Enhanced perioperative care in liver and pancreat surgery

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Enhanced perioperative care in liver and pancreatic surgery

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Enhanced perioperative care in liver and pancreatic surgery

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Mariëlle Maria Etiën Coolsen

Promotor

Prof. dr. C.H.C. Dejong

Co-promotor

Dr. S.W.M. Olde Damink

Beoordelingscommissie

Prof. dr. M.F. von Meyenfeldt (voorzitter)

Prof. dr. W.F. Buhre

Prof. dr. K.C. Conlon (University of Dublin, Trinity College)

Dr. I.H.J.T. de Hingh

Prof. dr. J.M.P. Kleijnen

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CHAPTER 1

Introduction and outline of the thesis

1.1 INTRODUCTION

Liver and pancreatic resections are complex surgical procedures, which can cause considerable surgical stress and possible disruption of metabolic and pulmonary function. Improved operative techniques and insight into perioperative management has lowered mortality after liver resection to its current level of 5% but morbidity rates remain high, ranging between 30% and 50%¹⁻³. In large series morbidity rates for pancreatic resections can be as high as 40 to 60%⁴⁻⁶. In order to improve postoperative outcome it is now recommended to centralize these major abdominal procedures in specialized, high-volume clinics. Because of this, mortality rates for pancreaticoduodenectomy (PD), which is the most common form of pancreatic resection, have decreased from 9.8 to 5.1% in the Netherlands⁷. Postoperative length-of-stay (LOS) after PD varies from 14 to 20 days in different studies⁸⁻¹⁰.

In many hospitals current perioperative care for liver and pancreatic surgery is still conservative. Nasogastric tubes are left in place for days after surgery with the patient either receiving no food at all or only through a needle jejunostomy⁸. Even though this delivers artificial nutrients it is an intervention that bypasses the cephalic-vagal digestive reflex and appears to be associated with considerable risk^{11,12}. Other conservative practices are late postoperative mobilization and placement of drains at the end of the surgical procedure^{5,8,13,14}. It has been shown that in liver surgery the placement of abdominal drains is not effective and may even increase the risk of intra-abdominal infections¹⁵⁻¹⁷. Similarly, in pancreatic surgery the use of abdominal drains is supported by little evidence. In a randomized controlled trial (RTC) comparing routine drainage versus no drainage after pancreatic surgery, the incidence of intra-abdominal collections of fistulas turned out to be higher after drainage¹⁸. Fasting from midnight also remains common practice in elective (liver and pancreatic) surgery even though this is not supported by evidence¹⁹. It has been shown that patients should be allowed to drink clear fluids up to 2 hours and ingest solid food up to 6 hours before surgery²⁰.

Enhanced Recovery After Surgery (ERAS) programs, also referred to as *fast track*, *clinical* or *critical pathway* programs, are multimodal, standardized care protocols implemented for a specific surgical field. An ERAS program addresses a variety of evidence-based perioperative interventions and demands a multidisciplinary approach in which surgeons, anesthesiologists, intensive care staff, and nurses work together as a team. The purpose of an ERAS program is to accelerate postoperative recovery and shorten postoperative length of stay (LOS) without increasing or even lowering morbidity and readmission rates. ERAS programs have been successfully implemented in colonic surgery and appear to reduce the length of stay and complication rates without compromising patient safety^{21,22}. The LAFA trial compared open colonic resection with laparoscopic resection using either an ERAS protocol or a standard care

protocol. This trial showed that laparoscopy combined with an ERAS protocol resulted in the optimal perioperative treatment of patients undergoing colonic resections²³. Numerous other studies have been published on the implementation of ERAS programs in many other surgical fields (e.g. musculoskeletal²⁴, breast²⁵, aortic^{26,27}, bariatric²⁸, and prostate surgery²⁹). All of these studies showed a decrease in LOS without increasing postoperative morbidity or mortality.

