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Aspects of ERAS-care pathways within colo-rectal surgery

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With joy and great relief

Contents

ABSTRACT

Almost half of all in-patients in Sweden are treated with surgery. Fast postoperative recovery is important not only for each patient undergoing surgery but also from a health economical perspective. Within traditional care, the rate of postoperative recovery after major abdominal surgery has been slow with high morbidity and long hospital stays. The enhanced recovery program (ERAS) designed to reduce surgical metabolic stress through a multimodal approach, has enabled a fundamental shift in terms of perioperative care. The aim with this thesis was to evaluate certain aspects of the ERAS-program.

The objective in **paper I** was to study the impact of different adherence levels to the ERAS-protocol and the effect of various ERAS-elements on outcomes following major surgery. In a single-centre prospective cohort study of 953 consecutive colo-rectal cancer patients at a colo-rectal surgical ERAS unit, patients treated in 2002-2004 were compared to patients treated in 2005-2007, i.e. before and after reinforcement of an ERAS-protocol. All clinical data, 114 variables, were prospectively recorded. All patients were also analysed across periods. Following an overall increase in adherence to the ERAS-protocol, postoperative complications as well as symptoms, declined significantly. Restriction of perioperative intravenous fluid volumes and the use of a preoperative carbohydrate drink were found to be major independent predictors for postoperative outcomes. Across periods, the proportion of adverse postoperative outcomes (30-day morbidity, symptoms delaying discharge, and readmissions) was significantly reduced with increasing adherence to the ERAS-protocol.

In **paper II** the objective was to study pre- and postoperative glucose control in patients undergoing colorectal surgery and whether preoperative HbA1c could predict hyperglycaemia and/or adverse outcomes. In this prospective cohort study, 120 patients without known diabetes underwent major colorectal surgery within an enhanced-recovery protocol. HbA1c was measured at admission and 4 weeks postoperatively. Postoperative plasma glucose was monitored five times daily. Patients were stratified according to preoperative levels of HbA1c above normal range (>6.0) and within normal range (≤6.0). We found that 26% of the patients had a preoperative value above the normal range. Among these, postoperative glucose and CRP concentrations were higher and complications were more common, compared to patients with HbA1c within normal range.

In **paper III**, the objective was to study if patients with Type 2 diabetes can be treated with a preoperative carbohydrate drink (one of the ERAS-elements) without effects on preoperative glycaemia and gastric emptying. Twenty-five patients with Type 2 diabetes and 10 healthy control subjects were studied. A carbohydrate-rich drink was given with paracetamol for determination of gastric emptying. It was found that glucose concentrations after intake of the drink were normalized after 180 vs. 120 minutes in diabetic patients and healthy subjects, respectively. After two hours, for both groups, approximately 10% of the paracetamol remained in the stomach.

The objective of **paper IV**, was to study the association between type of surgical approach (laparoscopic vs. open surgery), compliance to the ERAS-protocol and outcome from surgery in an ERAS environment. Between January 2007-December 2009, 96 consecutive patients underwent high anterior resection with laparoscopic-assisted (n=49) or open resection (n=47). All clinical data (114 variables) were prospectively recorded. We found no significant difference with regards to overall adherence to the preoperative ERAS-protocol between the laparoscopic and open surgery groups. Neither was there any significant difference between groups in terms of postoperative complications, overall postoperative symptoms delaying recovery or median hospital stay. The proportion of patients within target length of stay ≤3 days was however larger in the laparoscopic group, and some of the recovery parameters were also better following laparoscopy compared to open surgery.

In conclusion, it appears that one should strive to achieve highest possible adherence to the elements of the ERAS-protocol in order to improve surgical outcomes. Also, certain ERAS elements may be more important than others for beneficial outcomes. Unsatisfactory glucose control, as indicated by elevated HbA1c, is common in patients scheduled for colorectal surgery. Furthermore, postoperative hyperglycaemia appears to be prevalent even among patients with no history of diabetes and this may be even more important in patients with elevated HbA1c before surgery. It may be safe, within the current fasting guidelines, to administer a preoperative carbohydrate drink to patients with uncomplicated Type 2 diabetes preoperatively. Early recovery can be achieved after both laparoscopic and open resection using the ERAS program. There was some indication of improved recovery following laparoscopic resection compared to open surgery. Modification of the ERAS-protocol to achieve further improvements in association with laparoscopic technique may be warranted.

List of papers

I Ulf Gustafsson, Jonatan Hausel, Anders Thorell, Olle Ljungqvist, Mattias Soop, Jonas Nygren
Adherence to the ERAS-protocol and outcomes after colo-rectal cancer surgery
(Submitted for publication)

II Ulf Gustafsson, Anders Thorell, Mattias Soop, Olle Ljungqvist, Jonas Nygren
HbA1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery
(British Journal of Surgery 2009; 96: 1358-1364)

III Ulf Gustafsson, Jonas Nygren, Anders Thorell, Mattias Soop, Per. M Hellström, Olle Ljungqvist, Eva Hagström-Toft
Preoperative carbohydrate loading may be used in type 2 diabetes patients
(Acta Anaesthesiol. Scand. 2008 Aug; 52(7):946-51)

IV Ulf Gustafsson, Marit Kressner, Anders Thorell, Olle Ljungqvist, Jonas Nygren
Laparoscopic-assisted and open high anterior resection within an ERAS-protocol - A prospective cohort study
(Manuscript)

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ABBREVIATIONS

APR	Abdomino perineal resection
ASA	American Society of Anesthesiologists physical status
ARF	Atrial fibrillation
BMI	Body Mass Index
CHO	Carbohydrate drink
CI	Confidence interval
CRP	C-reactive protein
DVT	Deep vein thrombosis
EDA	Epidural anaesthesia
ERAS	Enhanced recovery after surgery
FT	Fast-track
FPG	Fasting plasma glucose
HAR	High anterior resection
HbA1c	Glycated hemoglobin
ICU	Intensive-care unit
IGT	Impaired glucose tolerance
i.v.	intravenous
LAR	Low anterior resection
LOS	Length of stay
OGTT	Oral glucose tolerance test
OR	Odds ratio
POD	Postoperative day
POS	Postoperative symptoms
RCT	Randomized clinical trial
vs.	Versus

INTRODUCTION

Traditional perioperative care within colo-rectal surgery

Forty-three percent of in-patients in Sweden are treated with surgery [(1)] accounting for a large proportion of national health care resources. Rapid postoperative recovery is important, not only for each patient undergoing surgery, but also from a perspective of health economics.
Colorectal cancer is one of the most common cancers in both men and women worldwide [(2)]. The average age at diagnosis with colo-rectal cancer is generally high and most of the patients are scheduled for major colo-rectal surgery. Within traditional care, the rate of postoperative recovery in this group of patients has been slow with high morbidity rates and long length of stays [(3-8)]. These postoperative outcomes may partly be explained by the fact that colo-rectal disorders normally require major surgery, but also that patients often are at high age with multiple comorbidities and malnourished. However, although the outcome from surgery in recent years has improved due to better surgical technique and improved organizational structure [(3-8)], patients still suffer from slow recovery, high morbidity rates and prolonged hospitalization [(3-8)].

Traditional perioperative care is based on hands-on experience passed on between surgeons for generations [(9)] and only in recent years have structured scientific investigations of perioperative care been performed. Key cornerstones in traditional care such as pre- and postoperative fasting, the use of intra abdominal drains, enforced bed rest and slow mobilization have been shown to be unnecessary or even harmful [(10)].

The absence of general guidelines for perioperative care has not only resulted in different types of practice in various clinics but also limited the possibility of congruent audits of perioperative processes and outcomes in different surgical centers. Thus, in surgical literature, there is a vast diversity in the way postoperative complications are reported [(11)] and significant variations in complication rates makes interpretation and evaluation difficult. For example, morbidity after colo-rectal surgery is reported to be 10-20% [(12)] in some studies but 45-48% [(13, 14)] or even 8-75% [(15)] in others. Differences in outcome definitions (some studies reports only major complications while others divide complications into local, general and surgical [(16)]), but also different definitions of a single complication can explain the diverging results seen in surgical reports [(17)]. Furthermore, 90% of medical centers in Europe record quality data retrospectively and the recording is often performed by residents physicians who have been shown to be more likely to underreport complications [(11, 18)].

Due to the lack of congruence in perioperative care across sites, the unsatisfactory recovery rates and diverse quality in terms of reporting outcomes, there is a need for new perioperative regimens, other than the currently practiced traditional perioperative care.

Enhanced recovery after surgery (ERAS)

Enhancing the overall recovery rate by the use of multi-modal interventions (hereafter also interchangeably called ERAS-elements, ERAS-components or ERAS-items) of patients following open abdominal surgery has been a fundamental shift in terms of perioperative care. In the early works of "fast track surgery", the pioneer in this approach, Henrik Kehlet (Denmark) focused on post-operative pain, gut function and mobility by combining interventions to reduce surgical stress and organ dysfunction [(19)]. Ten years ago, Basse et al, showed that it is possible to discharge patients 48 hours after colonic surgery (rather than 7-14 days in traditional care) with an accelerated stay program [(20)].
Inspired by the work of Kehlet et al and due to the lack of consistency in perioperative audit and large differences in reported rates of outcome after surgery in different surgical centers, the enhanced recovery after surgery (ERAS) collaboration was established in 2000. Today, the ERAS-study group includes six European centres; Sweden: Ersta Hospital; Norway: Tromsö University Hospital; United Kingdom: Royal Infirmary, Edinburgh and St Marks Hospital, London; Netherlands: Maastricht University Hospital; and, Germany: Charite University hospital, Berlin.

The aim with the collaboration has been not only to develop, improve and spread the ERAS-protocol, but also to implement the same perioperative regimen in all participating centres resulting in comparable outcomes. A central database [(21)] for prospective collection of perioperative data (more than 140 different variables) was specificially designed to enable such comparisons. The application of strict criteria for collecting the different variables in the database enables congruently defined and more reliable audits of pre- peri- and postoperative outcomes. Since nonphysicians are shown to be better data collectors, not underreporting morbidity like many clinicians do [(11, 22)], the data is prospectively collected by trained nurses.

ERAS, also known as fast-track surgery aims to accelerate recovery, shorten hospital stay and reduce complication rates following surgery by the use of multimodal perioperative programs. Enhanced recovery regimens have been demonstrated to result in improved physical performance, pulmonary function, and body composition [(23)]. The ERAS-protocol is designed to reduce surgical metabolic stress by supporting basal body functions through the use of careful preoperative preparations, optimal analgesia, early mobilization and early oral feeding. The protocol includes approximately 20 evidence-based care interventions [(24, 25)] carried out by a multidisciplinary team of surgeons, anesthesiologists, nurses and physical therapists to coordinate interventions to reach fast recovery after surgery [(10)]. Several studies have demonstrated that the ERAS-protocol as a whole compared with traditional perioperative care is associated with earlier recovery and discharge after colonic resection [(10, 20, 23, 26-30)]. Although some studies report improved outcome following pelvic surgery, the benefit in terms of recovery associated with the ERAS program remains uncertain [(16, 28, 31)]. In colo-rectal surgery, despite strong evidence regarding the effects on recovery and discharge it has been more difficult to find evidence for a reduction in postoperative complications following the introduction of ERAS-protocols. Recently, however, a few systematic reviews and smaller uncontrolled studies [(15, 26, 31, 32)] indicate a decline in surgical morbidity within ERAS care.
Despite increasing evidence for the ERAS-programs as best clinical practice, previous studies on ERAS-care have had some limitations. One being that the ERAS data-base has been under reconstruction during the last years and not yet reached its full potential impact within the ERAS-collaboration. Most centers practicing fast-track care do not yet participate in the collaboration,

thus, studies conducted so far are small and most exclusively single centre based. A comparison of data between different ERAS centers outside the collaboration, with diverse programs and a variety of interventions, has been difficult since perioperative results are not recorded in a uniform manner [15, 24]. In a systemic review [15] of the best clinical studies on ERAS-care, all between 4-12 ERAS- items were reported, in contrast to the predefined 20 interventions. Also, in order to truly evaluate the effect of ERAS-programs, the rate of adherence to the protocol should be described [33]. In addition to the lack of data on adherence to all the predefined ERAS-items, randomized data on the importance of single interventions within the ERAS program is still limited [24, 25]. Even if many of the interventions used in the ERAS-program are based on solid evidence from randomized trials, the role and relative contribution of each item when mixed together in the protocol as a whole requires further study and evaluation [24].

Surgical stress

In 1942, Cuthbertson [34] described different metabolic phases after trauma. The first phase, shock, is characterized by vasoconstriction and conservation of water aiming at immediate survival. The second phase is initiated by an ebb phase with decreasing energy expenditure and fuel mobilization, lasting approximately 24 hours and shifting gradually into the flow phase. The hypermetabolic flow phase only disappears late in recovery and is characterized by an initial state of catabolism and subsequent transition to anabolism and recovery. During the catabolic state, energy expenditure is elevated and the body increases the available amount of metabolic substrates through a general breakdown of body tissue. Glucose, amino acids and free fatty acids can then be used by vital organs.

Alteration of stress hormones have traditionally been considered to play an important role in the response after surgical trauma. The surgical injury initiates a neuroendocrine response that activates the hypothalamopituitary axis and the adrenergic system, resulting in increased circulating concentrations of cortisol, glucagon, adrenalin and noradrenalin [35] (Figure 1). The excess of these, so called counter-regulatory hormones, released in association to stress are shown to have metabolic effects opposing those of insulin. Insulin resistance and several other metabolic alterations associated with trauma have been seen when infusing cortisol [36], adrenalin [37], glucagon [38] and growth hormone [39] to healthy volunteers.

Insulin resistance, i.e. the state of reduced insulin sensitivity in the tissues, caused by hormone inhibition of insulin secretion and/or counteracting the peripheral action of insulin [37, 40], is thought to be one of the principal mechanisms behind catabolic response to surgery. With insulin resistance follows stimulated amino acid oxidation and muscle proteolysis, decreased glucose utilization and hyperglycaemia [41, 42]. These metabolic changes associated with surgery are similar to those typically observed in patients with type 2 diabetes and is therefore sometimes called *diabetes of injury* [35].
Thus, insulin resistance is a phenomenon central to catabolic states in all patients undergoing surgery, not only patients with diabetes.

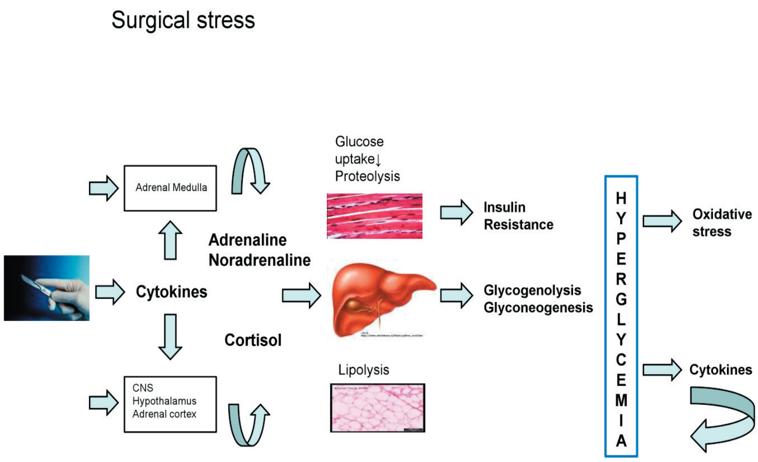


***Figure 1.** Metabolic stress induced by surgery*
Counter regulatory hormones induce reduced insulin sensitivity. Insulin resistance results in hyperglycaemia which causes an increase of release of proinflammatory cytokines. Cytokines, in turn, triggers the inflammatory response and further activation of the hypothalamopituitary and sympathoadrenergic system.

