0.001 and day 2: 1735 mL vs. 1344 mL; P< 0.05). Patients, succeeding the program and developing complications, retained fluid from postoperative day 3. Patients exceeding a daily total fluid intake of more than 2000 mL did not differ between ERAS success and ERAS failure for 5 postoperative days. On postoperative day 2 and 5, significant more patients in the ERAS failure group had a fluid balance >+500 than the success group (day 2: 51.8% vs. 20.8%; P>0.05 and day 5: 48.8% vs. 16.7%; P<0.05). Irrespective of ERAS, increased blood loss and intraoperative fluid supply was associated with the occurrence of adverse outcome (mean 820 mL vs. mean 376 mL; P<0.001 and mean 2705 vs. mean 1948 mL; P<0.01, respectively).

Laparoscopic colonic surgery

Median hospital stay was 5 days (range 3-20). No patient had to be readmitted. Of the 66 goals set, 78.8% could be reached. This percentage is comparable to open colonic procedures (73.4%). Failures comprised 8 goals regarding epidural anesthesia, 1 mobility goal and 5 goals in resuming a normal diet. 13 out of 22 patients (59.1%) were able to meet ERAS goals, compared to 9 (40.9%) who failed one or more goals. Solitary epidural failure occurred in 27.3% and 13.6% failed the dietary guidelines. 4.5% failed on epidural and dietary goals and 4.5% failed all three. Compared to open colonic surgery, significant fewer patients failed on two goals after a laparoscopic procedure (18.3% vs. 4.5%; P<0.05). No demographic differences could be found between patients who did succeed the program and those who were not. Dindo 1-2 complications were similar in both populations (success: 1 vs. failure: 3; not significant), as were Dindo 3-4 complications (success: 1 vs. failure: 1; not significant). Patients who were able to follow the program were hospitalized shorter (median 5 days, range 4-7 vs. median 7 days, range 3-20 ; P<0.05).

No differences could be found in blood loss, perioperative intravenous fluid supply, oral fluid intake and fluid balances for the first 5 postoperative days between patients who succeeded the program and ERAS failures.

Rectal surgery

Median hospital stay was 8 days (range 3-76). There were 8 (16.3%) readmissions, which are higher than after colonic surgery (2.9%; P< 0.01). 102 out of 147 goals were successfully reached (69.4%; not significantly different from open or laparoscopic colonic surgery). 14 epidural goals, 11 mobility goals and 20 dietary goals were not met. 12.2% had no epidural anesthesia following protocol, 4% had difficulties to reach mobility goals and 18.4% were not able to resume normal diet as scheduled. Compared to colonic surgery, the difference in epidural anesthesia failure was not significant, but more patients failed resuming a normal diet timely after rectal surgery (18.4% vs. 7.7%; P<0.05). Ten patients (20.4%) failed two goals and 2 (4.1%) failed all three. 20 patients succeeded the ERAS goals (40.8%), which is comparable to the 46.2% in colonic surgery. Demographic differences could not be found between patients able to follow the program and those who could not. In the success group, 9 patients developed 10 Dindo 1-2 and 3 Dindo 3-4 complications. In the failures, 20 patients experienced 22 Dindo 1-2 and 18 Dindo 3-4 complications. The Dindo 1-2 complication rate is comparable, but the Dindo 3-4 complications are more frequent in ERAS failures (P<0.01). Total complication rate is higher in ERAS failures (40 vs. 13; P<0.05), but the number of patients with complications is similar. Patients who failed epidural anesthesia goals were compared to those who were not. The number of Dindo 1-2 complications and hospital stay did not differ, but failures experienced more Dindo 3-4 complications (20% vs. 57.1%; P<0.05). For patients who failed the mobility goals, more Dindo 3-4 complication were found (18.4% vs. 72.7%; P<0.01) and hospital stay was prolonged (median 7 days, range 3-32 vs. median 22 days, range 7-76; P<0.001). No significant differences in complication rate and hospital stay could be found between patients who could en could not fulfill dietary ERAS goals. No differences could be identified in intraoperative blood loss and fluid supply between patients who were able to reach ERAS goals and those who could not, nor for patients with or without complications.

Patients who successfully follow ERAS received less intravenous fluids on postoperative day 2 (mean 700 mL vs. mean 1322 mL; P<005), 3 (mean 392 mL vs. mean 1081 mL; P< 0.01) and day 4 (mean 559 mL vs. mean 1211 mL; P<0.05) and drank larger volumes on day 2 (mean 1648 mL vs. mean 1126 mL; P<0.05) and 3 (mean 1585 mL vs. mean 1168 mL; P<0.05). There were no differences in the number of patients exceeding a daily total fluid intake of 2000 mL or a more than +500 mL positive fluid balance between ERAS success and ERAS failures.

Discussion

About 30% of the goals regarding epidural use, mobility and dietary intake are not reached in an ERAS program. Over half of the patients undergoing colonic and rectal resections do not meet one or more goals of the protocol. The number of patients experiencing complications does not differ between the population able to fulfill ERAS goals and those who are not. However, complications may interfere with reaching goals. Total complication rate was higher in ERAS failure. Dindo 1-2 complications could not be associated with ERAS failure, but Dindo 3-4 complications were found to be related to decreased protocol compliance. Patients who manage to reach protocol goals are hospitalized shorter after (open and laparoscopic) colonic and rectal surgery. In most articles on fast track surgery protocol compliance is hardly or not reported on.(5;8) In our institution, a written protocol is available, fulfilling all major ERAS criteria as formulated by Fearon et al. in their consensus review.(1) Moreover, doctors and nurses were frequently instructed and a bedside checklist was used in every single patient. Compliance was good for most ERAS denominators, but frequently pain management, postoperative mobilization and restoration of oral intake failed.

Epidural anaesthesia goals

Aconsiderable proportion of patients did not receive epidural anaesthesia as planned. Although exact reasons for failure could not be retrieved, this questions insertion technique, fixation method, preoperative testing and perioperative monitoring. There is no evidence as to the choice of the optimal anaesthetic method based on morbidity or recovery data from colorectal procedures. Several studies state that epidural anaesthesia provides superior pain relief as measured by postoperative pain scores. Patient controlled anaesthesia is thought to impair gut motility. Epidural anaesthesia may avoid systemic opioid use and is advocated to decrease the rate of postoperative ileus and pneumonia by some authors. There is clear evidence that a thoracic epidural can block many of the components of the stress response to injury and has been proven to reduce the duration of postoperative ileus. For colonic surgery, postoperative morbidity and hospital stay were similar in patients who had adequate epidural anaesthesia compared to patients with inadequate thoracic epidural anesthesia or patient-controlled anaesthesia.(10-13) This is in accordance with Zutshi et al.(14), who studied the use of preemptive epidural analgesia after laparotomy and intestinal resection in a fast track postoperative care plan found no advantage of thoracic epidural placement over patient controlled analgesia regarding hospital stay, pain scores, quality of life and complications. In a meta-analysis, Marret et al.(15) also concluded that epidural use did not shorten hospital stay, even after introduction of enhanced recovery programs. Levy et al.(16) questioned the use of epidural anesthesia in laparoscopic colorectal surgery and spinal or patient controlled anesthesia are advocated. Evans et al.(17) states that the use of transversus abdominis plain blocks is safe and effective in ERAS. Wongyingsinn et al.(18) found similar effects on bowel function of perioperative infusion of lidocain in patients undergoing laparoscopic colorectal resection in an enhanced recovery program compared

with thoracic epidural anesthesia. This finding is in accordance with Herroeder et al.(19) who found an accelerated return of bowel function and a reduction in hospital stay after colorectal surgery compared to placebo in patients not able or unwilling to have epidural anesthesia. Although epidural failure in laparoscopic colonic surgery was as high as in open surgery in this study, the limited number of performed laparoscopic procedures does not allow further conclusions on the efficacy of epidural anesthesia in laparoscopic surgery. In this study, epidural failure in rectal surgery was less frequent than in colonic surgery, but was associated with more Dindo 3-4 complications and prolonged hospital stay. The lower incidence might be explained by the fact that patients with rectal surgery often receive simultaneous patients controlled anesthesia for pelvic pain not adequately blocked by thoracic epidural anesthesia. Due to the systemic opioids, insufficient epidural pain blockade might be less prominent. The relationship with an increased complication rate is not clear, but one of the explanations could be the fluid shifts accompanied with epidural anesthesia that might cause hypotension and subsequent intravenous fluid loading. The efficacy of epidural anesthesia specified for rectal surgery only is underreported in the literature.

Mobility goals

Early mobilization after surgery is important to prevent complications by decreasing insulin resistance, muscle wasting, pulmonary dysfunction and improving tissue oxygenation.(20-22) Possible factors delaying mobilization are pain, fear, preexistent diseases and the inability of the nursing staff to help the patient. In colonic surgery, impaired mobility was not found to be associated with a higher complication rate but delayed discharge from the hospital. For rectal surgery, it was more likely that an increased incidence of Dindo 3-4 complications was responsible for impaired mobility and prolonged hospital stay.