Apart from a reduction in postoperative LOS the implementation of an ERAS program may also reduce complication rates after liver and pancreatic surgery. Concerns have been raised, however, regarding the safety of ERAS programs for these upper gastrointestinal (GI) procedures since they are still associated with relatively high morbidity rates and elicit a considerable stress response. A nil-by-mouth regimen is still widely practiced because of fear for gastric distention and anastomotic leakage³⁰⁻³². Especially in PD, where complications as delayed gastric emptying (DGE) regularly occur, there is a reluctance to allow volitional intake of normal food during the immediate postoperative period³³. This reluctance, however, is not justified by evidence obtained from randomized trials and may even be considered "obsolete" care^{34,35}. Even so, liver and pancreatic procedures are relatively infrequent procedures for which it may be difficult to implement an ERAS program that requires close collaboration between all caregivers. Anesthesiologists in particular must be willing to cooperate and apply all perioperative ERAS components. This includes allowing oral carbohydrate loading up to 2 hours before surgery, epidural anesthesia and the removal of nasogastric tubes directly after surgery.

Given the success of ERAS programs in colonic surgery as well as in many other surgical areas and the abundant evidence for the individual elements of the ERAS protocol we hypothesized that it should be possible to implement an ERAS program for liver and pancreatic surgery as well. Reducing the surgical stress response, thereby enhancing recovery, might even lower procedure-related morbidity. The reluctance to abandon conservative care surrounding upper GI surgery should be overcome thereby allowing room for the practice of evidence-based care. In this thesis we describe how we developed, implemented and evaluated ERAS programs for liver and pancreatic surgery. Most of the studies were carried out at Maastricht University Medical Center (MUMC) in Maastricht, the Netherlands. This is a tertiary referral center for Hepato-Pancreatico-Biliary (HPB) surgery of relatively high volume (90-100 liver resections and 45-65 pancreatic resections per year).

Our approach consisted of the following steps. First, we critically appraised the literature regarding earlier ERAS programs for liver and pancreatic surgery and prophylactic drainage after pancreatic surgery, which is one of the elements of the ERAS protocol. Second, we performed a study to enable research into PD by proposing uniform definitions and a composite endpoint to be used in further trials. Third, the

development of perioperative ERAS guidelines for PD was performed in close collaboration with the international ERAS society. Also, a randomized controlled trial was set-up in a multicenter, international setting in order to investigate the use of prophylactic drainage after PD for patients managed in an ERAS protocol. Fourth, the development and implementation of the ERAS program for liver surgery was carried out at MUMC and in the liver unit of the Royal Infirmary in Edinburgh, UK. The implementation and evaluation of the ERAS protocol for PD was carried out at MUMC only. Finally, we performed an international survey among both patients and caregivers in order to evaluate the relative importance of the different elements of an ERAS program.

1.2 BACKGROUND

Changes in traditional care

Until the early nineties perioperative care after abdominal surgery was very conservative. Patients were subjected to a preoperative fasting period lasting up to 29 hours³⁶. Large incisions were common and patients often suffered from perioperative hypothermia and intravenous fluids were used abundantly resulting in patients frequently leaving the operating theatre with a grossly positive fluid balance. The postoperative period after abdominal surgery was characterized by prolonged bed rest. Nasogastric tubes and intra-abdominal drains were left in place and patients were kept nil by mouth for days. Furthermore, pain control was not optimal^{37,38}.

From the nineties onwards anesthetic and analgesic techniques improved. For example, anesthesiologists started to use rapid short-acting volatile anesthetics (e.g. desflurane and sevoflurane) which shortened the early recovery period in the Post Anesthesia Care Unit (PACU). Furthermore, certain analgesics (remifentanyl)³⁹ and new analgesic techniques such as neurogenic blockade, local nerve block and epidural analgesia, were introduced^{40,41}. Also, surgical techniques improved because of the development of minimally invasive (open) and laparoscopic surgery. These advances in anesthesia and surgery together led to a significant reduction of the early and intermediate recovery phase. Already in the operating theatre patients in ambulatory surgery started to regain vital functions which allowed them to be transferred directly to the day care unit thereby foregoing the need for recovery in a PACU⁴².