Insulin resistance and hyperglycaemia

Insulin suppresses endogenous glucose production mainly in the liver and stimulates the uptake of glucose in insulin-sensitive tissues [(43)]. Surgical trauma causes a transient reduction in insulin sensitivity which in turn leads to increased glucose production as well as a decreased tissue uptake of glucose and glycogen synthesis, resulting in hyperglycaemia. The magnitude and duration of the operation and also perioperative blood loss is found to be related to the degree of reduction in insulin sensitivity [(44)]. After surgical procedures of moderate magnitude, such as open cholecystectomy, preoperative insulin sensitivity is reduced up to 50% which remains for at least 5 days with normalization within 3 weeks [(45)]. After colo-rectal surgery, where the magnitude of the operations is more variable, insulin sensitivity has been shown to be closely related to the length of operation [(45)]. The main sites for insulin resistance following surgical trauma seem to be extrahepatic insulin dependent tissues, mainly skeletal muscle but also the cardiac muscle and adipose tissue where data suggest that the glucose transport system is impaired [(46, 47).]

Hyperglycaemia is a metabolic condition historically interpreted as an adaptive stress response, essential for survival in supplying enough with substrates to vital organs. However, in modern medicin hyperglycaemia has been demonstrated to be associated with adverse clinical outcomes [(48-51)]. The link between hyperglycaemia and adverse outcomes is not fully understood, but hyperglycaemia is thought to induce cellular inflammation increasing the expression of proinflammatory cytokines and oxidative stress with increased formation of reactive oxidative species [(52-54)]. The function of endothelium, monocytes and neutrophils is also affected by hyperglycaemia [(52-54)]. The resulting negative effect on the innate immune system and the enhanced proinflammatory response might cause adverse events after surgery by enabling wound infection or sepsis with or without multiorgan failure [(49, 51)].

Although the surgical trauma itself may initiate postoperative insulin resistance, many other factors present before, during and after the operation also contribute to the metabolic condition. For example, prolonged fasting and immobilization has been shown to induce postoperative insulin resistance [55-57].

Avoiding surgical stress, insulin resistance and postoperative hyperglycaemia

Improved glucose control by insulin treatment has been shown to reduce mortality as well as morbidity in patients receiving intensive care after operation [51, 58].
The study by Van den Berghe and associates [51] provides the most convincing evidence that establishment of normoglycaemia improves surgical outcome. 1548 surgical ICU patients were randomized to receive intensive insulin therapy (serum glucose target value, 4.4 mmol/l - 6.1mmol/l) or conventional therapy (10.0 mmol/l – 11.1 mmol/l). In the treatment group, where the glucose levels were reduced by one-third, mortality was reduced from 8.0% to 4.6%. Also, bloodstream infections were reduced by 46%, acute renal failure by 41%, critical-illness polyneuropathy by 44% and the median number of red cell transfusions by 44%.

A large cohort study comparing two periods, before and after the launch of a protocol with intensive insulin therapy with glucose target of <7.75 mmol/l, found attenuated renal dysfunction and a reduction in mortality as well as in the number of patients requiring transfusions after the launch [58].
However, intensive insulin therapy is associated with difficulties. In the United States, 33% of fatal medical errors causing death within 48 hours were related to insulin treatment [59]. Recent studies in an ICU setting have also shown that intensive insulin treatment may be associated with significant hypoglycaemia [60, 61]. Thus, in patients treated outside the ICU where the availability of nursing staff is limited, insulin treatment targeting euglycaemia is currently not recommended. There are, however, other ways to reduce the risk of hyperglycaemia.

The ERAS-protocol is designed to reduce surgical stress and metabolic response, including attenuation of postoperative insulin resistance thereby aiming to preclude the need of postoperative insulin treatment. In particular, the use of ERAS-interventions minimally invasive surgery, epidural anaesthesia and preoperative carbohydrate drink has been shown to result in improved postoperative glucose control [25]. Moreover, insulin resistance associated with bed-rest [10] also makes early mobilization an important tool for avoiding postoperative hyperglycaemia.

Diabetes and surgery

The number of patients diagnosed with Type 2 diabetes is reaching epidemic proportions and some studies report a prevalence of over 6 % of the total population [62, 63]. The estimated number of unknown cases could be assumed to be large since the early stage of the disease may be asymptomatic. Thus, type 2 diabetes can remain undetected for years [64]. In some studies, the estimated proportion of undiagnosed Type 2 diabetes is almost as high as that of all the diagnosed cases [62]. Also, the prevalence of individuals with prediabetes or impaired glucose tolerance, a predictor for Type 2 diabetes, is unknown [64].

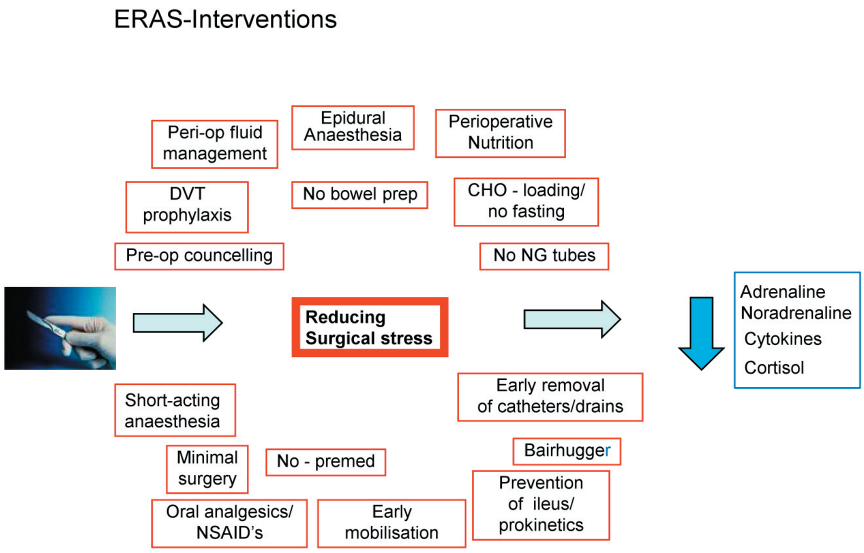
This problem is particularly serious when scheduling patients for surgery, since patients with diabetes are at particular risk of postoperative impaired glycaemic control, protein catabolism and complications [49, 65, 66]. In a previous study including 2030 patients, 12 % prevalence of undiagnosed diabetes in those admitted to general hospital wards were reported. Among patients with newly discovered hyperglycaemia, the in-hospital mortality rate was 16% compared to only 1.6% in patients without hyperglycaemia [67]. In a study including patients undergoing vascular surgery, 58% of patients with no diagnosis of diabetes had a suboptimal preoperative glucose control and a significantly higher 30-day morbidity compared to patients with normal preoperative glucose values [68].

Although the available evidence suggests that ERAS-protocols improve postoperative glucose control in colo-rectal surgery, detailed knowledge of perioperative glucose control is limited. The proportion of non-diabetic patients undergoing major colo-rectal surgery who suffer from poor preoperative glucose control is unknown. Nor is it known whether preoperative glucose control in non-diabetic patients is a determinant of postoperative outcomes. If so, early identification of patients at risk of hyperglycaemia would enable specific perioperative interventions that may improve postoperative recovery.

ERAS-interventions

In order to reduce surgical stress and postoperative catabolism, the ERAS protocol includes approximately 20 evidence-based coordinated care elements described in previous consensus reviews [24, 25, 68]. Some of these interventions (figure 2), with particular focus on the items related to the papers in this work, will be further described in the following section.

Figure 2*. Examples of ERAS-interventions designed to reduce surgical stress.*



Preadmission information

According to the ERAS-protocol, patients should preoperatively be informed to pay attention to the postoperative care plan. Faster postoperative recovery and improved pain control has been shown to be achieved by explicit preoperative information [69, 70]. Explanation of expectations regarding the patients role in the perioperative process such as targets for postoperative food intake, oral nutrition supplement and target for length of stay facilitates adherence to ERAS-care and allows early recovery and discharge [71, 72].

Preoperative carbohydrate drink

In traditional perioperative care elective surgery is usually performed after an overnight fast. This routine has been used to minimize the risk of aspiration of gastric contents in connection with general anaesthesia. However, no evidence has been found to support this fear of aspiration [73] and today, there is robust evidence that the preoperative fasting period allowing only clear fluids can be reduced up to 2 hours before surgery, without increasing morbidity [74].

Starving before surgery puts the patient in a catabolic state and increases risk for enhanced perioperative surgical stress. Thus, when a preoperative overnight treatment with intravenous infusion of glucose was administered to the patients, rather than the conventional preoperative fast, attenuation of the degree of insulin resistance after major abdominal surgery was found [75]. This preoperative carbohydrate load improves postoperative glycaemic control, most likely by inducing endogenous insulin release before the onset of surgery. This sets the metabolic state of the patient in a fed rather than a fasted state at the time of surgery.

Intravenous glucose treatment before surgery is inconvenient and a more physiological route of administration is warranted. Therefore, a carbohydrate-rich beverage was designed that safely can be given shortly before surgery [76]. The oral preparation used consists of 400 ml carbohydrate-rich (50g) clear beverage (CHO) containing mainly polymers of carbohydrates to minimize the osmotic load (Osmolality 285 mosmol/kg) and thus reducing the gastric emptying time (90 minutes) [76]. This beverage stimulates a release of insulin similar to that demonstrated after a mixed meal (plasma concentrations of 60µU/ml) [76] and has been seen to attenuate the postoperative development of insulin resistance by 50% measured on the first day after major abdominal surgery [77]. CHO treatment seems to hamper the development of insulin resistance mainly in peripheral tissues [43] thereby attenuating the reduction of glucose oxidation. Furthermore, preoperative carbohydrate loading is also associated with a decrease in postoperative urinary nitrogen loss (a marker of protein catabolism) [78], retained lean body mass and improved muscle strength [79, 80]. In addition to its metabolic effects, the CHO drink improves patient well-being (thirst, hunger, anxiety) preoperatively [81].

Diabetes and the preoperative carbohydrate drink

As stated above, a considerable number of patients who undergo surgery suffer from diabetes. This group of patients could be assumed to be at particular risk of postoperative hyperglycaemia. So far, patients with diabetes have been denied a pre-operative carbohydrate drink because of fear of slow gastric emptying and impaired glycaemic control [73, 82] preoperatively. Although impairment of vagal function, as part of generalized autonomic neuropathy, is thought to cause slow gastric emptying in patients with diabetes, data on gastric emptying in these patients are conflicting and the true prevalence of significant gastroparesis is unknown. According to cross-sectional studies, approximately 30-50% of outpatients with long-standing type 1 or 2 diabetes have slower gastric emptying than normal individuals [83]. However, most often the magnitude of delay seems to be modest.

In contrast, it has been reported that the gastric emptying rate is increased in type 2 diabetes patients, at least early after the onset of the disease [83]. With an increasing amount of patients with diabetes and a large estimated number of patients with unknown prediabetes undergoing surgery, it is important to explore the possibility of providing CHO with regard to the potential risk of impaired glycaemic control and pulmonary aspiration during anaesthesia.

Preoperative bowel preparation

In colonic surgery, bowel preparation has been shown to be unnecessary and most probably harmful due to the risk of fluid and electrolyte abnormalities [84-86]. In addition to the fact that some studies indicate an increased risk of anastomotic leaks with this routine [87, 88], bowel preparation is stressful and prolongs postoperative ileus [89]. However, in rectal surgery (i.e. LAR with temporary loop ileostomy), bowel cleansing still is considered standard of care [90].

No premedication (preanaesthetic medication)

In traditional care, long-acting sedatives have been used in order to calm down anxious patients before surgery, thereby facilitating the preoperative process.
However, the use of preanaesthetic long-acting sedatives is associated with impaired ability to drink immediately after surgery, which in turn negatively affects the potential for early mobilization. This results in prolonged length of stay [91]. No prolonged recovery or length of stay is found when using short-acting anxiolytics instead of long-acting sedatives [92].

Intraoperative warming

During surgery, patients are subjected to cold stress since general anaesthesia affects the regulatory set point of the cold exposure defense [93] and since the temperature in operative rooms is usually maintained low [94]. During surgery, the body core temperature may decline 2-4 degrees which augments the stress response to the trauma induced by surgery [94].
Intraoperative hypothermia may be prevented by warm i.v fluids and by the use of heating pads (Bair Hugger®) reducing sympathetic responses, cardiac adverse events and the risk of wound morbidity [95, 96].

Perioperative fluid management

Standard practice in traditional care is infusion of i.v fluids in volumes in excess of perioperative losses. A volume of 3.5 to 7 litres on the day of surgery and more than 3 litres/day postoperatively, may induce 3-6 kg of weight gain [97, 98].
Recent evidence shows that fluid overload is associated with increased morbidity [98, 99] in terms of delayed return of gastrointestinal function [98], impaired wound or anastomotic healing and impaired tissue oxygenation [97, 99].

Although the results from studies comparing liberal vs. restrictive fluid regimens [20, 97-101] are not uniform and too little perioperative fluid treatment may result in functional hypovolemia and a triggered vasoactive hormonal response [102-104], most evidence supports fluid restriction in order to maintain weight balance and to reduce the risk of postoperative complications [98, 99]. Perioperative fluid therapy should therefore be optimized. Individualized optimization of fluid therapy with concurrent assessment of heart stroke volume by the use of Doppler shows promising results in reducing postoperative morbidity [105, 106], and may be useful, in particular in high-risk patients.

Early mobilization

As mentioned above, bed rest increases insulin resistance but the supine position also decreases muscle strength, pulmonary function and tissue oxygenation [10]. The increased risk of thromboembolism associated with bed rest is well known. Therefore, in an ERAS-protocol, the target for early mobilization is to be out of bed for 2 hours on the day of surgery and thereafter at least 6 hours per day until discharge.

Epidural anesthesia (EDA)/Pain relief

There is no evidence that intraoperative epidural analgesia improves outcome after colo-rectal surgery. However, postoperative optimisation of pain relief with EDA has been shown to keep the patients free of pain and to allow early mobilization [24, 25].
Epidural anesthesia suppresses the endocrine response to surgery by blocking visceral sympathetic and parasympathetic pathways [107]. This may also lead to reduced postoperative insulin resistance [108] and postoperative ileus [109-111].

When the epidural catheter is withdrawn (target 2 days following colonic surgery and 3 days after rectal surgery; ERAS-care) effective treatment of postoperative pain is necessary in order to further facilitate mobilization.
An increasing body of evidence shows that opioid sparing postoperative pain treatment reduces nausea, vomiting and sedation enabling faster mobilization [112]. Non-steroidal anti-inflammatory drugs and various techniques for local or regional anesthesia have been shown to reduce the need for opioid pain treatment after surgery [113]. The μ-opioid receptor antagonist alvimopan reduces pain and concurrently improves gastrointestinal motility and may be well-suited in postoperative ERAS-care [114, 115].