Dietary goals

Gastro-intestinal function is impaired after laparotomy. Several measures in the ERAS protocol are aimed at improving gastro-intestinal transit, amongst which is oral feeding. After colonic surgery, the patients not able to fulfill the dietary goals had more often Dindo 3-4 complications and were hospitalized longer. It can be questioned what the effect of resuming a diet the first and second postoperative day is on the return of gastrointestinal function and adverse outcome. Patients, succeeding the program and developing complications, retained fluid from postoperative day 3. It is known that the inability to tolerate oral intake in the early postoperative phase is associated with fluid overload.(23-26)

Fluid

Fluid restriction appears to be an important part of the ERAS protocol. The largest intravenous fluid volumes were administered during surgery, part of which can be explained by the 500 ml bolus that was given routinely to all patients with an epidural catheter to prevent hypotension. Regional anesthesia to the upper thoracic dermatomes is associated with reduction in preload and cardiac sympathic drive, resulting in reduced cardiac output and hypotension. Holte et al.(27) have questioned the necessity of a fluid bolus since low levels of epidural anesthesia (T8) only result in minimal circulatory changes, as the upper part of the body is sufficient to offset the dilatation in the lower extremities. Probably it is wise to abandon a routine intravenous fluid bolus in patients with epidural anesthesia to prevent excessive fluid intake. Patients who failed ERAS suffered significant more blood loss during colonic surgery than patients who succeeded the ERAS program. Subsequently, intraoperative fluid volumes supplied were larger in ERAS failures. Despite increasing awareness on fluid supply, the most common cause for postoperative overloading was insufficient adaptation of the intravenous fluid management to changes in oral intake and diuresis during the day. Fluid overloading during and early after surgery might induce complications that typically appear later in the postoperative course. It is likely that a positive fluid balance on the third postoperative day onwards, is rather a consequence of complications (ileus, surgical site infections) than a causal factor. In this study, fluid overloading was similar between patients who succeeded and failed ERAS, but oral intake was higher in patients who succeeded. This indicates that patients who failed received more intravenous fluid volumes. The impact of intravenous saline on postoperative complications might differ from oral fluids taken and needs further study. However, until now insufficient data are available to give evidence-based guidelines for perioperative fluid management.(20;21;28) Intraoperative Doppler-guided titration of fluid is a promising technique to determine fluid requirements during colorectal surgery but heterogeneity of published trails, improvements in perioperative care and surgical technique limit this technique to be used as a routine.(29;30)

This study indicates that about 30% of the goals regarding epidural use, mobility and dietary intake are not reached in an ERAS program. Over half of the patients undergoing colonic and rectal resections do not meet one or more goals of the protocol. It is likely that the more severe complications interfere with protocol compliance, but other factors might contribute also. The influence of epidural analgesia is remote in colonic surgery, but its role in rectal surgery is less clear. Impaired early mobility causes prolonged hospital stay in colonic surgery and is more frequent after complicated rectal surgery. The ability to fulfill ERAS dietary guidelines is diminished due to complications after colonic surgery. Problematic dietary intake has a less prominent relationship with complications and hospital stay after rectal surgery. Intravenous fluid overloading is associated with ERAS failure and the occurrence of complications and should receive attention. Further research is necessary to point out most beneficial aspects of enhanced recovery programs.

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Submitted

6

Intraoperative Doppler-guided fluid management in colorectal surgery

A meta-analysis

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Abstract

Background

Esophageal Doppler monitoring is a minimally invasive technique to determine cardiovascular status and the response to fluid loading. The aim of this meta-analysis was to obtain evidence regarding the effect of intraoperative Doppler-guided fluid titration on the recovery after colorectal surgery.

Methods

Studies were selected for inclusion if they were randomized clinical trials including adult patients who underwent colorectal surgery. The intervention was intraoperative Doppler-guided fluid titration, compared with standard fluid management. Methodology of all reports was assessed according to the Cochrane Handbook. Primary outcome measures were the Doppler variables stroke volume and corrected flow time. Secondary outcome measures were hospital stay, complications and time to tolerance of oral solids.

Results

In patients with intraoperative Doppler-guided fluid administration, stroke volume was increased with 14.6 ml (Weighted mean difference, 95% CI = 9.0 to 20.1) and corrected flow time was prolonged with 0,025 sec (Weighted mean difference, 95% CI = 0.014 to 0.036) compared to the control group. The difference in hospital stay was not significant (-1.1 days; Weighted mean difference, 95% CI = -2.3 to 0.1).

In the experimental group, total complication rate was reduced by 15.8% (Weighted mean difference, 95% CI = -0.29 to -0.02) and patients were able to tolerate oral solids 1.4 days earlier (Weighted mean difference, 95% CI = -2.1 to -0.8).

Conclusion

Intraoperative Doppler-guided titration of fluid reduces morbidity and the time to tolerate oral solids after colorectal surgery. This conclusion must be interpreted with care because the studies are heterogeneous and results may be confounded by improvements in surgical technique and perioperative care.

Introduction

Fast track surgery and enhanced recovery programs are rapidly developing and are becoming standard of care. (1-4) One of the key elements of these programs is peri-operative fluid management. Especially, patients who undergo colorectal surgery are threatened by hypovolemia due to fasting, bowel preparation, epidural anaesthesia, blood loss and insensible fluid loss. So far, no widely accepted recommendations are available for the optimal perioperative fluid regimen. A normovolemic state is a prerequisite for optimal cardiac and pulmonary function thus guaranteeing adequate tissue oxygenation and wound healing. Moreover, gastro-intestinal motility, renal function and coagulation may all benefit from optimal perioperative fluid administration.(5-10)
To optimize cardiovascular function, several invasive methods were developed to assess the circulatory status. The Swan-Ganz catheter is the gold standard in evaluating fluid responsiveness and cardiac function. However, this technique is expensive and has a considerable complication rate not outweighing its benefits.(11-13) Esophageal Doppler monitoring is a minimally invasive method to determine cardiovascular status and response to fluid loading. Esophageal Doppler measures blood flow in the descending aorta by a Doppler probe in the esophagus. It generates a flow velocity waveform. The most important parameters determined are: stroke distance, stroke volume and flow time. Stroke distance is the distance a column of blood moves in the descending aorta after each left ventricular contraction. Stroke volume, one of the most essential parameters, is the product of stroke distance and aortic cross-sectional area. The flow time indicates the time of antegrade blood flow in the descending aorta with each ventricular stroke. This flow time needs to be corrected for heart rate: 'the corrected flow time (cFT)', which normally varies between 0.33 and 0.36 seconds.(14)
The splanchnic perfusion is of utmost importance for patients undergoing colorectal surgery. Hypovolemia is accompanied with a redistribution of blood at the expense of the splanchnic circulation. Redistribution may remain unnoticed because pulse rate and systemic blood pressure may remain normal whereas tissue oxygenation of the viscera, especially the gut mucosa, is at risk.(15;16)
Mythen and Webb(17) found that optimalisation of the cardiac output with the help of Doppler guided fluid management decreased gut mucosal hypoperfusion in coronary artery bypass surgery. An accumulating number of clinical trials report on the value of hemodynamic monitoring by esophageal Doppler in patients undergoing colorectal surgery. The aim of this meta-analysis was to analyze studies concerning the effect of intraoperative Doppler-guided fluid titration on the recovery after colorectal surgery.

Methods

Study selection

The PubMed and Embase databases as well as the Cochrane Central Register of Clinical Trials were searched without limits in order to identify randomized clinical trials which studied the value of intraoperative esophageal Doppler-guided fluid management compared to standard fluid administration during anesthesia in adult patients undergoing colorectal surgery. Relevant studies were initially identified by title, then by abstract and finally by full text. References of included articles were searched for further trials.

Assessment of study quality

Only prospective randomized clinical trials, comparing intraoperative Doppler-guided fluid titration and standard fluid management during colorectal surgery were included in the meta-analysis. Studies had to meet the quality criteria of the Cochrane Collaboration. The quality of each publication was assessed using the Cochrane Handbook as reported by Parker et al.(18) This is a ten-point instrument indicating methodological quality of randomized clinical trials. Each included study can obtain a maximum score of 12 points. Concealment of allocation is the most dominant criterion (maximum of 3 points). All other criteria are graded 0 or 1.

Outcome measures

Primary outcome measures were the Doppler variables stroke volume and corrected flow time at baseline and at the end of surgery. Secondary measures were complication rate, hospital stay and the time to tolerance of oral solids.

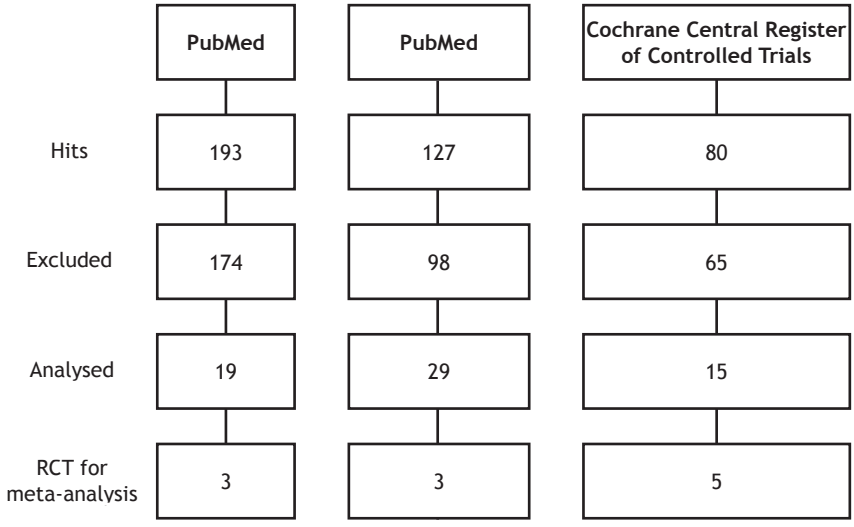
Statistics and analysis

Data on the Doppler variables, complication rate, hospital stay and time to tolerate oral solids were pooled. Bias assessment plots were constructed for each effect size. Heterogeneity was assessed by the Cohran Q test for non-combinability for studies. If inconsistency was lower than 20% fixed effects were used according to Mulrow Oxman. DerSimonian-laird random effects were calculated if inconsistency was more than 20%. The weighted mean difference (WMD) and the 95%-confidence interval were extracted for stroke volume, corrected flow time, complication rate, hospital stay and time to tolerance of oral solids.

Results

The search yielded 193 PubMed and 127 Embase hits. Eighty articles were found in the Cochrane Central Register of Controlled Trials. After screening, full-text articles were retrieved for assessment of eligibility. A further 63 studies were excluded, which left 6 studies to be included in the meta-analysis. An algorithm of the search is shown in Table 1.