Fast track surgery

“Fast tracking”, a term used to describe a streamlined postoperative treatment pathway in order to shorten recovery, was first applied in ambulatory surgery. Procedures that previously required a multi-day admission, e.g. laparoscopic cholecystectomy⁴³, gastro-esophageal reflux surgery⁴⁴ and mastectomy⁴⁵, could now be

performed in an ambulatory environment with a 1-day stay. Fast tracking not only appeared to accelerate recovery of the patient but also reduced the workload of nursing staff and decreased hospital costs^{42,46}. Because of its success the fast track concept was soon applied to more complex surgical procedures such as pneumonectomies⁴⁷, prostatectomies²⁹, colectomies⁴⁸, total hip and knee replacements⁴⁹, and various vascular procedures^{27,50}. The fast tracking approach allowed these procedures to be performed in a short-stay environment.

Multimodal rehabilitation

In 1997 Kehlet was the first to describe an extension of the fast track concept which he termed *multimodal rehabilitation*⁵¹. Kehlet hypothesized that multimodal interventions in perioperative care could lead to a reduction of the surgical stress response as well as a reduction in organ dysfunction thereby accelerating recovery and reducing postoperative morbidity. An improved understanding of the pathophysiology of the different components of the surgical stress response led to the conclusion that it cannot be modified by any single technique or drug. Rather, a multimodal approach is necessary to positively influence the response, thereby improving surgical outcome. Several factors were identified that contribute to a delayed recovery (Figure 1.1).

Figure 1.1 Factors contributing to postoperative morbidity.

For instance, prolonged bed rest is known to result in muscle atrophy and weakness, it impairs pulmonary function and predisposes the patient to venous thrombo-embolism (VTE)⁵². Scheduled early mobilization under the guidance of a physiotherapist can prevent these negative effects and may lead to faster recovery. Postoperative pain amplifies the surgical stress response and increases organ dysfunction but could be managed by better analgesic techniques. The aforementioned factors are just a few reasons for a prolonged recovery after surgery. A multimodal rehabilitation program addresses all factors that are known to delay recovery (Figure 1.2)⁵³.

Figure 1.2 Interventions needed for major improvement in surgical outcome.

Enhanced recovery after surgery

In 2001 the Enhanced Recovery After Surgery (ERAS) study group was established to further develop the concept of multimodal surgical care as proposed by Kehlet et al. This group, consisting of members from five North-European countries (UK, Denmark, Norway, Sweden and The Netherlands) established early on that surgical care all over the world often relies on a wide variety of traditions. Furthermore, the group concluded that a discrepancy exists between optimal practice, as described in scientific literature, and actual practice. This incited the group to examine the process of changing from actual practice, based on traditions, to optimal practice, based on scientific evidence. The group identified several key factors that keep patients in the hospital after surgery. Among these are (1) the need for parenteral analgesia, (2) the need for intravenous fluids secondary to gut dysfunction and (3) bed rest caused by lack of mobility. Subsequently, the group developed ERAS guidelines addressing these factors. In 2005 the group published an evidence-based ERAS consensus protocol for patients undergoing colonic surgery⁵⁴. The most important elements of this protocol are shown in Figure 1.3.

Figure 1.3 Elements of the ERAS protocol for colonic surgery.

Actual practice was evaluated for colonic surgery in a case mix of both conventional and fast track care performed in hospitals of the five participating countries of the ERAS group⁵⁵. 451 consecutive patients were included of which 118 in the fast track unit in Denmark and 333 in the other units practicing traditional care. There were no differences in morbidity or 30-day mortality between the different centers. The median length of stay was 2 days in Denmark and 7–9 days in the other centers ($p < 0.05$). However, readmission rates were higher in the fast track group (22%) as compared to the traditional care group in the other centers (2–16%, $p < 0.05$). After this study into ERAS for colonic surgery, more studies have followed. Meta-analyses of these studies have shown that the use of an ERAS pathway can reduce postoperative complications by up to 50%^{21,56}. Additionally, hospital costs are lower when patients are treated in an ERAS pathway^{57–60}.