Prevention of nausea

The common postoperative complaints nausea and vomiting are often experienced even more stressful than pain itself [116-119] and may limit recovery resulting in delayed hospital discharge [10]. Risk-factors for nausea include female sex, non-smoking status, previous history of motion-sickness, anxiety, dehydration and postoperative administration of opioids [120, 121]. In risk individuals, prophylaxis with dexamethasone sodium phosphate at induction or serotonin receptor antagonist at the end of surgery [122] reduces the risk for nausea and vomiting and should therefore be considered as part of the ERAS-protocol.

Drainage

Suprapubic catheterization has shown to be more tolerable to patients and to reduce morbidity compared to urethral catheterization [123]. Most of the studies conducted include patients with 4-7 days of urinary drainage. Thus, the use of suprapubic catheters could be beneficial in pelvic surgery. However, in colonic surgery within an ERAS care, where urinary catheters should be withdrawn after 2 days, the risk of urinary retention is low during epidural anaesthesia [124], and the expected advantage of the use of suprapubic catheters is probably smaller.

Drains after colonic surgery have not been found to reduce the incidence of postoperative complications [125, 126], while the use of drains for 24 hours following rectal surgery is supported by data from the literature [127].

The routine of keeping nasogastric tubes for decompression of the stomach after colo-rectal surgery should be abandoned since the risk of fever, atelectasis and pneumonia is reduced and the return of bowel function is improved in patients without nasogastric tubes [128, 129].

Prevention of postoperative ileus

The major cause of delayed discharge in colo-rectal surgery is postoperative ileus [130]. Several interventions within the ERAS-protocol are found to reduce the risk of this condition. Compared to the use of intravenous opioid analgesia, mid-thoracic epidural analgesia has been shown to prevent postoperative ileus [109, 110]. As stated above, perioperative fluid overloading impairs gastrointestinal function and should therefore be avoided [98, 100]. Compared to open surgery, laparoscopic surgery has been reported to reduce mast cell activation and the inflammatory response which in turn may reduce the length of postoperative ileus [131]. Although no prokinetic agent seems to be effective in treating postoperative ileus, oral magnesium oxide has been reported to promote postoperative bowel function [132]. The μ-opioid receptor antagonist alvimopan accelerates gastrointestinal recovery and is approved for clinical use in postoperative ileus and show promising results [114, 115].

Minimally invasive surgery

A laparoscopic approach to resect adenocarcinoma of the colon has been found to be oncologically safe [133-135], while some concerns in this respect regarding laparoscopy and rectal cancer still remain [136]. Smaller wound size in laparoscopic surgery compared to open surgery is thought to decrease surgical stress, inflammatory response, postoperative pain and ileus as well as catabolism [130, 137, 138]. The drawbacks of laparoscopy include a protracted learning curve for surgeons [139, 140], prolonged operating times [141, 142] and higher initial costs [141].

Considering that laparoscopic colo-rectal surgery has been practised for 20 years [143] and now is being adopted in clinical practise worldwide, one would expect robust evidence for improved clinical outcomes compared with open surgery. However, three large multi-centre studies [135, 136, 144] show no or relatively modest gains in short-term outcomes when comparing laparoscopic to open colonic surgery. One meta-analysis [145] of smaller single-center studies reports that significant improvements in short-term outcomes could be achieved by laparoscopy-assisted resection. Laparoscopy was associated with significant reductions in time to first bowel movement, short-term wound morbidity and discharge from hospital. Importantly, however, these studies were conducted within a traditional perioperative setting without the use of fast-track perioperative care.

Previous reports of outcomes after laparoscopic colo-rectal surgery have been criticized by ERAS proponents [146, 147] since the laparoscopic results have been compared with open surgery within a traditional perioperative care, often with sparsely described protocols. For example, reports on length of stay in laparoscopic surgery within traditional care have not reached the short hospital stays achieved after open surgery with the use of an ERAS-protocol.

The availability of controlled data comparing laparoscopic vs. open colo-rectal surgery within an ERAS setting is very limited. A recent meta-analysis [(148)], reported that two randomized controlled studies (RCT) [(149, 150)] and three controlled clinical trials [(33, 146, 151)] together pointed in a more favourable but non-significant direction for laparoscopic vs. open surgery regarding hospital stay, readmission rates and morbidity. However, these studies had several methodological limitations: the sample-size was generally small, different colonic surgical procedures were mixed in the same data analysis, and, the resulting outcome parameters varied largely between the different studies. In addition to these five studies, recent reports on laparoscopic colonic surgery within an fast-track environment show promising results in enhanced postoperative recovery [(152-155)]. However, these studies are large case-series conducted without any control group and do not allow any firm conclusions to be drawn.

ERAS programs share the same objective as laparoscopic surgery, namely reducing surgical stress and improving outcome after surgery. The role of laparoscopic surgery within the ERAS-program is, however, still uncertain since it is unclear if laparoscopic surgery contributes with any additional benefits compared to those achievable with the ERAS-protocol alone. Furthermore, if laparoscopy is to be considered as an intervention within the ERAS-protocol, it has to be clarified if and how the protocol should be modified to ascertain improved outcomes from laparoscopy [(156)].

Perioperative nutrition

Traditionally, major surgery is followed by a period of 7-14 days of hypocaloric nutrition until recovery enables the patient to resume full oral diet [(157)]. Concurrently, studies have reported that a caloric deficit of 6000-10000 kcal over one week in critically ill patients increases mortality rates 2-fold [(158, 159)]. Also, prolonged fasting has been shown to aggravate postoperative insulin resistance [(160)]. Although some authors claim that oral perioperative nutrition per se to patients without malnutrition and with short length of postoperative stay does not seem to improve postoperative outcome [(161)], other studies suggest that early postoperative nutrition reduces postoperative infections, complications and length of stay (LOS) compared to traditional hypocaloric nutrition [(162)].
The reason for avoiding immediate oral feeding postoperatively has been the concern for nausea, vomiting, aspiration and the assumed potential risk of anastomotic leakage.

The use of parenteral nutrition could be one option to avoid the above mentioned concerns but, early parenteral nutrition increases the risk of postoperative hyperglycaemia [(163)], complications [(164)] and the risk of overloading the patient with fluids.
Furthermore, compared to patients fed orally, patients with i.v. solutions are to a higher degree restricted to the hospital bed, inhibiting mobilization.
The risk of postoperative nausea and vomiting are nowadays minimized with the use of modern postoperative care and available evidence does not support an increased risk associated with early oral feeding [(165)]. Therefore, in ERAS-care, patients receive their first full meal 4 hours after completed surgery.

In malnourished patients, postoperative oral nutrition for 8 weeks has been shown to improve recovery of nutritional status, protein economy and quality of life [166]. Nutritional supplements have also been shown to be associated with positive clinical outcomes in patients without prior malnutrition [167, 168]. ERAS-programs therefore use such supplements the day prior to surgery and four days postoperatively to achieve the recommended level of energy intake.

Rationale for further research in ERAS-care

Although interventions within ERAS or fast-track programs have been shown to improve postoperative recovery in colo-rectal surgery [9, 15, 32, 169], such protocols have not been widely adopted, and in most centers old traditions prevail [170]. One reason could be that ERAS programs are considered too complex and resource-demanding [33]. Another that the ERAS concept as such, possibly appears elusive as the relative contribution of each single intervention in the programme remains uncertain. The lack of data regarding the importance of adherence to the protocol [33] may also add to the uncertainty. Introducing ERAS-protocols usually requires a major shift in clinical routines and requires a firm organizational and economic environment. Launching an ERAS-programme is demanding and devoted staff from all of the involved disciplines is necessary to succeed. The large efforts and requirements needed for implementation of an ERAS-programme may explain why modified "lighter" versions of the programme have been introduced recently [171]. Also, selected items of the ERAS-protocol such as omission of routine bowel preparation for colonic resections, no routine use of postoperative drains, early removal of nasogastric tubes, early feeding and mobilisation have already been incorporated in traditional care [170, 172].

However, so far, the proven benefits of using an ERAS-program are based on studies of the entire protocol, not on single protocol items. It is not known whether the improved outcomes associated with ERAS result from the combination of all the intervention elements due to a synergistic effect, rather than from the impact of each parameter alone [24]. As the enhanced recovery field develops, certain interventions may turn out to be non-essential. However, decisions to omit any specific components in the protocol should be based on a closer understanding of the importance of each single element in the ERAS- program. Thus, there is a need for further evaluation and, if plausible, a more detailed description of the impact of the ERAS-protocol on postoperative recovery. The importance of the rate of adherence to the protocol has to be clarified, a closer understanding of the separate impact of specific ERAS-interventions is necessary and identification of biological factors contributing to the adverse events of surgical stress are of great importance to further improve and modify the ERAS-protocol.

Aims

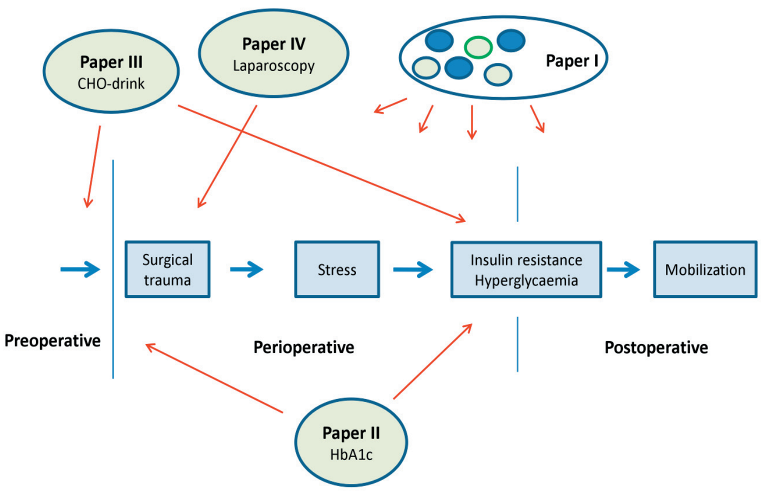
The overall aim of this thesis is to further evaluate the impact of using an ERAS-protocol in colorectal surgery and to increase the knowledge about specific ERAS-interventions. Specifically, the following research questions were addressed:

1. What is the impact of adherence to the ERAS- protocol and the relative contribution of specific interventions on postoperative outcomes?
   (Paper I, prospective cohort study)

2. Is preoperative glucose control in non-diabetic patients scheduled for colo-rectal surgery a determinant of postoperative outcome?
   (Paper II, prospective cohort study)

3. Can Type 2 diabetes patients be treated with a preoperative carbohydrate drink?
   (Paper III, interventional study)

4. What is the value of laparoscopic surgery within an ERAS-protocol?
   (Paper IV, prospective cohort study)



METHODS

The ERAS protocol and the ERAS database

In paper I, paper II, and paper IV, all patients were treated according to a standardised ERAS-protocol [24, 25] and perioperative data have been prospectively recorded in the ERAS-database [21]. At Ersta Hospital, all patients undergoing elective major colo-rectal surgery are consecutively included in the ERAS- protocol which is standard of care since 2002. Key components in this protocol (described in the ERAS-intervention section) are thoracic epidural analgesia (activated before onset of surgery and discontinued on postoperative day (POD) 2-3), preoperative oral carbohydrate treatment up until two hours prior to surgery and avoidance of preoperative oral bowel preparation and perioperative fluid overloading. Early oral diet (4 hours after surgery) and early mobilisation (2 hours out of bed on the day of surgery and then 6 hours daily) is also part of the protocol.

The perioperative process was carefully tracked and recorded by ERAS-trained nurses at the surgical wards. After completed hospital stay and 30 days after surgery, altogether 114 variables including 21 key ERAS adherence variables were entered in the database by a specifically trained nurse. In paper I, paper II and paper IV, all clinical data including extent of postoperative mobilisation, symptoms delaying discharge, length of hospital stay (LOS) and 30-day morbidity and mortality was prospectively captured in the ERAS database. In addition, daily dietary intake and fluid/energy balance were recorded for the analyses included in paper I and paper IV.

In paper I, paper II and paper IV, patients were considered fit for discharge using the following discharge criteria: postoperative pain adequately controlled on oral analgesics (visual analogue pain score less than 40 of 100), intravenous nutrition or fluids no longer needed, mobilisation out of bed ≥ 6h daily (or at preadmission level), return of bowel function (stool or repeated flatus) and no complications in need of treatment in the hospital. Complications were diagnosed following the Veterans Administration Total Parenteral Nutrition Trial definitions and classifications [173]. All patients were examined by a surgeon at Ersta Hospital two weeks after discharge and interviewed by a trained nurse on postoperative day (POD) 30 to register any late occurring complications.

Definition of Symptoms and Complications

Definitions of symptoms and complications were established, after several international meetings and discussions within the ERAS-study group. The definition of complications is a modified version of the original version defined by Buzby et al in 1988 [173]. All symptoms and complications are prospectively recorded in the ERAS-database.

The following definitions were used when calculating rate of symptoms and complications in paper I, paper II and paper IV.

Definition of symptoms

Symptoms that are not part of a complication listed below, and that clearly:

1. Caused a prolonged length of stay or
2. Caused an unplanned contact with doctor after discharge or
3. Caused a readmission or a reoperation.

Definition of complications

Cardiovasculary

1. Cardiac failure, cardiac index <2litres per min per m2, or clinical diagnosis, (treated by diuretics, inotropes or other vasoactive agents)
2. Acute myocardial infarction (electrocardiograph and enzyme diagnosis)
3. Cardiac arrhythmia (debut of arrythmia verified with electrocardiograph)
4. Cerebrovascular incident (neurological deficit lasting more than 7 days)
5. Deep venous thrombosis (Doppler ultrasound or venography)
6. Other cardiorespiratory event (causing treatment to be initiated)

Pulmonary

1. Respiratory failure (any mechanical ventilation)
2. Pulmonary oedema (clinical diagnosis +/- radiological diagnosis)
3. Pleural fluid (radiographic diagnosis)
8. Pulmonary embolism (digital angiography or spiral CT and clinical diagnosis)

Renal failure

1. Acute renal failure (need for haemofiltration)

Infective

1. Sepsis (pyrexia >38°C and septic focus or positive blood culture)
2. Postoperative peritonitis (clinical diagnosis)
3. Abdominal abscess (ultrasonography, CT-scan or operative diagnosis)
4. Necrotizing fasciitis
5. Wound infection (pus or cellulitis +/- positive wound swab culture)
6. Pneumonia (radiological diagnosis)
7. Chest infection (e.g. mediastinitis, empyema or positive sputum culture treated with antibiotics)
8. Urinary tract infection (positive urine culture)
9. Disseminated intravascular coagulation (DIC)
10. Other infectious complication (causing treatment to be initiated)

Surgical

1. Bowel perforation (ultrasonography, CT-scan or operative diagnosis)
2. Wound dehiscence (ultrasonography, CT-scan or operative diagnosis)
4. Postoperative bleeding (overt blood loss requiring >2 units transfusion with normal clotting profile)
5. Ileus: delayed oral intake / ileus (intravenous fluids >1week owing to postoperative ileus)
6. Anastomotic leak (clinical diagnosis +/- radiology)
7. Other surgical (causing treatment to be initiated)

Design, patients and settings

Each study was approved by the regional Institutional Ethics Committee and carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All studies were conducted at Ersta hospital, Stockholm, Sweden.

Paper I

Design: A single-centre prospective cohort study of 953 consecutive colo-rectal cancer patients at a colo-rectal surgical ERAS unit.

Objective: To study the impact of different adherence levels to the ERAS-protocol and the effect of various ERAS-elements on outcomes following major surgery.