Table 1. Search algorithm.



All studies achieved more than 9 points on methodologic assessment according to the Cochrane Handbook (Table 2).

Stroke volume and corrected flow time were reported for both the intervention group as well as the control group in most studies. Stroke volume was mentioned in five studies, including 578 patients. Pooled stroke volume at the start of the surgical procedure was similar in the Doppler and the control group: mean 76.7 ml (SD 7.5) vs. 76.0 ml (SD 6.8); P=0.87. Pooled stroke volume did not differ either at the end of surgery (Doppler: mean 92.5 ml (SD 14.1) vs. Control: mean 77.5 (SD 11.5); P=0.10. Weighted mean difference in stroke volume at baseline did not differ significantly between the Doppler and the control group: -0.24 ml (95% CI = -4.13 to 3.66). At the end of surgery, weighted mean difference stroke volume was significantly increased by 14.0 ml (95% CI = 10.1 to 18.0) in the Doppler group compared to the control group. The corrected flow time was reported in four studies, resulting in a pooled population of 444 patients. At the start of surgery, cFT was similar in both groups (Doppler: mean 0.363 sec (SD 0,017) vs. Control: mean 0.361 sec (SD 0.014); P=0.86).

Table 2. Assessment of study quality according to Parker (29).

	Gan	Noblett	Wakeling	Conway	Senagore	Challand
Concealment of allocation	3	3	3	3	2	2
Inclusion and exclusion criteria	1	1	1	1	1	1
Comparability of groups at baseline	1	1	1	1	1	1
Treatment protocol	1	1	1	1	1	1
Were the care programs identical, other than trial interventions?	1	1	1	1	1	1
Were outcome measures defined clearly?	1	1	1	1	1	1
Were outcome assessors blind to treatment group?	1	1	0	0	1	1
Timing of outcome measures	0	0	0	0	1	1
Intention to treat analysis	1	1	1	1	1	1
Loss to follow up	1	1	1	1	1	0
Total (max. 12)	11	11	10	10	11	10

At the end of the procedure, however, corrected flow time was longer in patients with Doppler titrated fluid administration (mean 0.390 sec (SD 0.007) vs. mean 0.361 sec (SD 0.002); P=0.002). Weighted mean difference in baseline corrected flow time was similar in both populations (0.002 sec; 95% CI = -0.006 to 0.01). At the end of surgery, flow time was significantly increased by 0.028 sec (95% CI = 0.020 to 0.035) in the Doppler group. Pooled differences in effect size were calculated for both Doppler variables between the baseline values and those at the end of surgery. This is shown in Figure 1 and 2.

Figure 1. Pooled weighted mean difference of stroke volume (ml).

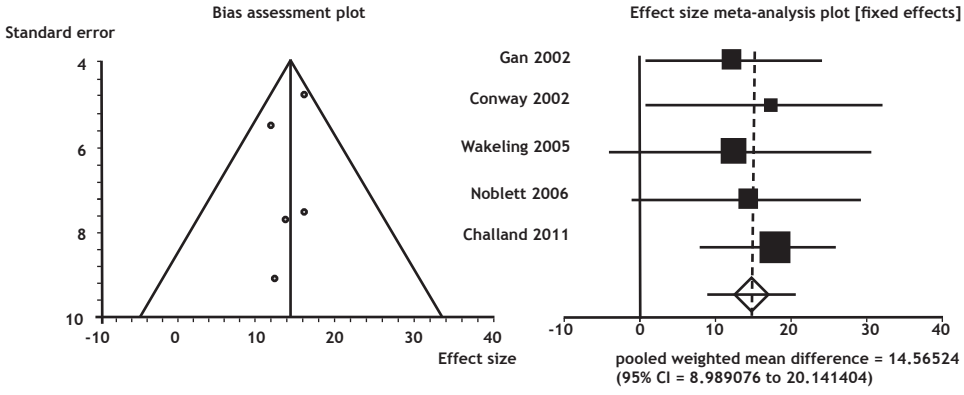
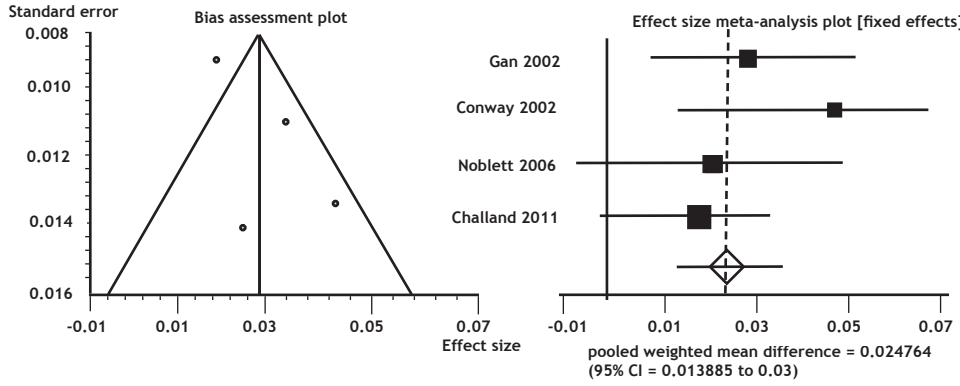
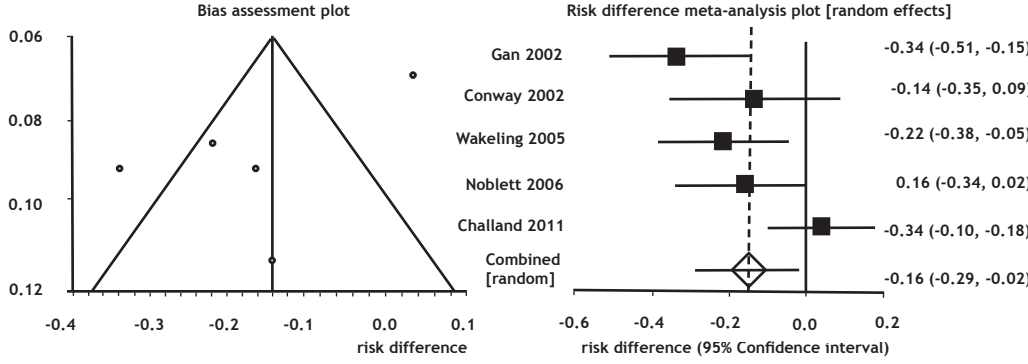


Figure 2. Pooled weighted mean difference of stroke volume (ml).



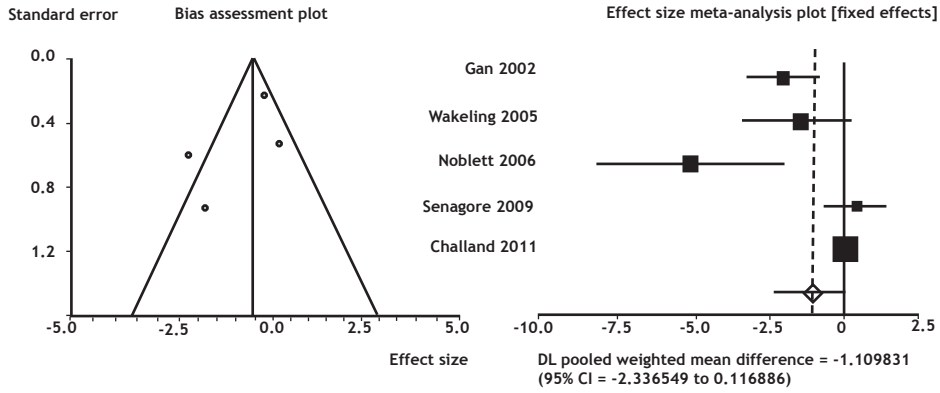
All six studies, including 642 patients, reported on total complication rate. Doppler titrated fluid administration reduced total complication rate by 15.8% (pooled random effect size, 95% CI = 2.1 – 29.4%) compared to controls (Figure 3).

Figure 3. Pooled weighted mean difference in total complication rate.



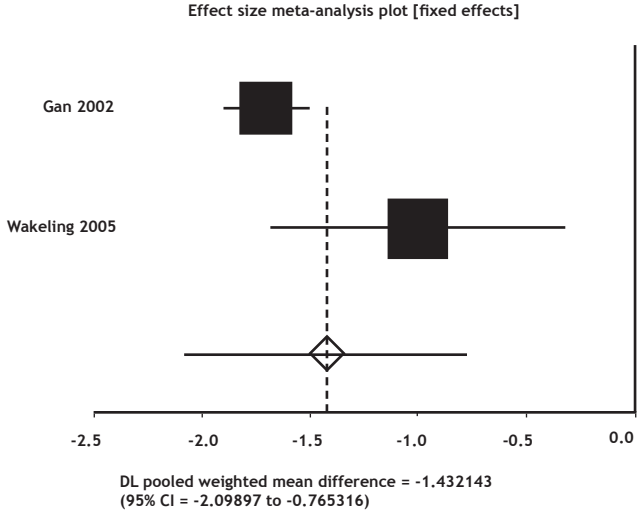
Only three studies (including 298 patients) specified complications. Differences between specific complications could not be objectified. Regarding complication rate, heterogeneity between studies was considerable (Cohran Q test: inconsistency 67.8%). Hospital stay was reported by all studies and did not differ between patients treated with esophageal Doppler and those who were not (weighted mean difference: -1.1 day; 95% CI -2.3 to 0.1; Figure 4).

Figure 4. Pooled weighted mean difference of hospital stay (days).



In the assessment of hospital stay, high inconsistency between studies was found (Cohran Q test: 81.8%).
In the evaluation of the time to tolerate solid food after surgery between Doppler treated patients and conventional treated patients, only the data of Gan and Wakeling (including 234 patients) allowed comparison. Patients in the Doppler population were able to tolerate oral solids 1.4 days earlier than control patients (95% CI = 0.8 -2.1 days; Figure 5).