In 2010 the ERAS society was officially founded and stated its mission as follows: "to develop perioperative care and to improve recovery through research, audit, education and implementation of evidence-based practice." In 2013, the ERAS society published several recommendations and guidelines for ERAS perioperative care in colon^{61,62}, rectal/pelvic surgery^{63,64} and pancreaticoduodenectomy (chapter 6)^{65,66}. The ERAS society also offers an ERAS training program, which can help perioperative care teams to implement the protocol and maintain high compliance levels to the protocol standard.

1.3 THE SURGICAL STRESS RESPONSE AND ERAS

Surgery provokes a complex stress response, which is associated with endocrine-metabolic changes inducing hypermetabolism and catabolism. Also, surgical injury induces an inflammatory response with activation of a humoral cascade causing hyperthermia and immunosuppression⁶⁷. The aim of an ERAS program is to attenuate the surgical stress response by means of multimodal interventions. A recent randomized controlled trial (RTC) compared 299 patients undergoing colonic surgery based on an ERAS protocol with 298 patients receiving conventional care. In this study outcomes relating to nutritional, metabolic and stress index were measured on postoperative day (POD) 1 and 5⁶⁰. The insulin resistance index of the ERAS group appeared to be lower than that of the control group on POD 1 ($p < 0.001$). Cortisol levels of the control group were elevated on POD 1 and 5, while cortisol levels in the ERAS group remained stable until POD 5 ($p = 0.001$). Levels of TNF- α , IL-1b, IL-6, and IFN- γ were reduced in the ERAS group indicating a lower postoperative stress response. Additionally, gastro-intestinal function recovered faster in the ERAS group as compared to the group receiving conventional care.

Intraoperative hypothermia

Unintended hypothermia occurs in approximately half of the patients undergoing a surgical procedure. In abdominal operations lasting over 2 hours a drop in core temperature of 2-4 degrees is not unusual. This decline in body temperature stimulates cortisol and catecholamine release which consequently enhances the stress response to surgery⁶⁸. Furthermore, perioperative hypothermia is associated with a significantly increased intraoperative blood loss^{69,70}, a higher risk of operative and postoperative cardiac events⁷¹, a 3-fold increase in the risk of wound infections⁷², an increased catabolism and increased discomfort⁷³. Active prevention of hypothermia by heating the patient greatly reduces these risks, attenuating the stress of operation and improving outcome. For this reason, it is one of the targets of the ERAS program.

Analgesia

Postoperative pain triggers a surgical stress response and activates the autonomic system, which adversely influences different organ systems. The stress response induced by infusion of neuroendocrine hormones and cytokines causes tachycardia, fever and shock and increases minute ventilation⁷⁴. Epidural analgesia is known to modulate this stress response. Also, it appears that the use of regional anesthetic techniques (like epidural analgesia) using local anesthetics is indeed the best way to reduce adrenocortical, pituitary and sympathetic responses to surgery. Continuous epidural analgesia for a period of up to 24 to 48 hours has the largest inhibitory effect on the abovementioned negative responses to surgery⁷⁵. In abdominal surgery, a meta-

analysis showed that continuous epidural analgesia, with or without the use of opioids, offers the best pain control as compared to intravenous opioids and allows for early mobilization⁷⁶. Another meta-analysis demonstrated that the use of epidural analgesia results in fewer pulmonary infections and improved pulmonary function⁷⁷. More importantly, epidural analgesia also appears to improve gastrointestinal function and therefore contributes to a faster recovery as compared to opioids^{78,79}. For this reason, epidural analgesia currently is the recommended analgesic regimen in ERAS protocols for abdominal surgery.