Main outcome measures: The association between adherence to the ERAS-protocol and the incidence of postoperative symptoms, complications and length of stay following major colo-rectal cancer surgery, both between, as well as across the two time-periods was analysed.

Methodology: Due to unsatisfactory compliance, the ERAS- protocol was re-launched on 1 March 2005 to improve several aspects of the protocol itself and the adherence to the program. Preceding the re-launch, during autumn 2004, a site visit to the pioneering unit at Hvidovre, Hospital, Denmark, helped identify key areas of potential improvement. These improvements concerned a large number of details in the perioperative care protocol, as well as strategies to increase adherence (see appendix, page 77). All patients operated with a colon and/or rectal cancer resection during period 2002-2004 (1 January 2002-28 February 2005) and 2005-2007 (1 March 2005- 31 December 2007) were registered in the database and included in the study. During these two time-periods the surgical staff consisting of seven senior consultants, anaesthetists and nursing staff largely remained unchanged.

Patients: Altogether 464 consecutive patients in the first period (2002-2004) and 489 consecutive patients in the second period (2005-2007) were included in the study. Adherence to the ERAS-protocol was assessed among these 953 patients and analysed with regards to postoperative outcomes.

Data analysis: Results are presented as mean ± standard deviation (SD), median, odds ratio (OR) and 95% confidence interval (CI) when appropriate. Two-tailed t-test was used for crude group comparisons of continuous variables and multiple linear regressions for adjusted comparisons. Crude associations between categorical variables were analysed with chi-square tests or Fisher's exact test, as appropriate. Baseline characteristics were analysed to determine the univariate predictors of the different outcome variables: postoperative symptoms (POS), length of stay (LOS) and 30-day postoperative morbidity including infection rates. Multiple logistic regression was then used to assess the adjusted association between specific interventions and each outcome.

The adjustment variables were: age, sex, BMI (body mass index), ASA (American Society of Anesthesiologists physical status), surgical interventions and laparoscopic/open surgery. When calculating adherence to the twelve pre- and perioperative (day 0) ERAS interventions (table 3, highlighted in red), the cut off for adherence to the continuous variables was set at: Intravenous fluid (colon, perop. 2000ml + postop. 1000ml = 3000ml) (rectum, perop. 2500ml + postop. 1000ml = 3500ml), per oral fluid (>0 ml), intravenous kcal (<200 kcal) and per oral kcal (>0 kcal). When calculating impact on an outcome, pre- and perioperative interventions were added in the multiple regression model using stepwise modelling including all variables with a p-value < 0.15. A p-value of <0.05 was considered statistically significant. All data were analysed using STATA® Version 10.0.

Paper II

Design: A single-centre prospective cohort study of 120 patients undergoing colo-rectal surgery at a colo-rectal surgical ERAS unit.

Objective: To study pre- and postoperative glucose control in patients undergoing colorectal surgery and whether preoperative HbA1c could predict hyperglycaemia and/or adverse outcome.

Main outcome measures: The association between preoperative glucose control and postoperative glucose control and the incidence of postoperative complications after colo-rectal surgery was analysed.

Patients: Written informed consent was obtained from all subjects. During the period November 2005 – March 2007, 137 patients between 31-90 years of age scheduled for elective colorectal resection were included in the study. Patients with a known history of diabetes and patients unable to comply with the study protocol (due to psychiatric disease, dementia and/or limited knowledge of the Swedish language) were not eligible. Four patients did not consent to participate in the study. Seventeen patients were excluded from the data analysis (11 patients underwent smaller surgical procedures than initially planned and in 6 patients complete data was lacking), resulting in a total number of 120 patients.

Methodology: Venous blood samples were obtained from an antecubital vein. HbA1c was measured on the day before surgery and on POD 30. Blood haemoglobin, plasma electrolytes and c-reactive protein (CRP) were measured daily on POD 1-3. Capillary plasma glucose concentrations were measured five times daily (at 0600, 1000, 1400, 1800, 2200 h), starting immediately after surgery, for five days (OneTouch ® Ultra, Lifescan, USA). Samples at 0600 h were taken after an overnight fast, while samples at 1000 h, 1400 h, and 1800 h were taken after breakfast, lunch and dinner, respectively. Daily average glucose values were also calculated and analyzed within and between groups. The clinical service was blinded to these glucose measurements. Clinically indicated glucose determinations outside the study protocol, and any resulting insulin treatment, were decided upon at the discretion of the clinical service and did not follow a standardised protocol. HbA1c levels were analyzed using high pressure liquid chromatography (HPLC). Swedish standard for HbA1c, MonoS (reference range 3.4-5.0%) was recalculated to international standard, DCCT by formula (DCCT = 0,923XMono S + 1,345) [174] (reference range 4.5-6.0 %).

Data analysis: Results are presented as mean ± standard deviation (SD), median and range, odds ratio (OR) and 95% confidence interval (CI) when appropriate. Two-tailed t-test was used for crude group comparisons of continuous variables and multiple linear regression for

adjusted comparisons. Between-group comparisons of glucose concentrations were performed by repeated measures ANOVA. Crude associations between categorical variables were analysed with chi-square tests or Fisher's exact test, as appropriate. Baseline characteristics were analysed to determine the univariate predictors of 30-day postoperative morbidity including infection rates. Multiple logistic regression was then used to assess the adjusted association between outcome and HbA1c.
Patients with preoperative levels of HbA1c within recalculated normal limits (≤ 6.0) were compared to those with HbA1c levels above this range (> 6.0). The adjustment variables were: age, sex, BMI, ASA, peroperative bleeding and duration of surgery. A p-value of <0.05 was considered statistically significant. All data were analysed using STATA® Version 10.0.

Paper III

Design: A non-randomized interventional study of 25 diabetes type 2 patients and 10 healthy control subjects.

Objective: To study if patients with Type 2 diabetes can be treated with a preoperative carbohydrate drink without effects on preoperative glycaemia and gastric emptying.

Main outcome measures: The association between treatment with a preoperative carbohydrate drink and glucose control and gastric emptying was analysed.

Patients: Written informed consent was obtained from every participant before the study. Twenty-five patients with Type 2 diabetes were recruited from the outpatient clinic. Inclusion criteria were glycated haemoglobin (HbA1c) < 7% (Reference range 3.4-5%, MonoS, Swedish standard) and BMI <35kg/m² while subjects with clinical signs of autonomic neuropathy and / or peripheral sensory / motor neuropathy were excluded. Eleven patients were treated with insulin, (bedtime intermediate duration of action insulin (NPH) (n=5), biphasic human insulin 30 and bedtime NPH insulin (n=2), biphasic insulin lispro 25 and bedtime NPH insulin (n=2), biphasic insulin aspart 30 (n=2)). Out of these 11 patients, six were concurrently on oral anti-diabetic drugs (OAD) (metformin). Ten of the patients were on OAD only, (metformin (n=5), glibenklamid (n=3), repaglinid (n=1), glimeperid (n=1)) and four had diet treatment only. None of the included patients showed any symptoms or signs of upper gastrointestinal disease. Ten healthy age- and weight-matched subjects served as controls.

Methodology: All patients were fasting from 2200 h the night before the investigation. Alcohol, heavy meals, paracetamol intake or strong physical activitiy were prohibited the day before study. Patients arrived to the clinic at 0730 h. Body composition was determined with Bioimpedance analyzer, Tanita®, Model TBF-300, Tokyo, Japan, followed by bed-rest until taking their regular morning medication at 0800h. All patients were then given a 400 ml carbohydrate-rich beverage (12.5 g 100 ml^{-1} carbohydrates, 12% monosaccharides, 12% disaccharides, 76% polysaccharides, 285 mOsm kg^{-1}, Nutricia Preop®, Numico, Zoetermeer, The Netherlands). Paracetamol, 1.5 g (Alvedon Brus®, Astra Zeneca, Mölndal, Sweden) was dissolved in the beverage, for determination of gastric emptying. Patients stayed in a reclined position throughout the study period.

After intake of the carbohydrate drink venous blood samples were obtained from an indwelling catheter in the antecubital vein. Blood glucose concentrations were measured at –5 min, at t=0 (immediately after intake) and then every 30 min during 240 min post-administration of the carbohydrate-rich drink and analysed by a whole-blood glucose meter (Hemocue®, Ängelholm, Sweden). Plasma paracetamol concentration was determined before administration and at 0, 15, 30, 60, 90, 120 and 180 min after intake of fluids.

The gastric emptying rate was assessed using intestinal paracetamol absorption as a marker. Plasma samples were assayed for paracetamol by fluorescence-immunoassay (IMX, Abbott Laboratories, Chicago, IL, USA). The coefficient of variation was ±5%. Gastric emptying was evaluated as lag-time until 2% of the contents were emptied and as half-emptying time (T50) when 50% of the contents were emptied.

The paracetamol absorption test: Gastric emptying was measured using the paracetamol absorption technique as an indirect assessment of gastric emptying adapted from the description by Maddern et al [175]. Paracetamol administrated orally is poorly absorbed by the stomach but rapidly absorbed from the small intestine. The appearance rate of paracetamol in the blood reflects the gastric emptying rate [176-178]. Estimation of the gastric emptying profile is conducted by conversion of plasma paracetamol concentration values to cumulated values. This estimation reflects total absorption of the drug during 180 min after ingestion of the beverage. The inverted absorption values reflect the absorption of the drug in relation to total paracetamol absorption. Gastric emptying measured with paracetamol shows correlation to scintigraphic gastric half-emptying time and plasma concentrations of paracetamol at 30 min and 60 min ($r = -0.65$) as well as peak plasma concentrations of the compound ($r = -0.77$) [179].

Data analysis: Results are presented as mean ± standard error of the mean (SEM) or median and range for groups. One-way ANOVA and two-way ANOVA for repeated measurements were used when appropriate. A p-value of <0.05 was considered statistically significant.

Paper IV

Design: A single-centre prospective cohort study of 96 consecutive colo-rectal tumour patients undergoing high anterior resection (HAR) at a colo-rectal surgical ERAS unit.

Objective: To study the association between surgical technical approach (laparoscopic or open surgery) in an ERAS environment, compliance to the ERAS-protocol and outcome from surgery.

Main outcome measures: The association between adherence to the ERAS-protocol and surgical approach and the incidence of postoperative symptoms, complications and LOS following laparoscopic and open HAR was analysed.

Patients: All consecutive patients with a tumour in the sigmoid colon or upper rectum operated with HAR, defined as an anastomosis between 10-15 cm from the anal verge, in the period 1 January 2007- 31 December 2009 were registered in the database and included in the study.

This resulted in ninety-six consecutive patients undergoing laparoscopic-assisted (n=49) or open (n=47) HAR.

Methodology: In the unit, laparoscopic colorectal surgery was practised to a larger extent from the end of year 2006. One experienced colo-rectal laparoscopic surgeon has since then trained four experienced open surgeons with previous laparoscopic training, but no experience of the colo-rectal laparoscopic technique. Five surgeons performed open surgery only. There was no systematic selection behind the decision of which patients were planned for open or laparoscopic surgery, respectively. Rather, environmental circumstances such as surgeon on duty at the first visit in the outpatient clinic and available surgeons at the day of operation decided the surgical approach selected. However, known T4 tumours were not chosen for laparoscopic resection. All laparoscopic resections were defined as laparoscopic-assisted (colonic mobilization and division of the colonic vessels performed laparoscopically, extracorporeal division of the large bowel through a small pfannenstiel incision and intracorporeal anostomosis with circular stapler). Open resection was performed through a midline incision and circular stapler was used for all anastomoses. The resections were performed only on Tuesdays or Thursdays.

Data analysis: Laparoscopic and open HAR were compared, while taking compliance to the ERAS-protocol into account. Outcomes included postoperative 30-day morbidity, symptoms delaying discharge and LOS. All data for patients converted from laparoscopic to open surgery (including the diagnostic laparoscopies) were analyzed on intention-to-treat basis if not indicated otherwise. Results are presented as mean ± SD, median, range, OR and 95% CI when appropriate. Two-tailed t-test was used for crude group comparisons of continuous variables and multiple linear regressions for adjusted comparisons. Crude associations between categorical variables were analysed with chi-square tests or Fisher's exact test, as appropriate. Baseline characteristics were analysed to determine the univariate predictors of the different outcome variables: postoperative symptoms, LOS and 30-day postoperative morbidity including infection rates. Multiple logistic regression was then used to assess the adjusted association between specific interventions and each outcome.
The adjustment variables were: age, sex, BMI, ASA, preoperative radiation-therapy, benign tumour and diabetes. A p-value of <0.05 was considered statistically significant. All data were analysed using STATA® Version 10.0.

Results

In total, 1211 patients and 10 healthy volunteers were included in the papers. Eighty patients in paper II and twenty-one of the patients in paper IV were also included in paper I. A total of 18 patients, one in paper III and 17 in paper II were subsequently excluded (see sub-analysis, paper II,). In paper III, one insulin-treated patient (female, 70 years of age, BMI 23) experienced mild hypoglycaemia at 150 min (B-glucose 2,7 mmol/L) resulting in termination of the experiment.

Paper I

Demographical and operative characteristics

Patients treated in 2002-2004 were at lower anaesthetic risk compared to patients operated upon in 2005-2007 (ASA 1, 21.6% vs. 14.5%, p=0.009, ASA 3, 14.6% vs. 19.7%, p=0.048). There were no other significant differences between the groups in baseline data (Table 1).

In the second period, there was a small increase in the proportion of patients operated upon laparoscopically (Table 2). Furthermore, a smaller proportion of both low anterior resection (LAR) and Hartmann's operations were performed in the second period compared to the first period, which in turn had a lower proportion of abdomino-perineal resections (APR) (p<0.05). Fewer patients underwent pelvic surgery in the second vs. first period (Table 2).

Table 1. Paper I: Demographical and operative characteristics

	02-04 (n=464)	05-07 (n=489)
Age, mean, SD	69.3 ± 11.9	69.0 ± 11.6
BMI, mean, SD	25.4 ± 4.3	25.2 ± 4.4
Gender (M/F)	231/233	237/252
ASA 1, %	21.6	14.5
ASA 2, %	63.1	64.4
ASA 3, %	14.6	19.7
ASA 4, %	0.7	1.4
Colorectal cancer (CRC), (n)	464(100)	489(100)
Dukes (CRC), C/D, (n)	192(41.4)	191(39.1)
Preoperative radiation, (n)	141 (30.4)	126 (25.8)
Complex-group, (n)	68(14.7)	65(13.3)

Values in parentheses are percentages unless indicated otherwise. ASA, American Society of Anaesthesiologists physical status. Complex-group, patients with additional intraoperative procedures (for example, Small bowel resection). (n)= number.

Table 2. Paper I: Operative data

	02-05 (n=464)	05-07 (n=489)
Right hemicolectomy	97(21)	137(28)
Sigmoid resection	31(7)	20(4)
Left hemicolectomy	23(5)	39(8)
Anterior resection (>10 cm from anus)	61(13)	77(16)
Anterior resection (<10 cm from anus)	128(28)	89(18)
Abdomino-perineal resection	49(11)	94(19)
Hartmanns operation	46(10)	26(5)
Other	29(6)	7(1)
Laparoscopic surgery, no†	6(1)	23(5)
Peroperative bleeding (ml)*	363±409	366±448

Values in parentheses are percentages unless indicated otherwise; *values are mean (s.d). †p=0.002. In total 221(47.6%) vs. 198(40.5%) underwent pelvic surgery in the (02-04) versus (05-07) groups respectively (p=0.026).