Figure 5. Pooled weighted mean difference in time to tolerate oral solids (days).



Discussion

The use of esophageal Doppler seems to have moderate advantages to optimize fluid management during surgery. It increases stroke volume and prolongs corrected flow time. Moreover, it reduces total complication rate and the time to tolerate oral food intake. However, these findings have to be interpreted with caution. Heterogeneity between published randomized trials published so far, is considerable. Since all trials under study are found to have reasonable methodology, inferior study quality is not likely to be responsible for this heterogeneity. Another major limitation of selected trials is the use of poorly defined outcome measures. Although all studies report that hospital stay is predefined, the criteria for discharge are not mentioned. Some studies use hospital stay, other report only time to surgical fitness for discharge. Complications are not defined, grouped by severity or organ system. In only one study complications were adequately reported using the Dindo classification.(19) This limits pooling of data and threatens conclusions on the value of esophageal Doppler monitoring. Furthermore, duration of follow up was short, cost-effectiveness analysis was not performed and complications related to the use of Doppler were not mentioned in any study. Stroke volume and corrected flow time, which are the main outcome measures of Doppler guided intervention, were significantly higher at the end of surgery, when Doppler guided intervention was utilized. Bundgaard-Nielsen et al. (20) questioned the use of corrected flow time as a marker of preload in fluid algorithms because it is likely to be affected by several other factors. In fluid challenges, cFT values may increase not as pronounced as the stroke volume.

Although stroke volume and corrected flow time are frequently used as the main parameters in esophageal Doppler monitoring, it is important to realize that the relationship with gut perfusion and restoration of gastrointestinal function after colorectal surgery is not clear. One of the main ideas of non-invasive cardiac output esophageal Doppler monitoring is that fluid management can be individualised to the Frank-Starling curve to safely deliver intravenous fluids to optimise stroke volume. The main advantage of measuring flow in a major central vessel is that measurements are not affected by peripheral arterial compliance. So, esophageal Doppler is likely to reflect intravascular volume more accurate than clinical parameters (e.g. pulse rate and blood pressure). Mythen and Webb(17) found that optimisation of cardiac output with colloids during cardiac surgery, guided by esophageal Doppler, reduced gut mucosal hypoperfusion as measured with gastric intramucosal pH. This resulted in a shorter intensive care and hospital stay. Whether Doppler guided fluid management also improves perfusion of the splanchnic circulation and the gut mucosa needs to be determined in future studies. The finding that the incidence of complications was reduced in the Doppler intervention group should be interpreted with caution. The definition of complications and the criteria for discharge were unclear and may not be uniform as mentioned before. Secondary outcome measures such as hospital stay

and complication rate are more likely to be influenced by other factors than by the use of intraoperative esophageal Doppler-guided fluid administration. It is likely that trials to determine the effect of Doppler guided fluid titration are affected by the changes in perioperative care and surgical technique. Most trials under study randomly used bowel lavage and epidural anaesthesia. Therefore further research on Doppler guided fluid titration integrated in Enhanced Recovery After Surgery programs are needed. Fluid therapy in colorectal surgery is widely discussed in the literature. Only three out of six studies reported the type and volume of the infused fluids. It is likely that the type of fluid is a relevant variable. Senagore et al.(21) state that larger volumes of crystalloid solutions are necessary to reach desired stroke volumes compared to colloids. Lang et al.(22) report an improved tissue oxygen tension in favour of colloids compared to crystalloids in patients undergoing major abdominal surgery. It is remarkable that the administered amount of fluid was larger in the Doppler group than in the controls in this meta-analysis. This is not consistent with recent comparative reports on different fluid regimen in colorectal surgery in which most authors report a more favourable outcome and better functional recovery after restricted or goal-directed fluid therapy than in patients treated with standard fluids supply. Furthermore, Doppler only assessed intraoperative fluid management but postoperative intravenous fluid supply might play an important role as well.(8;23-28)

It is the final conclusion of this meta-analysis that the found statistical differences have to be interpreted with caution. Trial heterogeneity and confounding factors limit conclusions on the value of intraoperative esophageal Doppler monitoring in colorectal surgery. An important limitation in the pooling of data is the use of poorly defined outcome measures. It is to be questioned if used hemodynamic variables are indicative for optimal gut perfusion and restoration of gastrointestinal function. Further research on Doppler monitoring and alternative techniques to properly assess cardiovascular status, end-organ perfusion and the impact on surgical outcome in a standardized enhanced recovery program is necessary.

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7

Hybrid F-18-fluorodeoxyglucose positron emission tomography- computer tomography of colonic anastomosis: a possibility to detect anastomotic leakage?

A pilot study

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Abstract

Background

F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a known method to diagnose inflammatory processes and thus may be a promising imaging technique to detect anastomotic bowel leak. The aim of this study was to assess postoperative FDG uptake in colorectal anastomosis in patients without suspicion of active infection or anastomotic leakage.

Methods

Design of a prospective observational pilot study in order to assess normal FDG uptake in the patent anastomosis after colorectal surgery. Patients that underwent colorectal surgery with primary anastomosis received FDG-PET of the abdomen, 2-6 days postoperatively.

Results

Thirty-five patients met the inclusion criteria. Three patients were not scanned for various reasons. Of the remaining 32 patients, one demonstrated an increased uptake of FDG at the site of the anastomosis. In the other 31 patients FDG uptake was negligible (n=17) or scored as physiological (n=14). None of the scanned patients developed a clinical relevant anastomotic leakage within the first 30 days after surgery.

Conclusion

The results of the present study show that FDG uptake in colorectal anastomosis remains low within the first 6 days after surgery in patients without anastomotic leakage. Therefore, FDG-PET might be useful to investigate further as a tool to detect anastomotic leakage in an early stage postoperative phase.

Introduction

Anastomotic leakage remains a serious adverse event after colorectal surgery. Its reported incidence varies from 1-25%. This wide range is mainly caused by the lack of a uniform definition.(1;2) Diagnosing leaks relies on the clinical and radiographic findings. Early diagnosis and prompt treatment are essential since delay is associated with increased mortality and morbidity.(3;4) Den Dulk et al.(5) developed a leakage-score based on clinical parameters associated with anastomotic leakage. The leakage-score was implemented in a standardized postoperative surveillance and scoring led to a reduction in delay in diagnosis and mortality. Radiological diagnosis by means of e.g. contrast radiography or computer tomography are often advised when a leakage is suspected in a patient. However, sensitivity of both contrast radiography and computer tomography for diagnosing anastomotic dehiscence are rather low, being 65% and 54% respectively. Interobserver variability may be as high as 10%.(6;7) Meller et al.(8) studied the use of F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in 18 patients with postoperative fever. Sensitivity for detection of infectious and oncological foci was 100%. However, specificity was low as a result of false positive scans due to increased FDG uptake at the surgical wounds. Since leakage of bowel contents elicits at least a local inflammatory response, F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) may be a promising imaging technique to improve the detection of anastomotic bowel leak, at an early stage when granulocytes and macrophages migrate to the inflammatory process. A first condition for such an application would be that the signal remains low during undisturbed healing.(9-11) Since negligible uptake of FDG at the site of the healing anastomosis is a prerequisite for early and accurate diagnosis of anastomotic dehiscence, we performed a prospective study to assess postoperative FDG uptake in colonic and colorectal anastomosis in patients without evidence of active infection or anastomotic leakage.

Methods

Patients who underwent a colorectal resection with primary anastomosis and gave informed consent were included in the study. The institutional review board of the Radboud University Nijmegen Medical Centre, the Netherlands, approved the study. Exclusion criteria were: suspicion of or proven infection, pregnancy, preoperative neutropenia, known HIV infection, known hypogammaglobulinaemia (IgG <50%), the use of prednisolone 10mg per day for the duration of at least 2 weeks in the three months prior to surgery, known inflammatory bowel disease, metastatic disease and uncontrolled diabetes (glucose level > 10 mmol/L or the use of insulin within 6 h prior to FDG-PET).

F-18-fluorodeoxyglucose positron emission tomography

All included patients underwent FDG-PET between two and six days after surgery. Patients fasted for at least 6 h before injection of FDG. Intake of non-caloric beverages was permitted. Intravenously administered fluids, if still necessary, contained no glucose. Hybrid PET/CT scans of the abdomen were acquired using a Biograph Duo (Siemens Medical Solutions USA, Inc.) containing a 2-slice CT scanner. A low-dose CT scan for localization and attenuation-correction purposes was acquired in the caudocranial direction from the thighs up to the diaphragm. Scanning parameters included 40 mA•s (50 mA•s for patient weight >100 kg and 60 mA•s for >120 kg), 130 kV, 5-mm slice collimation, 0.8-s rotation time, and pitch of 1.5, reconstructed to 3-mm slices for smooth coronal representation. CT scans were acquired during timed unforced expiration breath-hold. No intravenous contrast was applied. For PET, a 3-dimensional (3D) emission scan of the abdomen was acquired during free breathing, 60 min after intravenous injection of 13,8 [MBq] • patient weight [kg] / (min/bed position), which is approximately 250 MBq FDG (Mallinckrodt Medical, Petten, The Netherlands) and 10–15 mg furosemide. (12) The acquisition time per bed position was 4 min for emission only. Uncorrected emission images as well as images with CT-based attenuation correction were reconstructed, both using 2 iterations, 8 subsets (for visual interpretation) or 4 iterations, 16 subsets (for quantitative interpretation), and a 5-mm 3D Gaussian filter.(12)

Image interpretation

Two experienced nuclear medicine physicians blinded to the postoperative course and results of other diagnostic tests interpreted all FDG-scans independently. The degree of FDG uptake at the site of the anastomosis was scored as absent or negligible (0), normal physiological bowel uptake (1) and pathologically increased FDG uptake (2). Disagreements were resolved by consensus.