Postoperative ileus

Postoperative ileus (POI) is an undesirable event after abdominal surgery which increases patient discomfort and delays nutritional intake and recovery. POI is one of the major causes of prolonged length of stay (LOS)⁸⁰ and increases in hospital morbidity, regardless of the specific type of surgery⁸¹. The relationship between POI, which is based on the disturbance of the *migration motor complex*, and tissue inflammation, as a reaction to surgical stress, is a recent area of interest⁸². Surgical manipulation of the bowels leads to paralysis of the mucosal myocytes and POI as a result. Minimally invasive surgery (as part of the ERAS concept) limits surgical trauma and has been shown to reduce POI significantly⁸³. Furthermore, opioids are known to have negative effects on gastrointestinal (GI) motility and may lead to GI paralysis. The use of opioids as postoperative analgesia should therefore be reduced and preferably be replaced by an alternative analgesic medication, e.g. non-steroidal anti-inflammatory drugs (NSAIDs)³⁸. In colonic surgery, a RCT showed that earlier return of gut function can be achieved with the use of clear carbohydrate-loaded drinks up to 2 hours before surgery⁸⁴. Moreover, preoperative carbohydrate loading decreases postoperative insulin resistance and reduces hunger, thirst and anxiety⁸⁵⁻⁸⁷. Routine use of laxatives has been shown to result in a quicker gastrointestinal recovery with earlier bowel movements in a RCT among patients undergoing liver resection⁸⁸. Also, in pancreatic surgery, in a series of 255 pancreatic resections (almost 60% PDs), oral administration of magnesium and lactulose in addition to metoclopramide on POD 1 supported early start of normal bowel function⁸⁹. So, reduction of opioid use, carbohydrate-loaded drinks up to 2 hours before surgery and use of laxatives are recommended in the ERAS protocol.

1.4 STANDARDIZATION OF OUTCOMES

Meta-analyses and RCTs deliver the highest level of evidence about current practice. Conclusions of meta-analyses and large RCTs are incorporated in the latest guidelines and help to optimize care and outcome in surgical practice. In the field of pancreatic

surgery, however, very few RCTs have been performed^{90,91}. An important factor contributing to this is the large number of patients needed to adequately power RCTs for relevant clinical single endpoints. Furthermore, definitions used in different trials into pancreatic surgery are not uniform which complicates the comparability of trials and the conduct of meta-analysis. A composite endpoint (CEP) is a minimal set of outcomes that can be used as a primary endpoint in RCTs. It facilitates the conduct of RCTs by reducing the number of patients needed to adequately power an RCT. The single endpoints included in a composite endpoint are well defined and agreed upon by experts worldwide. Composite endpoints are already widely used in cardiovascular and pulmonary research⁹²⁻⁹⁶ and have recently been developed for liver surgery by our group⁹⁷. To also improve research and standardization of outcomes in pancreatic surgery we investigated the use of uniform definitions and the development of a composite endpoint for pancreaticoduodenectomy.

1.5 AIMS OF THIS THESIS

As previously shown, there is abundant evidence demonstrating ERAS programs are preferred over traditional care in colonic surgery. However, the feasibility and implementation of ERAS programs in major operations such as HPB surgery has not yet been demonstrated and might be a challenge because perioperative care in HPB surgery has been conservative for a long time. In this thesis we present the results of our research into the feasibility of ERAS in HPB surgery. More specifically, our aims were the following:

- To critically appraise literature regarding ERAS programs for HPB surgery and endpoints in pancreatic surgery (chapter 2,3,4,5)
- To develop perioperative ERAS guidelines for pancreaticoduodenectomy (chapter 6)
- To initiate a trial evaluating the effect of prophylactic intra-abdominal drainage for patients undergoing pancreaticoduodenectomy in an ERAS program (chapter 7)
- To evaluate the implementation of an ERAS program in HPB surgery (chapter 8,9,10,11)

Outline of this thesis

Part I: Critical appraisal of literature: ERAS programs in HPB surgery and endpoints in pancreatic surgery