Adherence to the ERAS-protocol

Overall, the mean pre- and peri- (day 0) operative adherence to the twelve specific elements of the ERAS-protocol increased from 43.3% among patients undergoing colo-rectal surgery 2002-2004 to 70.6% in 2005-2007 (p<0.001). Adherence to most of the post-operative intervention parameters also improved significantly (Table 3).

Table 3. Paper I: Protocol compliance

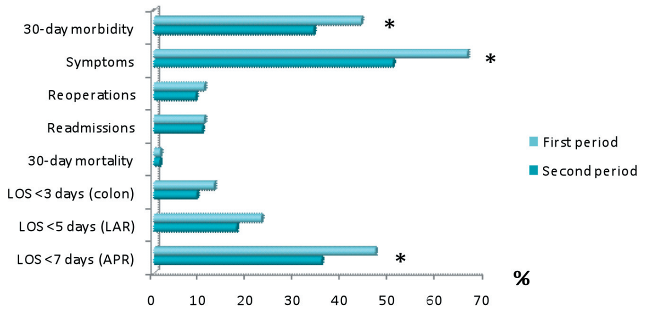
	02-04	05-07	p-value
Preoperative compliance			
Preadmission counselling, (n)	361/454(79.5)	465/487(95.5)	p<0.001†
Carbohydrate drink, (n)	200/398(50.3)	311/465(66.9)	p<0.001†
Without Bowel preparation, (n)	66/446(14.8)	322/481(66.9)	p<0.001†
Without premedication, (n)	100/463(21.6)	289/486(59.5)	p<0.001†
Active warming**, (n)	229/372(61.6)	428/439(97.5)	p<0.001†
EDA, (n)	446/464(96.1)	475/487(97.5)	p=0.221†
Perioperative compliance			
Intravenous fluid day 0 (ml)*	5220±1560	3820±1210	p<0.001‡
Per oral fluid day 0 (ml)*	550±560	790±570	p<0.001‡
Intravenous kcal day 0*	398±193	204±159	p<0.001‡
Per oral kcal day 0*	122±308	299±379	p<0.001‡
Out of bed day 0, (2hrs)(n)	166/406(40.9)	222/459(48.4)	p=0.027†
Oral nutrition supplements day 0, (n)	51/413(12.3)	271/476(56.9)	p<0.001†
Postoperative compliance			p#
Intravenous fluid day 1-3 (ml)*	2640±2970	2090±2640	p=0.016
EDA-removal , day*	3.8 ± 2.4	3.9 ± 2.5	p=0.314
Urinary-catheter removal, day*	4.7 ± 3.8	4.7 ± 3.6	p=0.488
Per oral fluid day 1-3(ml)*	4320±2330	5220±1990	p<0.001
Out of bed day 1, (6hrs) (n)	61/260(23.5)	111/404(27.5)	p=0.289
Oral nutrition supplements day 1, (n)	85/433(19.6)	276/485(56.9)	p<0.001
Solid food day 1, (n)	387/459(84.3)	438/484(90.5)	p=0.008
Without drip infusion day 1, (n)	150/457(32.8)	286/485(59.0)	p<0.001
Contact with nurse day 7, (n)	304/416(73.1)	466/486(95.9)	p<0.001

Values in parentheses are percentages unless indicated otherwise. The denominator represents values recorded in the database; *values are mean (s.d). †Pearson`s x^2 test, ‡Two-tailed *t* test, #Multiple linear and logistic regression. Adjusted for age, gender, ASA, BMI, type of operation and laparoscopic surgery. **By Bair Hugger® (Arizant Healthcare, Eden Prairie, Minnesota, USA). Highlighted in red = The twelve ERAS interventions used in calculations of overall mean adherence.

Outcome between periods

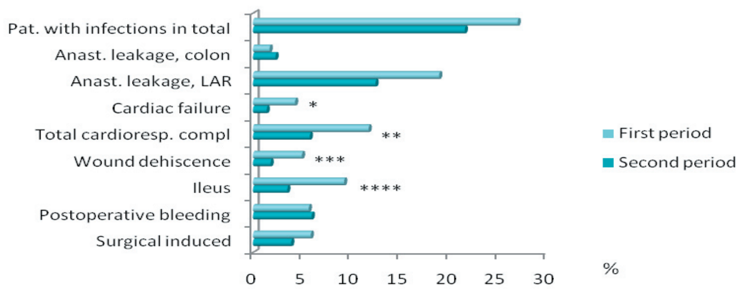
Following the overall increase in mean pre- and perioperative adherence to the ERAS-protocol between study periods, the number of patients suffering from at least one complication declined from 203 (43.8%) in 2002-2004 to 165 (33.7%) in 2005-2007 and the number of patients with symptoms delaying discharge (unspecified fever, pain, fatigue, obstipation, dizziness, diahorrea) also declined from 307 (66.2%) to 247 (50.5%) (Figures 3 and 4). Thus, a 27 % increase in overall adherence to the ERAS protocol was associated with a 27% reduction in relative risk of any 30-day postoperative morbidity (OR 0.73, 95% CI 0.55-0.98) and a 47% reduction in relative risk of symptoms delaying discharge (OR 0.53, 95% CI 0.40-0.70), adjusting for confounding. Although the median LOS went from 7 days to 6 days with higher adherence to the ERAS-protocol, this was not statistically significant (p=0.140). However, the proportion of patients with LOS within clinic target for APRs (<7 days) increased significantly from 35.4% to 46.8% (OR 2.34, 95% CI 1.01-5.38) between the first and second period (adjusted for confounding) (Figure 3). The difference in proportion of patients with LOS within clinic targets for colonic surgery (<3 days) 9.0% vs. 12.7% and LAR (<5 days) 17.4% vs. 22.7% was not significant. No significant difference was found in the proportion of reoperations (10.6 vs. 8.8%), readmissions (10.6 vs. 10.2%) or 30-day mortality (1.3% vs. 1.2%) between the first and second period, respectively.

Figure 3. *Paper I: Postoperative outcomes*



Multiple logistic regression. Adjusted for age, gender, ASA, BMI, type of operation and laparoscopic surgery.
LAR (low anterior resection). APR (abdomino-perineal resection). Colon (includes high anterior resection).
*Significant difference between periods.

Figure 4. *Paper I: Postoperative complications 2002-2004 vs. 2005-2007.*



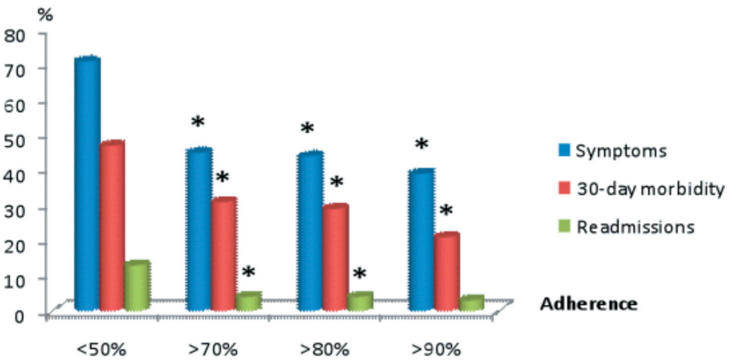
*OR (Odds Ratio) 0.34(95% CI 0.13-0.88), p=0.025. **OR 0.52 (95% CI 0.31-0.87), p=0.013. ***OR 0.31(95% CI 0.12-0.80), p=0.015. ****OR 0.40(95% CI 0.21-0.76), p=0.005. (Multiple logistic regression. Adjusted for age, gender, ASA, BMI, type of operation and laparoscopic surgery). LAR (Low anterior resection). Colon (includes High anterior resection)

Outcome across periods

The effect of the mean pre- and peri- (day 0) operative adherence to the twelve specific elements in the ERAS-protocol (table 3), regardless of time period, was analysed, comparing patients with an overall adherence >90% (n=76), > 80% (n=183) and >70% (n=284) to patients with a low overall adherence <50% (n=333). Across periods, the proportion of patients with symptoms delaying discharge and 30-day morbidity were significantly reduced with higher levels of ERAS adherence using multivariate logistic regression adjusting for age, gender, ASA, BMI, type of operation and laparoscopic surgery (Figure 5). The ORs for postoperative symptoms was 0.35 (95% CI 0.25-0.51), 0.34 (95% CI 0.22-0.52) and 0.31(95% CI 0.17-0.55) with >70%, >80% and >90% adherence, respectively. The OR for 30-day-morbidity was 0.62 (95% CI 0.43-0.89), 0.57 (95% CI 0.37-0.89) and 0.33 (95% CI 0.16-0.66) with >70%, >80% and >90% adherence, respectively, and, the OR for readmissions was 0.36 (95% CI 0.17-0.76), OR 0.38 (95% CI 0.15-0.95), OR 0.16 (95% CI 0.02-1.19) with >70%, >80% and >90% adherence, respectively vs. <50% adherence.

In univariate analysis, mean LOS was significantly shorter in patients with high ERAS protocol adherence >70% (7.4 days, p<0.001), > 80% (7.0 days, p<0.001), >90% (6.0 days, p<0.001) compared to patients with low adherence <50% (9.4 days). Multiple regression revealed a significant difference in LOS among patients with adherence >90% (p<0.025), vs. <50% adherence, while the difference among patients with adherence >70% (p=0.066) and >80% (p=0.081) was borderline significant.

Figure 5. *Paper I: Association between adherence to the ERAS-protocol and postoperative outcomes.*



The proportion with adverse postoperative outcomes (symptoms delaying discharge, 30-day morbidity and readmissions) was reduced with increasing adherence to the ERAS-protocol (>70%, >80%, >90%), compared to low ERAS adherence (<50%). Multiple logistic regression, adjusted for age, gender, ASA, BMI, type of operation and laparoscopic surgery. *Significant difference (high adherence vs. <50% adherence, p<0.05).

The impact of single ERAS elements

In paper II and paper IV the number of patients was too small for conclusions regarding the impact of single ERAS-interventions. In paper I however, in both time-periods altogether, the effect of each single intervention within the protocol were analyzed with regards to the impact on postoperative symptoms, complications and LOS.

Multiple regression analysis adjusted for basic characteristics and other protocol interventions revealed that peri-operative intravenous fluid management (i.v. day 0=day of surgery, table 3) and pre-operative carbohydrate drink were major single and independent predictors of postoperative outcomes. The amount of fluids given the day of surgery was concurrently associated with preoperative oral bowel preparation. Patients receiving bowel preparation had a mean amount of 1000 ml additional fluids given during the day of surgery, OR 1.33 (95% CI 1.14-1.54) while patients given pre-operative carbohydrates received a mean 450 ml less fluids on average, OR 0.75 (95% CI 0.66-0.87). For each additional litre of fluids given during the day of operation, the risk of postoperative symptoms delaying recovery increased by 16%, OR 1.16 (95% CI 1.02-1.31) and the probability of postoperative complications increased by 32%, OR 1.32 (95% CI 1.17-1.50).

In particular fluid overload increased the risk of cardio respiratory complications, OR 1.20 (95% CI 1.10-1.31). If patients were treated with preoperative carbohydrates, the risk of postoperative symptoms was reduced by 44%, OR 0.56 (95% CI 0.40-0.77). In particular pre-operative carbohydrates significantly reduced the risk of postoperative nausea and vomiting (PONV), pain, diarrhoea and dizziness. Also, the risk of postoperative wound dehiscence was reduced by the preoperative carbohydrate drink, OR 0.16 (95% CI 0.05-0.50). Most of the other pre- and perioperative ERAS interventions had a positive effect on the different outcome parameters, but the majority did not retain statistical significance in multivariate analyses, adjusting for confounding.

Paper II

Demographical and operative characteristics

In paper II, patients were stratified by whether preoperative levels of HbA1c were above normal (> 6.0) or within normal range (4.5-6.0) (6.4 ± 0.3 vs. 5.6 ± 0.3 mM). Thirty-one out of the 120 patients had an HbA1c > 6.0. In this group patients were older ($p = 0.013$) and had higher BMI ($p = 0.015$) as compared to those with HbA1c levels ≤ 6.0. There were no other significant differences between the groups in baseline data (Table 4).
Surgical procedures were similar in those with HbA1c > 6.0 as compared to those with HbA1c ≤ 6.0 (Table 5). In total 16(52%) vs. 44(49%) underwent pelvic surgery in the groups respectively.

Table 4. Paper II: Demographical and operative characteristics.

	Hba1c > 6.0 (n=31)	Hba1c ≤ 6.0 (n=89)
Age, mean (range)	70 (46-84)	64 (31-90)
BMI, mean, SD	27.7 ± 5.2	25.3 ± 4.2
Gender (M/F)	16/15	47/42
ASA 1 no, (%)	2 (6)	15 (17)
ASA 2 no, (%)	23 (74)	61 (68)
ASA 3 no, (%)	4 (13)	13 (15)
ASA 4 no, (%)	2 (6)	0 (0)
Colorectal cancer (CRC), no, (%)	23(74)	67(75)
(CRC) Dukes C/D, no, (%)	9(29)	29(32)
IBD, no, (%)	5(16)	13(15)
Diverticulosis, no, (%)	2 (6)	2 (2)
Anal cancer, no, (%)	0 (0)	2 (2)
Other Benign, no, (%)	1 (3)	5 (6)
Duration of surgery, mean minutes, SD	230 ± 149	189 ± 97
Peroperative bleeding, mean ml, SD	522 ± 119	350 ± 45

IBD = Inflammatory bowel disease

Table 5. Paper II: Operative data

	Hba1c > 6.0 (n=31)	Hba1c ≤ 6.0 (n=89)
Anterior resection	10 (32)	26 (29)
Abdomino-perineal resection	4 (13)	15 (17)
Total colectomy	2 (6)	5 (6)
Right hemicolectomy	6 (19)	23 (26)
Left hemicolectomy	2 (6)	8 (9)
Other resection	7 (23)	12 (13)

Surgical procedures, n, (%)

Adherence to the ERAS-protocol

In paper II, altogether 120 patients completed the study protocol. Sixty patients (50%) had achieved functional recovery on POD 2 (no i.v infusions, meals of solid food, passage of gas and stools and mobilization at least 6 hours out of bed). The epidural and urinary catheters were kept for a median of four postoperative days. Patients with HbA1C > 6.0 required postoperative intravenous fluids as a complement to oral intake for a longer period than patients with HbA1c ≤ 6.0 ($p = 0.013$) (Table 6). However, the length of stay (LOS) and the number of days required until patients fulfilled protocol criteria's for discharge was not significantly different between the two groups (Table 6). There was no statistically significant difference in postoperative mean caloric intake during the first five postoperative days between the groups (1357 ± 202 vs. 1339 ± 47 kcal/day, HbA1C > 6.0 and ≤ 6.0 respectively). However, significantly more patients with a preoperative HbA1c > 6.0 were treated with insulin during the first five postoperative days (24 (77%) vs. 46(52%), $p = 0.012$, total daily insulin dose in median 23 IE vs. 12 IE Actrapid® (Novo Nordisk, Bagsvaerd, Denmark) / patient, $p = 0.019$).

Table 6. Paper II**:** Recovery and inflammatory response among patients after colorectal surgery.