Results

Eighteen males and seventeen females, mean age 66.3 years (range 43- 85 years), were included in the study. Three patients were classified as ASA-I (American Society of Anesthesiologists), 21 ASA-II and 11 patients were categorized ASA-III. The indication for surgery was (pre-) malignancy (n=28), diverticulitis (n=2) and restoration of bowel continuity (n=5). Procedures performed included ileocecal resection (n=1), right hemicolectomy (n=15), left hemicolectomy (n=4), resection of the sigmoid (n=2), (low) anterior resection (n=8) and restoration of continuity (n=5; of which 2 ileorectal anastomosis). Median hospital stay was 6.5 days (range 3-34). The location was the anastomosis was in the right upper abdomen in 16 patients, in the left lower quadrant in 6 and 10 were located in the pelvis region. FDG-PET was performed after a median of 4 days (range 2-6) after the construction of the anastomosis. FDG-PET could not be performed in the early postoperative phase in 3 out of 35 included patients. In two patients the intravenous infusion of glucose was erroneously not discontinued. One PET could not be performed since the patient was too ill. No complication was observed during the follow-up of this patient. Seventeen scans were given a score 0, fourteen a score 1. Figure 1 shows an example of a patient after right hemicolectomy with normal FDG uptake. In only 1 out of 35 scans, there was a disagreement between score 0 and score 1. After consensus, it was decided that score 1 was most appropriate. So, interobserver variability was below 3%.

One of the scans showed abnormal FDG uptake at the site of the anastomosis (score 2; Figure 2). The involved patient was an eighty-year-old woman who was treated for a symptomatic colonic stenosis, highly suspicious for malignancy. She underwent a left hemicolectomy and resection of the proximal jejunum. The postoperative course was prolonged due to ileus, for which she required parenteral nutrition.

She went home 16 days after surgery with a normal gastrointestinal function. Pathology examination revealed Crohn's disease, without disease activity in the resection margins.

The median time interval between surgery and FDG-PET acquisition was 4 days in both the PET-score 0 and the PET-score 1 group. Overall morbidity in both groups did not differ either (PET-score 0: 9/17 vs. PET-score 1: 8/14; not significant, Table 1). Three patients underwent extensive adhesiolysis: two patients had PET-score 0 and one patient had PET-score 1.

Figure 1. The arrow indicates normal FDG uptake after right hemicolectomy.

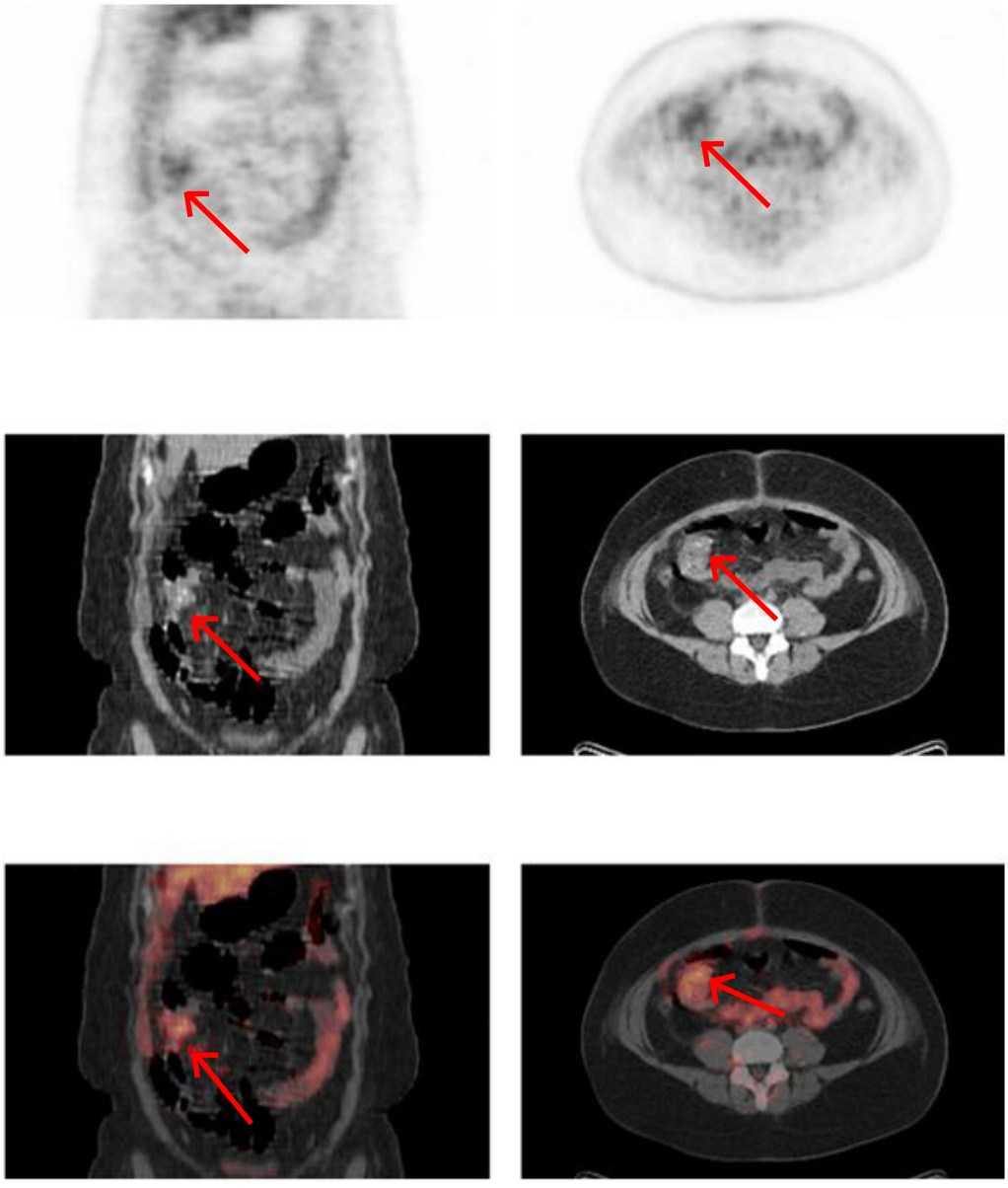


Figure 2. The arrow indicates normal FDG uptake after left hemicolectomy.

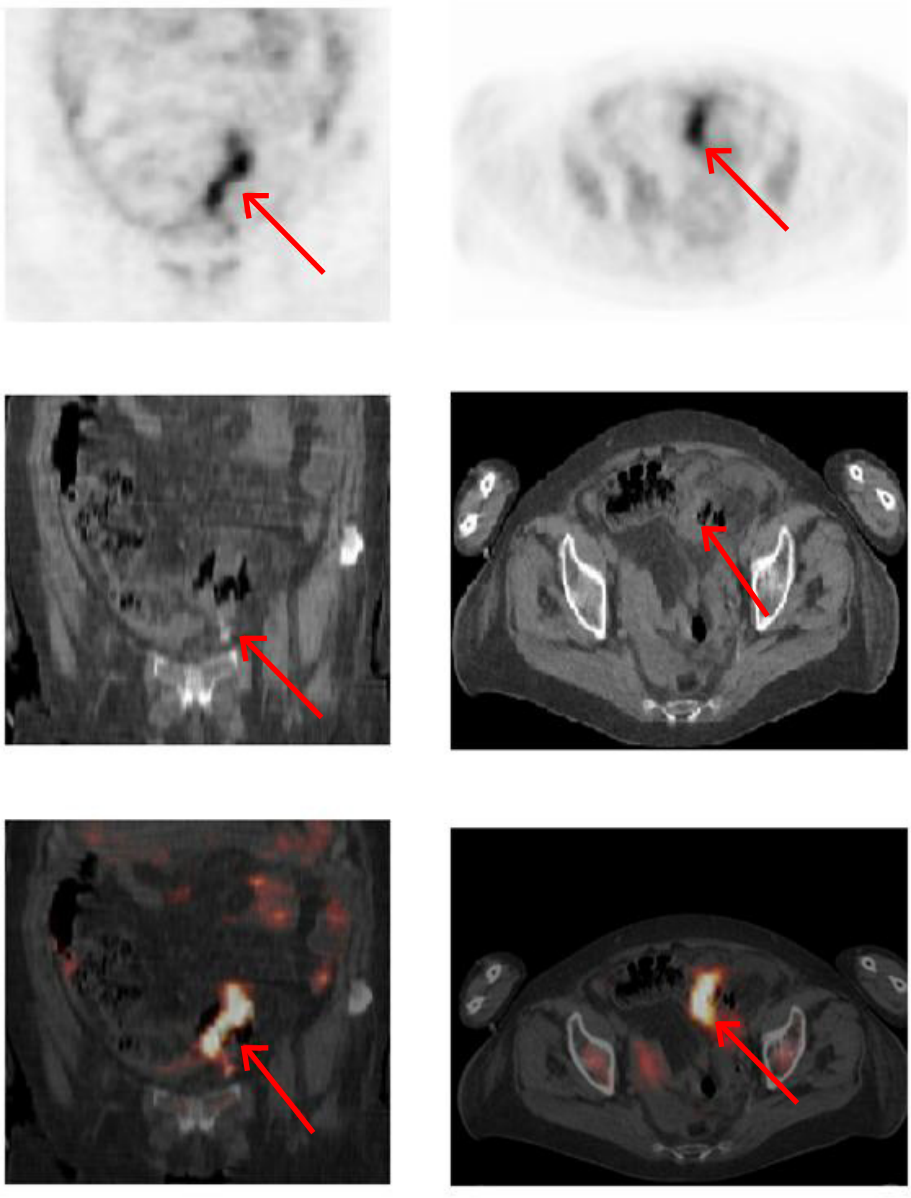


Table 1. Complications after surgery (absolute numbers).