In order to (a) assess what is already known about ERAS programs in HPB surgery and (b) compare existing studies we performed a systematic review and meta-analysis of ERAS programs in pancreatic surgery (chapter 2). Chapter 3 describes a systematic review of ERAS programs in liver surgery. In most abdominal surgical procedures prophylactic intra-abdominal drains did not prove to be beneficial and may even be considered harmful. For this reason, one of the components of an ERAS program in colonic surgery is the omission of prophylactic postoperative intra-abdominal drains. However, whether this component is also a candidate for inclusion in an ERAS program for pancreatic surgery is still unclear since drains may indicate a bleeding or leakage of the pancreatic anastomosis. A systematic review and cumulative meta-analysis on prophylactic drainage after pancreatic surgery was performed to evaluate whether there is conclusive evidence to omit prophylactic intra-abdominal drains in an ERAS program for pancreatic surgery (chapter 4). RCTs for pancreatic surgery are rare and often lack sufficient power. Also, there is a need for uniform definitions and outcomes in studies. In chapter 5 the development of a composite endpoint for pancreaticoduodenectomy is described. This endpoint consists of well-defined components and can be used as a primary endpoint in future RCTs. Its use increases the power of RCTs, enhances the ability to compare outcomes between RCTs and allows for better performance of meta-analysis.

Part II: Development of ERAS guidelines and a multicenter trial for pancreaticoduodenectomy

Chapter 6 covers the development of ERAS perioperative guidelines for pancreaticoduodenectomy by the international ERAS group. While consensus was reached on many items, no consensus was reached regarding omission or inclusion of prophylactic intra-abdominal drainage since the evidence from literature remained inconclusive. For this reason, we decided to design a multicenter RCT comparing prophylactic abdominal drainage with a no-drain policy in patients undergoing pancreaticoduodenectomy (chapter 7). All patients in this study are treated according to the developed ERAS guidelines (chapter 6). The composite endpoint for pancreaticoduodenectomy (chapter 5) will be used as one of the outcomes.

Part III: Evaluation of implementing an ERAS program in liver and pancreatic surgery

In this part of the thesis the implementation and evaluation of an ERAS program in liver surgery is described (chapter 8). The implementation of an ERAS program for patients undergoing pancreaticoduodenectomy is evaluated in chapter 9. Chapter 10

demonstrates that it is also feasible to subject patients of advanced age to an ERAS program after pancreatic surgery. Finally, a multicenter international study was performed to evaluate the relative importance of principal components of an enhanced recovery after surgery program by means of a survey of patients, surgeons, nurses, and anesthesiologists (chapter 11).

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PART I

Critical appraisal of literature: ERAS programs in HPB surgery and endpoints in pancreatic surgery

CHAPTER 2

Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies

MME Coolen, RM van Dam, AA van der Wilt, K Slim, K Lassen, CHC Dejong
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ABSTRACT

Background

In the past decade, Enhanced Recovery after Surgery (ERAS) protocols have been implemented in several fields of surgery. With these protocols, a faster recovery and shorter hospital stay can be accomplished without an increase in morbidity or mortality. The purpose of this study was to review systematically the evidence for implementation of an ERAS protocol in pancreatic resections, with particular emphasis on pancreaticoduodenectomies (PDs).

Methods

A systematic search was performed in Medline, Embase, Pubmed, CINAHL, and the Cochrane library for papers describing an ERAS program in adult patients undergoing elective pancreatic surgery published between January 1966 and December 2012. The primary outcome measure was postoperative length of stay. Secondary outcome measures were time to recovery of normal function, overall postoperative complication rates, readmissions, and mortality. Subsequently, a meta-analysis of outcome measures focusing on PD was conducted. This systematic review and meta-analysis was performed according to the PRISMA statement.

Results

The literature search produced 248 potentially relevant papers. Of these, eight papers met the predefined inclusion criteria: five comparative studies with historical controls, two retrospective studies, and one prospective study, describing a total of 1,558 patients. Only three of the studies reported data on discharge criteria and assessed time to recovery and return to normal function. Implementation of an ERAS protocol led in four of five comparative studies to a significant decrease in length of stay (reduction of 2–6 days in different studies). Meta-analysis of four studies focusing on PDs showed that there was a significant difference in complication rates in favor of the ERAS group (absolute risk difference 8.2%, 95% confidence interval (CI) 2.0–14.4, $p=0.008$). Introduction of an ERAS protocol did not result in an increase in mortality or readmissions. Delayed gastric emptying and incidence of pancreatic fistula did not differ significantly between groups. All studies reporting on hospital costs showed a decrease after implementation of ERAS.