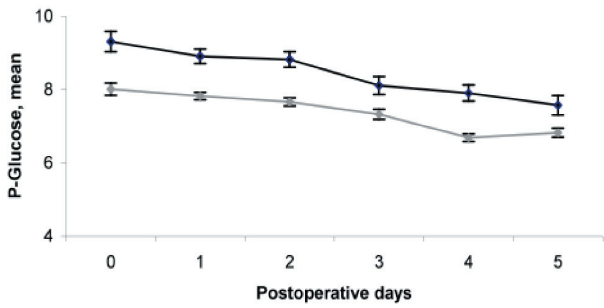
	HbA1c >6 %	HbA1c ≤ 6 %	Crude p-value	Adjusted p-value
CRP, postop. (d1-3)	137± 65	101± 52	0.003	0.008
Oral food only, no drip, first day.	5.9± 4.3	3.3 ±6.2	0.012	0.013
First bowel movement, day.	3.4 ± 3.1	2.9 ± 1.9	0.261	0.995
EDA removal, day.	4.1 ± 1.9	3.9 ± 2.4	0.606	0.770
Fulfilled discharge criteria.	6.6 ± 4.8	5.3 ± 4.3	0.206	0.244
LOS (length of stay) day.	8.5 ± 5.4	7.3 ± 5.6	0.337	0.482

Adjusted for age, sex, BMI, ASA, preoperative bleeding and duration of surgery. Mean, SD

Postoperative glucose control

Means of the five daily measurements of capillary plasma glucose concentrations peaked the day of surgery and were higher in patients with HbA1C > 6.0 (9.3 ± 1.5 mM) than HbA1C ≤ 6.0 (8.0 ± 1.5 mM) ($p < 0.001$). Mean daily glucose concentrations declined over time in both groups but remained higher in patients with HbA1C > 6.0 (7.6 ± 1.5 vs. 6.8 ± 1.1 mM at day 5, $p < 0.001$, Figure 6). Four weeks after surgery, HbA1c was unaltered compared to preoperative HbA1c in both groups (6.3 ± 0.5 and 5.7 ± 0.3).

Figure 6. *Paper II: Means of five daily capillary plasma glucose concentrations in patients following colorectal resection (mM/l)*



Black line = HbA1c > 6 (n= 31); Gray line = Hba1c ≤ 6 (n= 89) Error bars = Standard error of the mean (SEM). Glucose concentrations were elevated among patients with HbA1c > 6 vs. ≤ 6 throughout the study (0-5 days) and the difference between groups remained constant over time ($p<0.001$).

Glucose control and outcomes from surgery

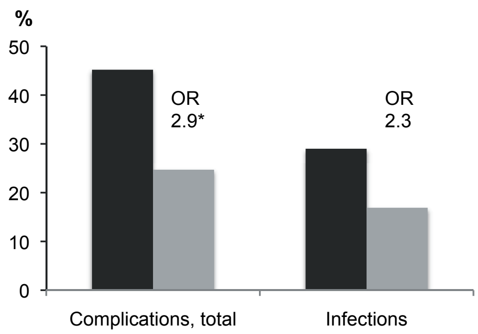
The mean CRP response during POD 1-3 was higher among patients with HbA1C > 6.0 (p = 0.008) (Table 6). Of the 120 patients studied, 36 patients (30%) had at least one postoperative complication, and of these, 24 (20%) had at least one postoperative infection during the 30 days follow-up (Table 7). Postoperative complications were more common in patients with HbA1c > 6.0 than in patients with HbA1c ≤ 6.0 (14 (45%) vs. 22 (25%), OR 2.9 (95% CI 1.1-7.9). The apparent difference in patients with infections between the two groups (9 (29%) vs. 15 (17%), OR 2.3 (95% CI 0.8-5.2) was not statistically significant (Figure 7). 1/31 vs. 3/89 in both groups, respectively, were reoperated, and 3/31 vs. 6/89 were readmitted to the hospital. Two patients had anastomotic dehiscence, both in the HbA1c ≤ 6.0 group. There was no 30-day mortality.

Table 7. Paper II: Complications in total among patients after colorectal surgery.

	Hba1c ≤ 6.0 (n=89)	Hba1c > 6.0 (n=31)
Respiratory failure	1	0
Plural fluid	0	1
Cardiac failure	1	0
Cardiac arrhythmia.	2	1
Postop. bleed	4	1
Postop. Ileus	1	3
Anastomotic leak	2	0
Stoma necrosis	0	1
Wound infection	7	2
Pneumonia	3	3
Sepsis	1	0
Urinary infection	3	3
Other infection	1	1
Total, no. (%)	26 (29)	16 (52)

Six patients had more than one complication (two in group HbA1c > 6.0, four in group ≤ 6.0).

Figure 7. *Paper II: 30-day morbidity (%).*



Black bars = patients with preoperative HbA1c >6.0 (n = 31). Gray bars = Patients with Hba1c ≤ 6.0 (n= 89).
*Statistically significant. OR was adjusted for age, sex, BMI, ASA, peroperative bleeding and duration of surgery.

Subanalysis

Of the 17 patients excluded from analysis, 11 had minor surgery without bowel resection and of them one patient also lacked data on preoperative HbA1c. Furthermore, HbA1c values were lacking in 6 patients revealing 10 patients for analysis. Of them, four patients had a preoperative HbA1c above 6.0 per cent and 6 patients had a HbA1c within the normal range. The four patients with high preoperative level of HbA1c were older, had a higher BMI and were at higher anesthetic risk compared to the 6 patients with HbA1c within normal range. Means of three daily measurements of capillary plasma glucose concentrations peaked the day of surgery in patients with HbA1C > 6.0 (8.8 ± 1.5 mM) and ≤ 6.0 (8.0 ± 1.9 mM) and declined over time in both groups, 7.9 ± 0.8mM and 6.6 ± 1.6 mM at day 3. There was no significant difference in 30-day morbidity.

Paper III

Demographical characteristics

Demographical characteristics are shown in table 8.

Table 8. Paper III: Demographical characteristics.

	Diet/OAD- treated subjects (n=14)	Insulin treated subjects (n=11)	Healthy subjects (n=10)
Age, mean (range)	58 (45-73)	63 (50-70)	59 (45-71)
Diabetes duration in years, mean (range)	6.6 (1-14) a	11.6 (6-31)	0
Gender (M/F)	(12/2)	(5/6)	(6/4)
HbA1c %	5.6 ± 0.1 ab	6.8 ± 0.2 c	4.5 ± 0.1
BMI	27.5 ± 0.9 b	29.6 ± 1.0 c	24.6 ± 0.9
Fat mass (%) (Bio-imped.)	28.2 ± 1.8 a	36.0 ± 2.1 c	26.5 ± 2.4
Total insulin dose (U/24h)		54 ± 14	

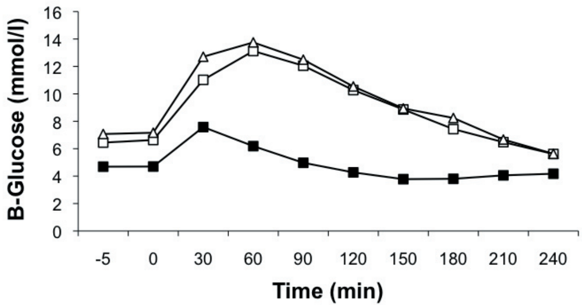
OAD=Oral anti-diabetic drugs. Glycated haemoglobin (HbA1c) (Ref.range 3,4-5%)
MonoS, Swedish standard. Mean ± SEM
P<0.05, a = OAD vs insulin treated
b= OAD vs healthy
c= insulin treated vs healthy

Carbohydrate drink and glucose control

In paper III, before ingesting the carbohydrate drink, the fasting glucose concentrations were 6.7 ± 0.2 and 4.7 ± 0.1 mM in diabetic patients and healthy subjects, respectively (p< 0.01) (Figure 8).
In patients with diabetes, peak glucose concentrations (13.4 ± 0.5 mM) occurred 60 min after intake of the carbohydrate drink whereas corresponding values, 7.6 ± 0.5 mM were achieved at 30 min in healthy subjects (p<0.01). Glucose concentrations returned to baseline after 180 min in patients with diabetes and after 120 min in healthy subjects. Peak blood glucose concentrations and glucose at 180 min did not differ between OAD/diet-treated and insulin treated patients (Figure 8).

It was not possible to verify any statistically significant association between gastric half-emptying time and Hba1c %, fasting glucose values, peak glucose concentration or gender.

Figure 8. *Paper III: Blood glucose concentrations after carbohydrate drink.*

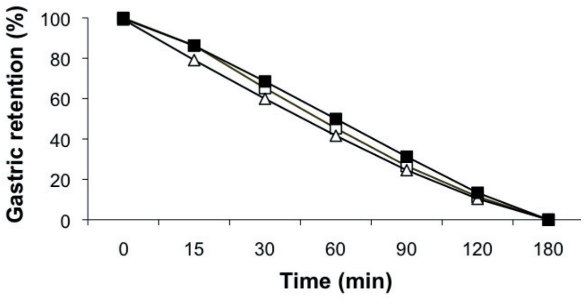


Blood glucose concentrations after intake of a 400ml carbohydrate rich drink. Peak values occurred later in patients with diabetes compared to healthy controls and returned to baseline after 180 minutes. White triangles = insulin treated; white squares OAD/diet treated; black squares = healthy subjects

Gastric emptying

Appearance of paracetamol reflecting emptying of fluids followed a close to linear pattern in both diabetic patients and healthy subjects (Figure 9). Gastric half-emptying time (T50) occurred at 49.8 ± 2.2 min in patients with diabetes and at 58.6 ± 3.7 min in healthy subjects ($p<0.05$). At 120 min, 10.9 ± 0.7 % and 13.3 ± 1.2 % of paracetamol given, remained in the stomach in diabetic patients and healthy subjects, respectively. Overall, gastric emptying was slightly faster in diabetic patients than in healthy subjects ($p<0.05$).
At 180 min 100% of the paracetamol was absorbed in all subjects. T50 and retention after 120 min did not differ between OAD/diet-treated and insulin-treated patients. The amount of paracetamol remaining in the stomach after 120 min equalled approximately 40 ml of the carbohydrate drink given to all groups. It was not possible to verify any statistically significant association between gastric half-emptying time and Hba1c %, fasting glucose values, peak glucose concentration or gender.

Figure 9. *Paper III: Gastric retention.*



Gastric retention (%) after intake of 1.5g paracetamol dissolved in a 400ml carbohydrate drink. Overall slightly increased gastric emptying rate in diabetic patients vs. healthy subjects ($p<0.05$). “white triangles = insulin treated; white squares = OAD/diet treated; black squares = healthy subjects”

Paper IV

Demographical and operative characteristics

In paper IV, ninety-six consecutive patients undergoing laparoscopic-assisted (n=49) or open (n=47) HAR were included in the study. In the laparoscopic group, the experienced colo-rectal laparoscopic surgeon performed 24 operations and supervised another 14 procedures. In 11 cases, after gaining sufficient experience in the technique, the other surgeons performed the operation. Eleven patients (22%) were converted to open surgery. Out of them six (12%) were converted immediately after a diagnostic laparoscopy while five (10%) were converted due to failure to complete the resection laparoscopically. No significant differences in baseline characteristics were found (Table 9).

Table 9. Paper IV: Demographical characteristics

	Lap (n=49)	Open (n=47)
Age, mean, SD	69.6 ± 9.7	65.8 ± 11.1
BMI, mean, SD	26.1 ± 4.3	25.5 ± 3.9
Gender (M/F)	22/27	26/21
ASA 1, %	6.1	14.9
ASA 2, %	77.6	70.2
ASA 3, %	16.3	14.9
ASA 4, %	0	0
Colorectal cancer (CRC), (n)	42(85.7)	44(93.6)
Tumor hight, cm from anal verge, mean, SD	23.3 ± 6.2	23.7 ± 7.4
Previous abdominal surgery, (n)	13(26.5)	11(23.4)
Preoperative radiation, (n)	0(0)	2(4.3)
Diabetes, (n)	3(6.1)	1(2.1)

Values in parentheses are percentages unless indicated otherwise.

Adherence to the ERAS-protocol

The specific items of the ERAS protocol classified as pre-, per- (day 0) and postoperative compliance are listed in Table 10. Overall preoperative compliance (Table 10) to the ERAS-protocol was 82.7% in the laparoscopic group compared to 86.8% among patients undergoing open surgery (p=0.155). There were no significant differences in compliance to the preoperative intervention parameters although there was a trend to a lower compliance with regard to CHO treatment 51.0% vs. 63.8% (p=0.205) and avoidance of preoperative bowel preparation 53.1% vs. 72.3% (p=0.051) in patients undergoing laparoscopic vs. open resection. The administered amount of per-operative i.v. fluids did not differ between groups (Table 10), and was similar even after excluding to open surgery converted patients. However, a larger proportion of the patients operated with laparoscopic resection managed to drink oral fluids on the day of surgery (87.8% vs. open 68.1%, p= 0.020) and did not require intravenous infusions on the first day after surgery (61.2% vs. 38.3%, p=0.010).

Table 10. Paper IV: Protocol compliance

	Lap (49)	Open (47)	P
Preoperative compliance			
Preadmission counselling, (n)	48/49(98.0)	46/47(97.9)	p=0.976†
Carbohydrate drink, (n)	25/49(51.0)	30/47(63.8)	p=0.205†
Without bowel preparation, (n)	26/49(53.1)	34/47(72.3)	p=0.051†
Without premedication, (n)	48/49(98.0)	42/46(91.3)	p=0.147†
Active warming#, (n)	49/49(100)	47/47(100)	NS
EDA, (n)	47/49(95.9)	45/47(95.7)	p=0.966†
Peroperative compliance			
Intravenous fluid day 0 (ml)*	3542±989	3533±617	p=0.959‡
Per oral fluid day 0 (ml)*	795±520	861±602	p=0.575‡
Intravenous kcal day 0*	170±57	182±53	p=0.276‡
Per oral kcal day 0*	432±353	453±461	p=0.800‡
Out of bed day 0, (2hrs) (n)	18/49(36.7)	22/47(46.8)	p=0.317†
Oral nutrition supplements day 0, (n)	31/49(63.3)	33/47(70.2)	p=0.470†
Oral fluid day 0, (n)	43/49(87.8)	32/47(68.1)	p=0.020†
Postoperative compliance			**p#**
Intravenous fluid day 1-3 (ml)*	1566±2345	1544±1665	p=0.855
EDA-removal , day*	2.7 ± 1.4	3.0 ± 1.4	p=0.302
Urinary-catheter removal, day*	3.2 ± 1.4	3.5 ± 1.7	p=0.370
Per oral fluid day 1-3(ml)*	5099±2224	5356±1920	p=0.916
Out of bed day 1, (6hrs) (n)	46/49(93.9)	39/47(83.0)	p=0.050
Oral nutrition supplements day 1, (n)	41/49(83.7)	33/47(70.2)	p=0.108
Solid food day 1, (n)	41/49(83.7)	36/47(76.6)	p=0.600
Without drip infusion day 1, (n)	30/49(61.2)	18/47(38.3)	p=0.010
Contact with nurse day 7, (n)	47/49(95.9)	45/47(95.9)	p=0.865

Values in parentheses are percentages unless indicated otherwise. The denominator represents values recorded in the database; *values are mean (s.d). †Pearson`s x^2 test, ‡Two-tailed *t* test, #Multiple linear and logistic regression. Adjusted for age, gender, ASA, BMI, preoperative radiation, benign tumour and diabetes. #By Bair Hugger® (Arizant Healthcare, Eden Prairie, Minnesota, USA). Adherence to the six preoperative ERAS interventions used when calculating overall compliance (highlighted in red).