Complication	PET score 0 N=17	PET score 1 N=14	PET score 2 N=1	Total N=32
Ileus	2		1	3
Gastro paresis		2		2
Superficial surgical site infection	2			2
Febris e.c.i.	2			2
Phlebitis		1		1
Atrial fibrillation	1	2		3
Pneumonia	2			2
Urinary tract infection		1		1
Delirium		2		3

PET score 0: absent/ negligible FGD-uptake at the location of the anastomosis
PET score 1: physiological uptake at the location of the anastomosis
PET score 2: pathological increased FDG-uptake at the location of the anastomosis

Discussion

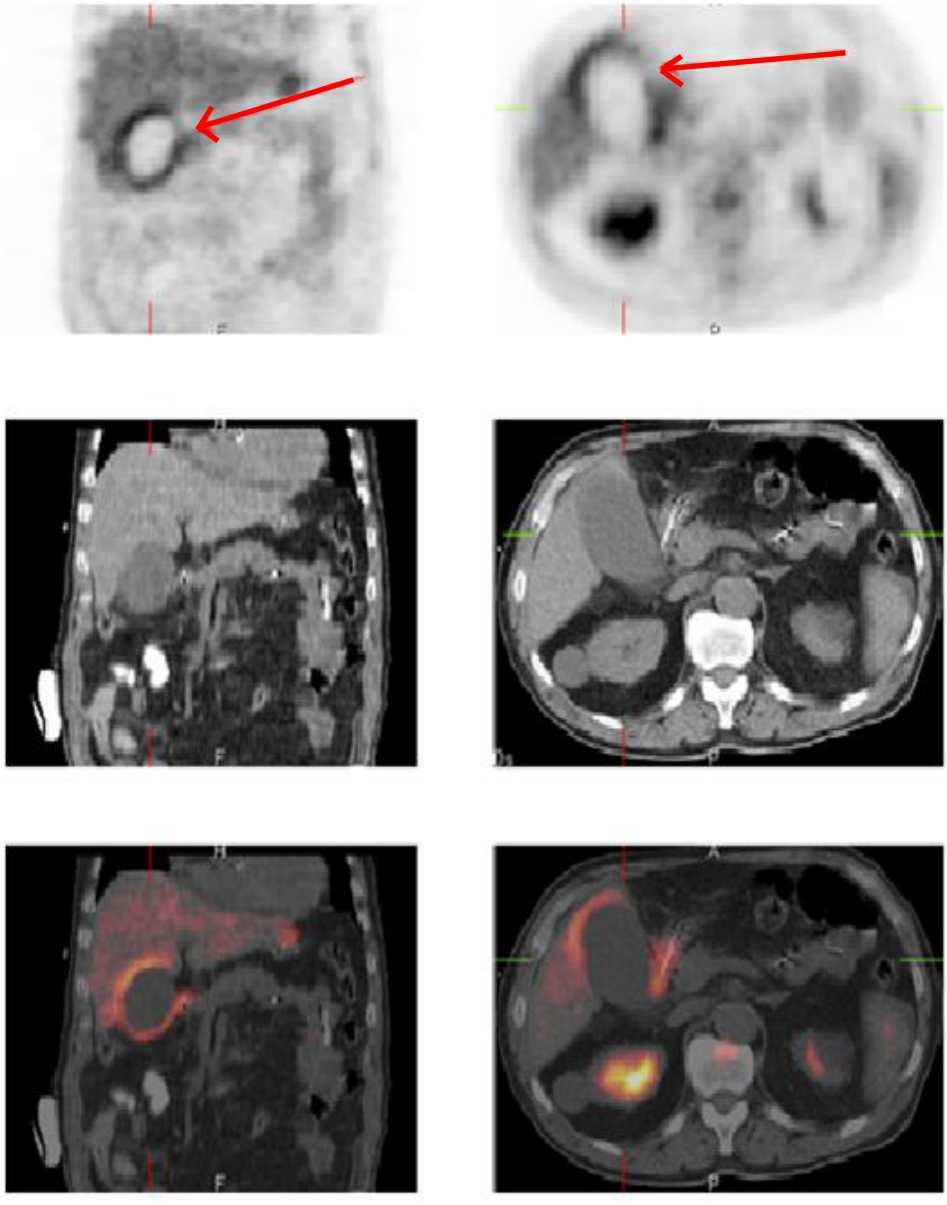
To the best of our knowledge, there are no reports on FDG-PET scanning of bowel anastomoses after colorectal surgery. The results of the present study show that FDG uptake in colorectal anastomosis is absent or physiological, in the first 6 days after surgery.
Early diagnosis of anastomotic leakage is considered important for timely initiation of treatment. It was hypothesized that FDG-PET scanning might be helpful to diagnose anastomotic dehiscence at an early stage since uptake of FDG will probably be increased due to inflammation by leakage of bowel contents. However, healing of the bowel anastomosis itself also initiates an inflammatory response, which may interfere with the diagnostic accuracy of FDG-PET to detect anastomotic leakage at an early stage. The results of our study indicate that the normal healing process at the anastomotic site does not increase the uptake of FDG, resulting in a high specificity of FDG-PET. In only one patient pathologically increased FDG uptake at the site of the anastomosis was observed. Pathology revealed Crohn's disease, but without disease activity at the resection margins. Although FDG-PET correlates well with disease activity in patients with inflammatory bowel disease, it is questionable if this is an explanation for the increased uptake in our patient since the resection margins were free of disease activity. Thus, this patient has to be considered as a false positive.(13;14) The advantage of FDG-PET is that it can recognize other foci of infection that can clarify patients' complaints. We found other FDG-avid lesions in two patients who had a normal FDG accumulation at the site of the anastomosis.
One patient had a cholecystitis (Figure 3); the other patient underwent an adhesiolysis for dense adhesions of the colon to the abdominal wall after Hartmann's procedure for perforated diverticulitis.

Since uptake of FDG in a colorectal anastomosis is normal and specificity is high, FDG-PET might indeed be a valuable diagnostic tool to detect anastomotic dehiscence in future. Further research is needed to determine its diagnostic value, and particular sensitivity and positive predictive value. Furthermore, it is important to define precise criteria in which cases FDG-PET is indicated. Routine scanning after all colorectal resections is not useful. If the sensitivity of FDG-PET scan proves to be high it could be a valuable diagnostic tool in high-risk cases and patients suspected for anastomotic leakage.

Acknowledgements

The authors thank Sharonne de Zeeuw en Rozemarijn van der Vijver for their help in the inclusion of patients.

Figure 3. Incidental finding of cholecystitis.



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8

General discussion

General discussion

Enhanced Recovery After Surgery is beneficial for patients undergoing colorectal surgery. It is associated with a reduction in postoperative morbidity and shortens hospital stay after both colonic and rectal surgery. For this reason, ERAS should become standard of care after colorectal resection.

Although the multimodal ERAS program proved to be beneficial for our patients, the protocol was breached in a considerable number of patients and 30% of the preset goals, regarding epidural anaesthesia, early mobilization, oral intake and fluid management, were not met. This was partly due to the development of postoperative complications, but other factors may have contributed as well. Improved protocol adherence may contribute to better results. Therefore its impact on the outcome of patients should gain more attention in future studies.

The ERAS program is beneficial even with only moderate protocol adherence, but one should question which elements contributes most to this effect. Epidural anaesthesia is thought to be of major importance in Enhanced Recovery after Surgery.(1,2) Although there is evidence that epidural analgesia has advantages, the effects may be more moderate as is thought. (3,4) In Chapter 3, it was concluded that postoperative care following ERAS was associated with a reduction in adverse outcome and hospital stay. There was no difference in epidural use between the ERAS group and those who had conventional postoperative care, so the beneficial effects is more likely to be explained by other elements of ERAS. It was concluded in Chapter 4 that ERAS was useful after rectal surgery. The use of epidural anaesthesia was also comparable in the populations studied after rectal surgery. This seriously questions the role of epidural anaesthesia as a reason for the found differences in postoperative recovery. Epidural failure was studied in more detail in Chapter 5. The incidence of solitary epidural failure was about 25% in colonic surgery. This represents a considerable proportion of patients, but epidural failure did not interfere with surgical outcome. There was no difference in morbidity and hospital stay between patients with adequate epidural anaesthesia according to the protocol and those in who epidural anaesthesia failed. The incidence of epidural failure was lower in rectal surgery (12.2%). This may be explained by different pain blockade of epidural anaesthesia after surgical procedures performed in the pelvis. Inadequate blockade may go unnoticed due to the simultaneous use of intravenous opioids for pain not relieved by epidural anaesthesia.
Although the use of epidural anaesthesia is advocated in fast-track colorectal surgery, some reports, including the results of this thesis, suggest that early mobilisation and timely resuming a normal diet have a more prominent effect on postoperative recovery than epidural analgesia.(5-7) A randomized controlled trial should be undertaken in order to assess the role of epidural anaesthesia in a enhanced recovery program more clearly.

The development and implementation of the fast-track surgery has profound implications for the future. One question is how enhanced recovery might evolve.(8) Further research is necessary to unravel which factors are most beneficial and should receive most attention in the recovery after colorectal surgery, in order to optimize ERAS. All efforts should be made to reduce perioperative risks and morbidity, instead of focusing on hospital stay as the primary outcome. Anaesthetic and (minimally invasive) surgical techniques should be assessed and developed further to reduce the surgical stress response. This thesis suggests that perioperative fluid management plays an important role on postoperative recovery. Although daily fluid balances received a lot of attention in the ERAS program under study, fluid overloading was very frequent with a negative impact on surgical outcome. Optimization of fluid supply in fast track surgery should be subject of further study. As put out in the meta-analysis in Chapter 6, current fluid regimes are not compared in a fast-track program. Whether esophageal Doppler fluid monitoring is helpful or not in fast track surgery needs further study.

It is obvious that Enhanced Recovery After Surgery has a positive impact on surgical outcome and clinicians will have to face the challenges of optimizing and integrating fast-track surgery in the care of patients undergoing colorectal procedures.