Operative data and pathology

The duration of surgery was longer among patients operated with laparoscopic compared to open resection (Table 11). There was no difference in per-operative bleeding between the groups (Table 11). However, when the diagnostic laparoscopies converted to open surgery were excluded the intra-operative bleeding was less during laparoscopic compared to open resection (128 ± 292 ml vs. 250 ± 156 ml, p=0.015). There were six and eight rectal cancers in the laparoscopic and open group, respectively. Significantly fewer lymph nodes were found, median 15 vs. 20 (p=0.002) and a larger proportion of patients with lymph nodes less than 12 in the specimen was detected (31.0 % vs. 11.4%) in the laparoscopic versus the open group. Even though not statistically significant, there was a trend towards more advanced tumors in the open group (Table 11).

Table 11. Paper IV: Operative data and pathology

	Lap (n=49)	Open (n=47)	P
Duration of surgery, mean, SD	209 ± 53	175 ± 48	0.001*
Peroperative bleeding, ml, mean, SD	166 ± 301	250 ± 156	0.093*
Anasthomotic level, cm, mean, SD	12.8 ± 1.7	13.2 ± 1.9	0.296*
T-stadium, 0, no	7	3	0.318‡
T-stadium, 1, no	6	2	0.269‡
T-stadium, 2, no	3	2	NS
T-stadium, 3, no	32	35	0.328†
T-stadium, 4, no	1	5	0.108‡
Lymph nodes, CRC, no, median	15	20	0.002*
Lymph nodes, CRC, <12, no	13/42(31.0)	5/44(11.4)	0.034‡
Metastatic lymphnodes, patients, no (%)	9/42(21.4)	18/44(40.1)	0.052†
R-0 recection, CRC, no, (%)	42/42(100)	44/44(100)	NS

Values in parentheses are percentages unless indicated otherwise. CRC, Colorectal cancer. T-stadium, Tumour stadium. *Two-tailed *t* test, †Pearson`s x^2 test, ‡Fisher´s exact test.

Surgical outcomes

No 30-day mortality occurred. There were no significant differences in postoperative complications 10.2% vs.14.9%, OR=0.69 (95% CI 0.16-3.02) (Table 12) or symptoms delaying discharge (unspecified fever, postoperative nausea and vomiting, urinary retention and diarrhoea) 22.4% vs. 27.7%, OR=0.63 (95% CI 0.22-1.79) in patients operated with laparoscopic and open surgery, respectively (Figure 10). Furthermore, no significant differences were seen in reoperations 2.0% vs. 4.3%, OR=0.50 (95% CI 0.01-17.01) and readmissions 2.0% vs. 10.6%, (OR=0.14 (95% CI 0.008-2.29) between groups (Figure 10).

The inflammatory response on POD 1, as reflected by C-reactive protein (CRP) was 60.7±28.0 vs. 68.8±29.4 (p=0.250) in the laparoscopic and open group, respectively. The time until first day of flatus 1.8±1.3 vs. 1.9±1.4 days (p=0.549) and first day of bowel movement POD 2.4±1.7 vs. 2.2±1.7 (p=0.677) did not differ between patients operated with laparoscopic vs. open resection, respectively. However, the first day of pain control (no epidural and no continuous need for morphine analgesics) occurred earlier in the laparoscopic group compared to the open group, POD 2.7±1.4 vs. 3.4±1.5 (p=0.031). The median LOS (range) was 4 (3-16) days in the laparoscopic group and 5 (2-12), p=0.492 in the open group. The proportion of patients with LOS within the target ≤3 days was significantly larger in those operated laparoscopically, 26.5% vs. 10.6%, OR=0.29 (95% CI 0.09-0.96) (Figure 10).

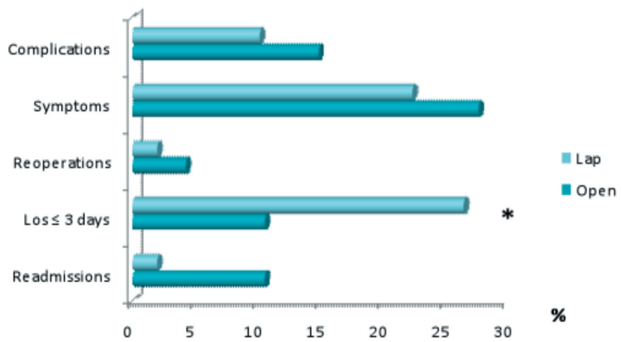
A sub analysis of the laparoscopic group, excluding the diagnostic laparoscopies converted to open surgery, showed that patients undergoing surgery on Tuesdays and Thursdays had a median LOS of three and five days, respectively (p=0.077). In contrast, median LOS was five days in patients in the open group regardless of whether they underwent surgery early or late in the week or not.

Table 12. Paper IV: Postoperative complications

	Lap (n=49)	Open (n=47)
Cardiac failure	1	0
ARF	1	2
Wound dehiscence	0	1
Anast. leak	2	1
Pneumonia	1	0
Urinary infection	1	1
Other infection	0	2
Sum	6*	7

*One patient in the laparoscopic group had two complications. Pneumonia and Atrial fibrillation (ARF).

***Figure 10.** Paper IV: Outcomes.*



OR (Odds Ratio), Multiple logistic regression. Adjusted for age, gender, ASA, BMI, preoperative radiation, malignant tumour and diabetes. *Statistically significant, p<0.05, laparoscopic vs. open surgery.

Discussion

The major novel findings in this thesis are the apparent strong dose-response relationship between improved ERAS-protocol adherence and improved outcome after surgery, and that single ERAS-interventions, within the context of the full ERAS-program, may be independent predictors of postoperative outcomes. Moreover, poor preoperative glycaemic control appears to be common among patients without diabetes scheduled for colorectal surgery. This metabolic condition seems to be associated with poor postoperative glucose control and increased risk of postoperative complications. In order to reduce insulin resistance and hyperglycaemia after surgery, the preoperative carbohydrate drink may also be used in patients with uncomplicated Type 2 diabetes. Further enhanced recovery may be achieved by the use of laparoscopic techniques within the ERAS-protocol.

The importance of adherence to the ERAS protocol

In the large prospective observational study of more than 900 consecutive patients with colo-rectal cancer undergoing major surgery within an ERAS program, an association between improved protocol adherence and improved outcome was found (paper I). Patients undergoing surgery with improved protocol adherence had more than 25% less risk of postoperative complications, almost 50% less risk of postoperative symptoms delaying discharge and a trend towards length of stay within target limits compared to patients operated with less optimal ERAS-protocol adherence. Overall, there was a strong indication of a dose-response relationship between enhanced adherence to the protocol (>70%, >80% and >90% compared to <50%) and improved outcome from surgery, reducing the relative risk for postoperative symptoms delaying discharge, 30-day morbidity and readmissions between 38%-69%.

Although there seems to be a potential for improvement in some single ERAS interventions with laparoscopic procedures, we found high adherence to the ERAS-protocol regardless of type of surgery (paper IV).

Several studies have shown that interventions within an ERAS program improves postoperative recovery after colo-rectal surgery, but few previous reports have evaluated the importance of each of the single ERAS-components [33] which may limit conclusions and clinical implementation. At the best to our knowledge, only two studies have focused on adherence to the ERAS-protocol [33, 180]. In the study by Polle et al [33], 55 patients were treated within fast-track (FT) care and compared to 52 patients treated with traditional care. A total of 13 FT modalities were identified with an average of 7.4 (56%) successfully achieved in the FT group. Despite this seemingly low adherence to the ERAS protocol length of stay (LOS) improved in the FT group but there was no difference in morbidity. In a more recent study among patients undergoing colorectal surgery, Ahmed et al [180] found no significant association between improvement of adherence to four ERAS modalities and postoperative outcome.

The re-launch of the ERAS protocol described in paper I, provided a unique opportunity to compare different rates of adherence in the same single center setting where a large number of consecutive standard clinical patients, without exception, were included in the study. A 27% increase in the overall mean adherence to the 12 specific elements of the ERAS-protocol between the two periods, resulted in improved outcome after surgery. Above all, the indicated dose-response relationship between adherence and outcome shows that one should strive to attain the highest possible adherence rate when implementing or running an ERAS-program.

However, compared to earlier reported data, the problem associated with the lack of similar intervention protocols prevails. Thus, the 12 vs. six specific ERAS-interventions in paper I and paper IV, respectively, are not the same as those analysed in the two previous studies mentioned above [33, 180]. Also, since pre- and perioperative interventions may influence many postoperative interventions and confound the interpretation of adherence, the former were left out of the analysis in paper I. A uniform consensus definition to enable audit and analysis of cross-site data, perhaps in the context of a multi-centre collaboration around a common database, may further improve our understanding of the importance of adherence to the ERAS-protocol.

The impact of single ERAS elements on outcomes

The interventions currently used in the ERAS-program are based on solid evidence from randomized trials, but the role and relative contribution of each item when being part of the complete ERAS-protocol remains unclear [24]. In paper I, the effect of each single intervention within the protocol was analyzed regarding the impact on postoperative symptoms, complications and LOS. Almost all of the single pre- and perioperative ERAS-interventions were found to significantly improve various outcome parameters in univariate analysis, but most failed to remain significant after adjustment for confounding in the subsequent multivariate analysis. In the multivariate analysis, only two factors were found to have an independent impact on clinical outcomes: perioperative i.v. fluid management and preoperative carbohydrate treatment.
Overloading patients with fluids was clearly negative for clinical outcomes after surgery. The risk of having a longer LOS than anticipated increased by 39% and the risk of postoperative complications increased by 32% for each additional litre of perioperative i.v. fluid given. This data is in line with previous reports of the deleterious effects of fluid overload [98, 99]. However, our data seems to confirm that controlling i.v. fluids is important also within an ERAS setting.

A carbohydrate drink not only reduced the need for perioperative parenteral treatment, but was also associated with a 44% lower risk of postoperative symptoms delaying discharge. The independent risk reduction of postoperative wound dehiscence found to be associated with intake of a preoperative carbohydrate drink may be related to the expected stress reduction from this treatment, including a reduction of postoperative insulin resistance possibly reducing the risk of postoperative wound infections, and/or, the attenuation of postoperative protein catabolism as shown in previous studies.

Although restriction of perioperative i.v. fluids and the use preoperative carbohydrate treatment appear to be more crucial than other ERAS interventions, our findings in paper I reflect the specific circumstances that prevailed during the study and do not contradict that it may be the combination of each of the different interventions that makes an effective regimen rather than a single intervention on its own.

The role of preoperative glucose control in colorectal surgery

In paper II, a large proportion (26%) of patients scheduled for major colorectal surgery without a history of diabetes, were found to have unsatisfactory glucose control already prior to the operation. Postoperatively, this group of patients had more pronounced hyperglycaemia, a more marked inflammatory response and a greater risk for complications than patients with HbA1c levels within normal range. Despite stress-attenuating perioperative treatment as part of the current ERAS protocol and occasional postoperative insulin treatment, nearly all patients displayed postoperative glucose levels above levels previously shown to negatively affect outcomes in surgical ICU patients (51).

Since early stage asymptomatic Type 2 diabetes can remain undetected for years, the estimated number of patients with undiagnosed diabetes and prediabetes could be assumed to be substantial (64). Previous studies on preoperative glucose control in non-diabetic patients have almost exclusively been conducted within cardiovascular surgery (68, 181, 182). In a study of patients undergoing vascular surgery, 58% of patients with no known diabetes had suboptimal preoperative HbA1c levels (6.0- 7.0 %), and this was associated with significantly higher 30-day morbidity compared to patients with HbA1c levels ≤ 6.0 (68). We found a smaller proportion (26%) of non-diabetic patients with elevated preoperative HbA1c (paper II). This may not be too surprising since patients undergoing cardiovascular surgery are more likely to suffer from obesity, dyslipidemia and hypertension which are known risk factors for atherosclerosis as well as insulin resistance, compared to patients undergoing colorectal surgery (68, 182). However, the fact that more than 1 out of 4 patients scheduled for colo-rectal surgery had such poor glucose control that it significantly affects the outcome of surgery, is noteworthy.

Surgical trauma induces insulin resistance and postoperative hyperglycaemia (44) which has been associated with adverse clinical outcomes (49, 51, 58). In paper II, high HbA1c levels before surgery were associated with elevated glucose levels postoperatively. However, also patients with preoperative HbA1c levels within the normal range, displayed some degree of postoperative hyperglycaemia, despite being treated within an ERAS-protocol designed to reduce surgical stress. It has previously been demonstrated that postoperative glucose levels ≤ 6.1 mmol/l are associated with improved outcomes (51), although this finding has recently been challenged (60). In the current study, postoperative glucose levels in both groups, particularly among patients with an elevated preoperative HbA1c were clearly higher than 6.1 mmol/l. We found that even minor elevations (i.e. 1 mM) in glucose concentrations in patients treated on the nursing floor rather than in the ICU after colorectal surgery, seem to have an impact on outcomes.

Patients with HbA1c > 6.0 had an almost three-fold increased risk of overall complications compared to patients with HbA1c ≤ 6.0 (paper II), mainly with regard to the relative risk of postoperative pneumonia, urinary tract infection, pleural effusion and ileus. This heterogeneous range of complications indicates different cause-effect mechanisms not investigated further in this study. However, the fact that the postoperative inflammatory response (CRP) was significantly elevated among patients with HbA1c > 6.0 compared to those with HbA1c ≤ 6.0, supports earlier findings that elevated glucose levels affect the immune system and the inflammatory response to stress (183). Inflammation may cause hyperglycaemia, but hyperglycaemia may also induce a proinflammatory state including cellular inflammation and oxidative stress (47).

To reduce the risk of postoperative hyperglycaemia, it is possible that the current ERAS protocol needs to include preoperative determination of HbA1c concentrations, also among non-diabetics. Recently, studies in the ICU setting, indicate that intensive insulin treatment could be associated with a significant hypoglycaemia [(47, 61)]. Therefore, in patients treated outside the ICU where the nursing availability is substantially more limited, it may be even more important to secure measures that prevent the development of hypoglycaemia. HbA1c as a screening method for both undetected and prediabetes could be useful in clinical practice in order to
1) indicate the need for closer postoperative monitoring of glucose levels,
2) speed up referral of obvious cases of diabetes to internists for preoperative optimization,
3) optimize patients with prediabetes for surgery by dietary interventions and preoperative physiological conditioning (prehabilitation) [(184)]. For patients treated outside the ICU setting, oral antidiabetic agents, such as Metformin, may be useful according to studies in burn patients [(185)]. However, the effect of insulin or other antidiabetic treatment in postoperative patients outside the ICU setting, the possible benefits of an ERAS protocol adjusted to preoperative HbA1c levels, as well as long term outcomes after possible adjustments of the protocol need to be further evaluated in randomised trials.

The effect of preoperative carbohydrate drinks in patients with Type 2 diabetes

Patients with diabetes mellitus are at risk of impaired postoperative glycaemic control and believed to be at greater risk of complications when subjected to surgery [(49, 65)]. Patients with diabetes are also assumed to be at risk of delayed gastric emptying and for this reason, they have not been given preoperative carbohydrates orally. However, the data on gastric emptying in patients with diabetes is conflicting. In many cases the magnitude of delay seems to be modest and it has also been reported that gastric emptying rate may be increased in Type 2 diabetes patients, at least early after onset of the disease [(83)].

Our study did not indicate any delayed gastric emptying after intake of a 12.5% CHO rich drink for preoperative use among patients with well-controlled Type 2 diabetes compared to healthy control subjects (paper III). If anything, a slightly faster gastric emptying rate was found in the diabetic population. Also, the residual gastric volume two hours after intake of the drink was similar in healthy subjects and in patients with diabetes. As expected, the peak glucose concentrations after carbohydrate intake were higher and occurred later in diabetic patients compared to healthy control subjects, but returned to baseline after 180 minutes.

The highest prevalence of slow gastric emptying in patients with diabetes is reported in studies where emptying of both solids and liquids have been measured. However, diabetes seems to affect gastric emptying of solids decidedly more than for clear fluids and nutrient liquids [(186, 187)]. Furthermore, compared to water or low nutrient liquids, high nutrient liquids show a delayed and a linear rather than exponential emptying pattern [(186-188)]. The carbohydrate-rich beverage used in paper III has a relatively high nutrient content which may explain the comparatively long gastric emptying times seen among all subjects [(189)]. The duration of diabetes has also been suggested to influence the risk of delayed gastric emptying in diabetic patients [(83)]. In paper III, the patients had a mean diabetes duration of 6.6 years in the OAD/diet group vs. 11.6 years in the insulin-treated group ($p<0.05$). Despite the difference in duration and possible severity of disease, the gastric emptying rate was similar between the two groups of diabetic patients and not different from that seen in healthy subjects.

In order to implement adequate fasting guidelines including preoperative carbohydrate loading as a routine also for diabetic patients, it would be advantageous if patients with a slower gastric emptying rate could be identified. However, physical examination and other indirect tests are of little value since there is a weak correlation between the rate of gastric emptying and autonomic neuropathy or upper gastrointestinal symptoms [190-192]. Using current techniques for measurement of gastric emptying in all diabetic patients scheduled for surgery is however not a realistic option.

With the exception of one patient who experienced mild hypoglycaemia during the experiment, implying that a liberal control of blood glucose levels is warranted, the present study indicates that it is safe, within the current fasting guidelines [73], to administer a preoperative carbohydrate drink to patients with uncomplicated Type 2 diabetes. However, due to the small sample size, it may be too early to safely recommend this type of regimen for all diabetic patients about to undergo surgery. Indeed, safety and efficiency issues from preoperative carbohydrate loading in diabetic patients undergoing major surgery need to be evaluated in a larger controlled study.

Laparoscopy and the ERAS-protocol

In paper IV, we compared outcomes from laparoscopic vs. open resection using a prospective observational study design among colo-rectal tumour patients undergoing high anterior resection (HAR) within an ERAS-protocol but found no major differences. However, data indicates a further enhanced recovery after laparoscopic resection with significantly improved oral fluid intake, earlier pain control, earlier avoidance of intravenous infusions and a larger proportion of patients with early discharge. This suggests that further improvements could be achieved by using laparoscopic techniques also within the ERAS-protocol.

In contrast to previous reports of laparoscopic colorectal resection within an ERAS protocol, this study investigates consecutive patients operated with one single standardized surgical procedure. Despite a higher expected 30-day morbidity following HAR compared to other colonic surgical procedures, the prospectively documented complication rates in our study was low in both the laparoscopic (10%) and the open resection (15%) group compared to previous studies on these different techniques for colo-rectal surgery [135, 136, 144] [33, 146, 149-151].
The lack of significant differences in the proportion of postoperative complications or symptoms delaying discharge comparing laparoscopic surgery to open resection may be explained by the sample size of the current study. It may also have been too small to detect less pronounced differences in morbidity, recovery and LOS between laparoscopic and open surgery. Although our study showed no differences in major outcome variables between these groups, some recovery variables such as time to pain control and time to termination of intravenous infusions were statistically significant in favor of laparoscopic resection. In addition, a higher proportion of patients achieved LOS within target after laparoscopic compared to open resection.

Even though multicenter studies have many advantages, there are some benefits in conducting prospective single centre cohort studies in an ERAS context. For example, the enrollment of consecutive patients with operations performed by surgeons with various experience reflects the clinical reality. In addition, a firm framework achieved by the ERAS-protocol enhances the potential for almost identical perioperative treatment both during laparoscopic and open surgery, reducing risk of bias. In addition, using the prospective ERAS database assists surgeons by offering a close audit and continuous feed-back of short-term results from surgery. Such surgical environments are well suited for evaluation of new surgical techniques.

Although the overall adherence to the protocol was acceptable in both groups, the tendency of a weaker adherence to the avoidance of preoperative bowel preparation, which in turn may lead to overloading patients with fluids, and a lower intake of CHO in the laparoscopic group is worth mentioning, since both fluid management and CHO were found to have an independent impact on clinical outcomes from colo-rectal surgery (paper I). It is plausible that some laparoscopic surgeons may prefer bowel cleansing before small tumour surgery if intra-operative colonoscopy would be required in order to visualise the tumour, but it may be argued that an enema would be sufficient for this purpose at least in distal tumours. The same amount of perioperative i.v. fluids was administered regardless of the type of surgical technique used. The expected lower amount in the laparoscopic group due to a presumed lower vaporisation in a closed abdomen was possibly counteracted by the fact that both preoperative bowel preparation and the omitting of CHO treatment increased the need of fluids during surgery (paper I). It is therefore possible that target volumes in the ERAS-protocol may need to be adjusted to laparoscopic surgery. Also, it is possible that modifications of the ERAS-protocol may be required to reach earlier pain control and a faster mobilization in laparoscopically operated patients. Furthermore, the target time for withdrawal of EDA may be too long in patients operated with laparoscopic surgery, and some reports indicate shorter LOS and lower complication rates if EDA is completely avoided [(152)]. Interestingly, patients undergoing laparoscopic resection on Tuesdays seem to have a shorter LOS than patients operated on Thursdays. A plausible reason for this might be that discharge during the weekends often is delayed for logistical reasons, particularly affecting laparoscopic surgery, potentially masking a greater difference in LOS between the groups. In summary, for laparoscopic surgery, the application of the ERAS-protocol in clinical daily work may need to be modified.

Potential weak points and bias

Paper I

It could be argued that other causes of clinical improvements than adherence to the protocol are possible. However, the turnover of surgical staff was minimal between periods. Secondly, although the mix of surgical procedures and the proportion of patients operated on laparoscopically differed slightly between the periods, the proportion of patients operated with pelvic and laparoscopic surgery were adjusted for in the multivariate analysis. Also, since APR, the procedure with the highest morbidity and longest recovery, was more frequent in the late study period, this would rather reduce the observed improvement in outcomes over time. However, the strongest argument for an independent association between overall adherence to the ERAS protocol and improved clinical outcomes is the indication of a dose-response relationship between level of adherence and postoperative morbidity, independent of study period.

The apparently high overall morbidity reported in paper I is mainly explained by the fact that both major and minor complications were prospectively recorded, that only colorectal cancer patients at a relatively high age were included and that a large proportion were operated with major pelvic surgery. It is thus unlikely that other factors than improved adherence to the ERAS-protocol could have caused the observed improvements in outcome.

It may be argued that a cohort study without randomization is a non-preferable study design for comparing rates of adherence and outcomes between two groups of patients. However, a randomized study design allocating patients to a traditional control regime is no longer an ethical option, considering the known clinical benefits of ERAS. A strength is that the data analyzed in paper I derives from a single center study where all patients, without exception, have been included in the protocol representing true daily practice in a center specialized in colorectal surgery.

Paper II

The cut-off for Type 2 diabetes is set to a HbA1c level ≥ 6.1 [64]. It could therefore be argued that the 31 patients defined to have impaired preoperative glucose tolerance in this study, actually were patients with diabetes and that other patients with impaired glucose tolerance remained undetected. HbA1c is not a very sensitive predictor of impaired glucose intolerance (IGT) (50% sensitivity) [64] and the oral glucose tolerance test (OGTT) is gold standard for detecting IGT [64]. Fasting plasma glucose (FPG) could have been used instead of HbA1c to detect diabetes /impaired glucose control prior to surgery. However HbA1c has been shown to be equally as effective as FPG for detecting Type 2 diabetes while both tests are equally ineffective for detecting IGT [64]. Both OGTT and FPG require overnight fasting and FPG has to be repeated at least twice to confirm diabetes. Moreover, OGTT has a low reproducibility, is time-consuming, costly and labour intensive [64] and thus difficult to use in a surgical setting. HbA1c testing is easier to perform in large patient populations and was therefore the measure of choice in this study. Even if the elevated risks associated with a preoperative HbA1c >6.0 could possibly be explained by undiagnosed diabetes, this study reflects a real-life situation where this type of patients will continue to undergo major surgery without any previous glucose tolerance tests.

Three quarters versus half of the patients with a preoperative HbA1c > 6.0 and ≤ 6.0, respectively, were treated with insulin postoperatively due to hyperglycaemia. However, the decision of insulin treatment was taken on clinical grounds based on glucose samples taken outside of the study protocol, making conclusions of the effect of insulin treatment difficult. Thus, without insulin treatment, postoperative hyperglycaemia would have been more pronounced in both groups than reported in the study.

Paper III

The choice of using the paracetamol absorption technique as a measurement of gastric emptying could be discussed. Even though scintigraphic methods may be considered to be gold standard when assessing gastric emptying, the technique is expensive and involves radiation exposure. The paracetamol absorption technique is well established and correlates well with scintigraphy of liquid phase gastric emptying [179, 193] and was therefore chosen for the present study.

One could argue that the sample size was too small to detect diabetic patients with slow gastric emptying despite absence of clinical symptoms and that the carbohydrate drink was not evaluated in patients with severe diabetes. Thus, gastric emptying of the preoperative carbohydrate drink may have been evaluated among diabetes patients with known severe symptoms of gastroparesis before conducting the study in paper III. However, since physical examination and other indirect tests are of little value for detecting slow gastric emptying [190-192], it would have been difficult to find such patients for inclusion in this study.

Paper IV
Previous studies comparing laparoscopic and open surgery within an ERAS-protocol are all associated with similar methodological limitations: the sample-size has generally been too small, different colonic surgical procedures have been mixed in the same data analyses, adherence to the ERAS-protocol is often vaguely described, and, the resulting outcome parameters vary between the different studies [33, 146, 149-151]. To some extent, paper IV also suffers from some of these limitations. Our study was not randomized, the sample size was small and there was no systematic selection behind the decision of which patients to include for open vs. laparoscopic surgery. However, consecutive patients were operated with one single standardized surgical procedure, operations were performed by surgeons with various experience reflecting the clinical reality and both major and minor complications were reported. Also, a close audit of adherence to the ERAS-protocol in both open and laparoscopic surgery increased the likelihood of almost identical treatment in both laparoscopic and open surgery, reducing risk of bias.

Randomized studies on laparoscopic surgery and ERAS-care are warranted. However, even multi-center RCTs usually have limited capacity to reflect real-life clinical situations since it is common that only selected patients that meet the enrolment criteria, e.g. a certain tumour stage, are subject to randomization. The fact that many operations in reality are performed by less experienced laparoscopic surgeons under training is rarely taken into account in RCTs. Also, differences in outcomes between centres can often be explained by local environmental factors rather than the actual intervention studied.

It could be argued that the 22% conversion rate may reflect poor laparoscopic technique, however more than half of the conversions occurred immediately after a diagnostic laparoscopy, which may be considered to be a relevant initial procedure in order to select patients for an open or laparoscopic approach.

Conclusions

1. The highest possible rate of adherence to the elements of the ERAS-protocol is crucial in order to improve surgical outcomes.

2. Some of the ERAS elements, restricted perioperative intravenous fluid management and preoperative carbohydrate drink, were found to be of major importance for beneficial outcomes following colo-rectal surgery.

3. A large proportion of patients scheduled for major colorectal surgery without a history of diabetes, was found to have unsatisfactory glucose control already prior to the operation.

4. Postoperative hyperglycaemia appears to be prevalent even among patients with no history of diabetes also when surgical metabolic stress and insulin resistance is minimized by the use of an enhanced-recovery protocol. This may be even more important in patients with elevated HbA1c before surgery.

5. It may be safe, under the current fasting guidelines, to administer a preoperative carbohydrate drink to patients with uncomplicated Type 2 diabetes.

6. An ERAS setting facilitates the evaluation of laparoscopic colorectal surgery by providing close audit and a firm framework for the perioperative process.

7. Early recovery can be achieved after both laparoscopic and open resection using the ERAS program.

8. A tendency of improved recovery variables following laparoscopic resection indicates benefits in favour of minimally invasive techniques. Modification of the ERAS-protocol to achieve further improvements with the laparoscopic technique may be warranted.

Future Perspectives

Enhanced recovery programs lower the risk of surgical stress, induced organ dysfunction and postoperative morbidity reducing the need for hospitalization. This may have major socio-economic implications [27]. However, despite the growing evidence of the benefits of ERAS-programs, adaption of evidence-based care in surgical units has been slow [170, 194]. Traditional perioperative care prevails, sometimes modified by a few selected components [170, 171] of the ERAS-protocol aiming to reach the same postoperative outcome but with less effort. To understand why fast-track programmes are not adopted on a larger scale is essential to be able to convince surgeons to use best clinical practise.

Possible explanations for slow adoption of fast-track care includes, a tradition among surgeons to focus on the operations and the technical aspects of surgery rather than on perioperative care, a lack of awareness of fast-track data or lack of belief that implementation of the ERAS program at their own institution is feasible or, alternatively, the data is not presented in a sufficient and convincing way.

In order to reach out with the ERAS-program firm and detailed step-by-step guidelines on how to implement the protocol must be adopted. Such a guideline should also provide enough information and guidance on ERAS-care to over-bridge potential multidisciplinary barriers and increase comprehension from the hospital administration.

A common prospective database would thus not only facilitate implementation of the ERAS-program but is most probably also required for continuous feed-back of adherence to the protocol and would enable a close audit of the perioperative process. This would allow for a firm framework for how to report adverse events, enabling comparisons between different institutions in a scientific manner. This, in turn would trigger ambitions for further improvement of perioperative care. Furthermore, ERAS-care institutions should recognize that the major part of data on ERAS-care currently presented comes from single institutions or small trials. This may be a reason for the slow scale up of programme adoption. Collaboration around a common data-base would enable large multicentre studies to be performed that are needed to further clarify and possible revise the ERAS-protocol.

In a smaller perspective, there is a further need to define the role of each individual ERAS-element in relation to rate of recovery**.** Also, new additional recovery items need to be continuously evaluated. The role of laparoscopic surgery within an ERAS environment is a large and very important issue. Furthermore, improved adherence to the ERAS-protocol must be prioritized in order to improve postoperative outcomes. Organizational support and restructure, doctors dedicated to ERAS-care, continuous audit and feedback of the perioperative process, multidisciplinary ERAS-agreements and repeated training of staff are some of the necessary ingredients to improve adherence to the ERAS-protocol.

The debate on perioperative glycaemic control will continue. Currently, no guidelines regarding perioperative glucose control are available. Appropriate postoperative glucose target level should be identified and preoperative interventions improving glucose control explored. Data on the value of measuring intraoperative glucose control in abdominal surgery is lacking. If glucose variability is an important cause of adverse events and not hyperglycaemia per se [195, 196], perhaps other measurements such as hyperglycaemic index should be used for monitoring glucose control after surgery.

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