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Summary

Summary

The multimodal approach as developed by Hendrik Kehlet, aims to reduce the surgical stress response with subsequent increased demands on organ function. All elements in the program have shown to improve patient outcome separately. The effects on surgical outcome of those elements implemented in an enhanced recovery program are studied widely since. In the year 2006, the enhanced recovery program was introduced in the Department of Surgery of the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. The effects of this program are evaluated in this thesis.

In order to assess the influence of an enhanced recovery program, it is necessary to adequately compare patient populations. In **Chapter 2**, the accuracy of preoperative risk prediction with Physiological and Operative Severity Score for the eNumeration of Mortality and morbidity (POSSUM), Portsmouth-POSSUM, colorectal POSSUM and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) score was assessed. When POSSUM is applied for patients undergoing colorectal resections for malignancy, inflammatory bowel diseases or diverticulitis, the most accurate mortality predictions with any of the POSSUM scores was in patients with diverticulitis. POSSUM scores overestimated mortality in the carcinoma group. ACPGBI scoring was found to be superior in predicting mortality after resection of colorectal cancer in both elective and acute interventions. Lowest mortality POSSUM scores were found in patients with inflammatory bowel disease, which corresponded with the observed death rate. POSSUM underestimated morbidity in this population. This study questions the role of POSSUM and ACPGBI in patient comparison and the prediction of surgical outcome. For this reason, the risk prediction models had no prominent role in the following studies of this thesis.

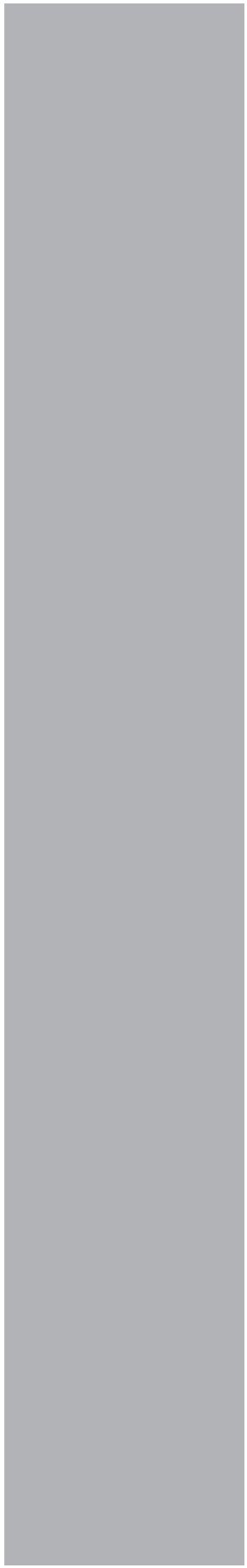
In **Chapter 3**, a historic cohort study with carefully matched controls to assess the effects of an Enhanced Recovery After Surgery (ERAS) program after colorectal surgery is described. The results of this study indicate that care delivered by ERAS is superior to conventional postoperative care for patients undergoing elective colorectal resection. Patients treated according to an ERAS program develop significantly less complications and spent significantly less time in the hospital. This did not result in more readmissions. This study demonstrates that the program as a whole is clearly beneficial and not flawed with unexpected negative effects.

It is known that surgical outcome differs after colonic and rectal surgery. The impact of ERAS in patients undergoing rectal surgery is studied in **Chapter 4**. A cohort study with carefully case-matched controls undergoing rectal surgery, resulting in two highly comparable groups, was undertaken. ERAS perioperative care was found to reduce length of hospital stay after low anterior resection and abdominoperineal resection. The use of epidural anaesthesia, readmission rates,

mortality and morbidity did not change significantly. In this study, patients within ERAS mobilized faster, resumed normal diets sooner with quicker return of gastrointestinal function and the duration of intravenous fluid administration was shorter.
In conclusion, this study shows that ERAS helps to reduce hospital stay after low anterior and abdominoperineal resections.

One of the most important questioned raised in studying the effects of ERAS in colonic and rectal surgery, is which key element(s) is (are) responsible for the improvements in surgical outcome. This led to the descriptive study as described in **Chapter 5**. For this study, definitions had to be formulated of how and when ERAS was considered to have failed. It appeared that about 30% of the goals regarding epidural use, mobility and dietary intake are not reached in an ERAS program. Over half of the patients undergoing colonic and rectal resections do not meet one or more goals of the protocol. The number of patients experiencing complications does not differ between the population able to fulfill ERAS goals and those who are not.
Total complication rate was higher in ERAS failures. The more severe complications were found to decrease protocol compliance. Patients who manage to reach protocol goals are hospitalized shorter after (open and laparoscopic) colonic and rectal surgery. The findings of this study suggest that the influence of epidural analgesia is remote in colonic surgery, and its role in rectal surgery is even less clear. Impairment in early mobility is associated with prolonged hospital stay. The ability to fulfil ERAS dietary guidelines is diminished due to complications after colonic surgery. Problematic dietary intake has a less prominent relationship with complications and hospital stay after rectal surgery. Intravenous fluid overloading is associated with ERAS failure and the occurrence of complications and should receive attention.
In order to optimize intravenous fluid supply, the value of intraoperative esophageal Doppler was assessed in a meta-analysis in Chapter 6. After reviewing the literature, it had to be concluded that the use of esophageal Doppler seems to have moderate advantages to optimize fluid management during surgery. It increases stroke volume and prolongs corrected flow time.
Moreover, it reduces total complication rate and the time to tolerate oral food intake. However, these findings have to be interpreted with caution. Heterogeneity between randomized trials published so far, is considerable. Since all trials under study are found to have reasonable methodology, inferior study quality is not likely to be responsible for this heterogeneity. A major limitation of selected trials is the use of poorly defined outcome measures. This limits pooling of data and threatens conclusions on the value of esophageal Doppler monitoring. It is likely that trials to determine the effect of Doppler guided fluid titration are troubled by the changes in perioperative care and surgical technique.
One of the main consequences of the implementation of an enhanced recovery program is a shortened hospital stay. This may interfere with latent symptoms of complications. Early discharge without an increase in readmission rate is

possible only if patients deviating from the normal postoperative course are recognized early after surgery. Anastomotic leakage remains one of the most serious adverse events after colorectal surgery. It was hypothesized that F-18-fluorodeoxyglucose positron emission tomography/ computer tomography (FDG-PET/CT) might be helpful to diagnose anastomotic dehiscence at an early stage since uptake of FDG will probably be increased due to inflammation by leakage of bowel contents. However, healing of the bowel anastomosis itself also initiates an inflammatory response, which may interfere with the diagnostic accuracy of FDG-PET/CT to detect anastomotic leakage at an early stage. Since negligible uptake of F-18-fluorodeoxyglucose (FDG) at the site of the healing anastomosis is a prerequisite for early and accurate diagnosis of anastomotic dehiscence, we performed a prospective observational pilot study to assess postoperative FDG uptake in colonic and colorectal anastomosis in patients without evidence of active infection or anastomotic leakage, as described in Chapter 7. Patients that underwent colorectal surgery with primary anastomosis received FDG-PET/CT of the abdomen, 2-6 days postoperatively. The results show that FDG uptake in colorectal anastomosis remains low within the first 6 days after surgery in patients without anastomotic leakage. Since uptake of FDG in a colorectal anastomosis is normal and specificity is high, FDG-PET/CT might indeed be a valuable diagnostic tool to detect anastomotic dehiscence in the future.



Samenvatting

Samenvatting

De multimodale benadering zoals geïnitieerd door Hendrik Kehlet in 1997, heeft als doel de chirurgische stress respons met de begeleidende verhoogde arbeid door orgaansystemen te doen reduceren. De voordelige effecten van de separate elementen in deze aanpak zijn vastgesteld. Of de combinatie van deze elementen, samengevoegd in een enhanced recovery after surgery program, voordelen heeft in de perioperatieve zorg en chirurgische uitkomst wordt uitvoerig onderzocht. In 2006 is enhanced recovery after surgery geïntroduceerd op de afdeling chirurgie van het Universitair Medisch Centrum St. Radboud, Nijmegen, Nederland. De effecten van deze implementatie worden geëvalueerd in dit proefschrift.

Hoofdstuk 1 begint met een korte introductie en uitleg over de inhoud en opzet van dit proefschrift. Om de effecten van het ERAS programma goed te kunnen vast stellen is het essentieel om de patiëntenpopulaties adequaat te kunnen vergelijken. In **Hoofdstuk 2** is de accuratesse getoetst van de Physiological and Operative Severity Score for the eNumeration of Mortality and morbidity (POSSUM), Portsmouth-POSSUM, colorectal POSSUM en de Association of Coloproctology of Great Britain and Ireland (ACPGBI) score. Indien POSSUM toegepast wordt bij patiënten die geopereerd worden omwille van een maligniteit, inflammatoire darmziekte of diverticulitis, geeft POSSUM de meest accurate voorspelling van mortaliteit bij patiënten met diverticulitis. POSSUM overschat de sterfte bij patiënten die geopereerd worden aan een maligne aandoening. De ACPGBI score is in deze populatie superieur aan POSSUM, zowel na electieve als acute operatie. Patiënten met een inflammatoire darmziekte hebben de laagste POSSUM scores, die goed overeenkomen met de werkelijke mortaliteit. POSSUM onderschat de morbiditeit in deze populatie. De resultaten van deze studie trekken het gebruik van POSSUM om te komen tot een adequate vergelijking van chirurgische uitkomsten tussen ziekenhuizen en accurate individuele risico predictie in twijfel.

In **Hoofdstuk 3** zijn de effecten van Enhanced Recovery After Surgery (ERAS) onderzocht middels een historische cohort studie met vergelijkbare controle patiënten. ERAS was superieur aan conventionele perioperatieve conventionele zorg voor patiënten die een electieve colorectale resectie ondergingen. Patiënten die behandeld werden volgens ERAS hadden minder complicaties en waren minder lang opgenomen. De gevonden kortere opnameduur resulteerde niet in meer heropnames. De resultaten van dit onderzoek pleiten voor een duidelijk voordelig effect van de implementatie van ERAS. Het is dan ook omwille van deze reden dat Enhanced Recovery After Surgery tot standaard verheven moet worden in de zorg voor patiënten die een colorectale resectie ondergaan.

Het is bekend dat de uitkomsten van patiënten die een colon resectie ondergaan verschillen van patiënten die een resectie van het rectum nodig hebben. De waarde van ERAS bij rectum resectie wordt gespecificeerd in **Hoofdstuk 4**. Hier wordt een cohort vergeleken met een vergelijkbare historische controle groep.

Het resultaat van dit onderzoek is dat ERAS de opnameduur na een low anterior of abdominoperineale resectie verkort. Het gebruik van epidurale anesthesie, mortaliteit en morbiditeit was vergelijkbaar. Patiënten die behandeld worden met ERAS mobiliseren sneller, hervatten het eten eerder met sneller herstel van de gastro-intestinale functie en zijn minder lang afhankelijk van intraveneuze vochttoediening. Gezien de gevonden voordelige effecten van ERAS bij rectum resecties lijkt het verstandig deze zorg als standaard te implementeren.

Een van de meest essentiële vragen die het ERAS programma oproept is welke van de elementen de grootste invloed heeft op de verbeterde uitkomsten. Dit is onderzocht in een beschrijvende studie zoals beschreven in **Hoofdstuk 5**. Dit onderzoek vereiste het formuleren en definiëren van het falen van ERAS. Het blijkt dat ongeveer 30% van de doelen die gesteld zijn aan het epiduraal gebruik, spoedig mobiliseren en hervatten van normale voeding niet gehaald worden in een ERAS programma. Meer dan de helft van de patiënten die een resectie van het colon of rectum ondergaan kan niet voldoen aan een of meer van de gestelde doelen. Hoewel er in absolute zin meer complicaties gevonden worden in de populatie die het programma faalt, is er geen verschil in het aantal patiënten die een complicatie ontwikkelen tussen de groep die er in slaagt de gestelde doelen te halen en de groep die hiertoe niet in staat is. Het optreden van ernstige complicaties doet de protocol compliantie verlagen. Patiënten die in staat zijn aan de gestelde doelen te voldoen zijn korter opgenomen na zowel (open en laparoscopische) colectomie en na een rectum resectie. De bevindingen van deze studie suggereren dat de invloed van epidurale anesthesie op het bespoedigen van het postoperatief herstel beperkt is. Belemmering in het spoedig mobiliseren na een operatie zorgt voor een verlengde opname duur. Na een resectie van het colon is er een relatie tussen het optreden van complicaties en het niet kunnen naleven van de doelstellingen omtrent het hervatten van een normaal dieet. Na rectum chirugie is deze associatie minder evident.
Het overmatig toedienen van intraveneus vocht is gerelateerd aan ERAS falen en het optreden van complicaties.

Ten einde meer inzicht te verkrijgen in de optimalisatie van intraveneuze vochttoediening, werd de waarde van intra-operatieve oesofagiale Doppler tijdens colorectale ingrepen onderzocht in een meta-analyse, zoals beschreven in **Hoofdstuk 6**. Na het reviewen van de literatuur, moet geconcludeerd worden dat het gebruik van intra-operatieve oesofagiale Doppler beperkte voordelen lijkt te hebben: het slagvolume is hoger, net als de ‘ corrected flow time’. Er zijn minder complicaties en de tijd tot het tolereren van voeding is verkort in patiënten die tijdens de operatie vocht toegediend krijgen met behulp van oesofagiale Doppler. Echter, deze conclusies moeten genuanceerd worden. De heterogeniteit tussen de onderzochte gerandomiseerde studies is aanzienlijk en waarschijnlijk niet te wijten aan een verminderde methodologische kwaliteit. Een andere belangrijke beperking is het gebruik van slecht gedefinieerde uitkomstmaten, wat het analyseren van data bemoeilijkt en de conclusies van dit onderzoek ondermijnen. Het is niet onwaarschijnlijk dat

verbeteringen in perioperatieve zorg en chirurgische techniek een rol spelen. Een van de effecten van ERAS is een kortere opnameduur. Het is niet ondenkbaar dat dit interfereert met latente symptomen van complicaties. De meest ernstige complicatie na colorectale resecties vanwege de duidelijke associatie met mortaliteit is naadlekkage. Het vroegtijdig onderkennen van naadlekkage is essentieel voor snelle behandeling en het voorkomen van verdere verslechtering van de toestand van de patiënt. Een verdere risico reductie in colorectale chirurgie kan bereikt worden door een vroege detectie van naadlekkage. Het stellen van de diagnose op klinische gronden is moeizaam en ook bestaande radiologische technieken hebben ernstige beperkingen. Een hypothese is dat F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) een rol kan spelen in de vroege detectie van naaddehiscentie omdat de opname van F-18-fluorodeoxyglucose (FDG) waarschijnlijk verhoogd is door inflammatie door de lekkage van darminhoud. Echter, het genezingsproces van de darm anastomose kent ook een inflammatoire respons. Dit kan interfereren met de diagnostisch accuratesse van de FDG-PET om naadlekkage in een vroege fase te ontdekken. De belangrijkste voorwaarde om te komen tot een accurate detectie van naadlekkage is een verwaarloosbare opname van F-18-fluorodeoxyglucose ter plaatse van een normaal genezende darmanastomose. **Hoofdstuk 7** beschrijft de resultaten van een prospectieve observationele studie om de opname van F-18-fluorodeoxyglucose in colon, dan wel colorectale, anastomose in kaart te brengen bij patiënten zonder aanwijzingen voor een actieve infectie dan wel naadlekkage. Patiënten ondergingen 2 tot 6 dagen na colorectale chirurgie met aanleg van een primaire anastomose, eenmalig F-18-fluorodeoxyglucose positron emission tomography. De opname van F-18-fluorodeoxyglucose bleek laag gedurende de eerste 6 dagen na operatie bij patiënten zonder klinisch relevante naadlekkage. Omdat de opname van FDG in een normaal genezende colorectale anastomose laag en de specificiteit hoog is, is het mogelijk dat FDG-PET behulpzaam kan zijn om naadlekkage in een vroeg stadium aan te tonen.

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List of publications

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Dankwoord

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Elke dag met jou is een feest. Wat is het toch makkelijk om heel veel van je te houden.

Curriculum Vitae

Curriculum Vitae

Pascal Teeuwen werd geboren op 16 september 1980 te Reuver. Hij behaalde zijn atheneum diploma aan het Bisschoppelijk College Broekhin te Roermond in 1998. Hierna studeerde hij gezondheidswetenschappen aan de Universiteit van Maastricht, waar hij in 1999 de propedeuse bemachtigde. In 1999 startte hij met de studie geneeskunde aan de Radboud Universiteit Nijmegen. Gedurende de klinische fase van deze studie werd de interesse voor de chirurgie gewekt. Tijdens zijn coschap chirurgie werd het onderzoek gestart, later uitmondend in een wetenschappelijke stage. Na het behalen van zijn artsexamen in 2005 werkte hij bijna 2 jaar als arts-assistent heelkunde niet in opleiding in het UMC St Radboud te Nijmegen. In 2007 begon de opleiding tot chirurg in het UMC St Radboud te Nijmegen (opleider: Professor Dr. R.P. Bleichrodt). In 2009 volgden twee opleidingsjaren in het Rijnstate ziekenhuis te Arnhem (opleider: Dr. M.M.P.J. Reijnen). Het eerste deel van zijn tweejarige differentiatie binnen de gastroenterologische en oncologische chirurgie vond wederom plaats in het UMC St Radboud (opleider: Professor Dr. C.J.H.M. van Laarhoven). In juli 2012 is gestart met het laatste jaar in het Rijnstate ziekenhuis te Arnhem (opleider: Dr. M.M.P.J. Reijnen), waar de opleiding tot chirurg zal worden voltooid in 2013.

Stellingen behorende bij het proefschrift

Perioperative care in colorectal surgery

Zolang uniforme definities van chirurgische uitkomsten ontbreken, heeft het geen zin risico predictie modellen te ontwikkelen. *dit proefschrift*

Het aanwenden van een Enhanced Recovery After Surgery programma bij de behandeling van patiënten die een electieve colorectale resectie ondergaan gaat gepaard met een reductie in morbiditeit en opnameduur. *dit proefschrift*

Meer dan de helft van de patiënten die een colorectale resectie ondergaan kan niet voldoen aan een of meer van de doelstellingen zoals gesteld binnen het Enhanced Recovery After Surgery programma, waarbij het optreden van ernstige complicaties in belangrijke mate interfereert met protocol compliantie. *dit proefschrift*

De waarde intra-operatief Doppler-geleide vochttoediening is niet eenduidig door de heterogeniteit van de verrichtte studies en de eventueel verstorende invloeden van verbeterde perioperatieve zorg en chirurgische technieken. *dit proefschrift*

De opname van F-18-fluorodeoxyglucose in een colorectale anastomose is laag bij patiënten die geen (klinisch relevante) naadlekkage ontwikkelen. *dit proefschrift*

As long as the abdomen is open you control it. Once closed, it controls you.
Moshe Schein

Beknoptheid is de ziel van de wijsheid. *Shakespeare*

One should advise surgery only if there is a reasonable chance of success. To operate without having a chance means to prostitute the beautiful art and science of surgery. *Theodor Billroth 1829-1894*

If one does not fail at times, than one has not challenged himself.
Ferdinand Porsche, 1875-1951

Volgens de uitspraak ‘De aanval is de beste verdediging’ zou de promovendus vragen aan de corona moeten stellen.

De promovendus is een van de weinigen die opgelucht is als zijn laatste uur geslagen heeft.

Pascal H.E. Teeuwen
Nijmegen, 2012