Conclusions

This systematic review suggests that using an ERAS protocol in pancreatic resections may help to shorten hospital length of stay without compromising morbidity and mortality. This seemed to apply to distal pancreatectomy, total pancreatectomy, and PD. Meta-analysis was performed for those studies focusing on PD and showed that there were no differences in readmission or mortality. Morbidity rates were significantly lower for patients managed according ERAS principles.

INTRODUCTION

Recent research in surgery focuses on reducing perioperative surgical stress to decrease the “postoperative dip” and to make patients recover better. Postoperative length of stay is consequently shortened and this reduces costs¹. In the context of these developments Enhanced Recovery after Surgery (ERAS) programs were introduced. ERAS programs, also referred to as “fast track”, “clinical”, or “critical pathways”, are multimodal, standardized care protocols implemented in a specific field of surgery. An ERAS program addresses a variety of evidence-based perioperative interventions and demands a multidisciplinary approach in which surgeons, anesthesiologists, intensive care staff, and nurses work closely together. The purpose of an ERAS program is to accelerate postoperative recovery and shorten postoperative length of stay (LOS) without an increase in morbidity or readmissions.

Kehlet and coworkers were the first to describe and implement such a multimodal care protocol successfully in colonic surgery². Subsequently, numerous studies have been published on this topic, not only in colonic surgery but also in many other fields of surgery (e.g. musculoskeletal³, breast⁴, aortic^{5,6}, bariatric^{7,8}, and prostate surgery⁹). All of these studies showed a decrease in LOS, without increasing postoperative morbidity, or mortality. Pancreatic surgery traditionally has been considered to be high-risk abdominal surgery associated with high morbidity and mortality rates. Advances in diagnostic and surgical techniques in the past decades and improved management of intensive care units have led to better outcomes after pancreatic resection and mortality rates are low while morbidity remains high¹⁰. Additionally, to further reduce morbidity and mortality to acceptable rates, centralization has been recommended for pancreatic resections. In high-volume specialized centers, mortality for the most common pancreatic resection, pancreaticoduodenectomy (PD), is now approximately 5%¹¹. However, morbidity remains high at a rate of 40–60%¹⁰⁻¹². Postoperative LOS after PD ranges from 14–20 days in various studies¹²⁻¹⁴. Complications, such as anastomotic leakage, pancreatic fistula, and delayed gastric emptying (DGE), are the main reasons for delayed recovery and frequent need for additional radiological or surgical interventions.

The benefit and safety of implementing ERAS programs in pancreatic surgery, including PD, has not yet been extensively studied. For this reason, a systematic review and meta-analysis of the available literature on ERAS pathways compared with traditional treatment in adult patients undergoing pancreatic surgery was performed with emphasis on PD, and time to recovery, length of postoperative hospital stay, morbidity, mortality, and readmissions were analyzed.

METHODS

Search strategy

A search was conducted by two researchers (MC and AvdW) in January 2013 of Medline, Embase, Pubmed, CINAHL, and the Cochrane library spanning a period from January 1966 to December 2012 with language restricted to English, Dutch, or German using the search terms: “clinical pathway”, “critical pathway”, “enhanced recovery”, and “fast track” and combinations of these with: “pancreas”, “pancreatic”, “Whipple”, “pancreatectomy”, “pancreaticoduodenectomy”, using the Boolean operators AND and OR. Synonyms of all of these terms also were used in the search. Reference lists of relevant publications were assessed for additional references. Furthermore, bibliographies from other systematic reviews or meta-analyses on the subject were searched.

Inclusion and exclusion criteria

Studies meeting all of the following selection criteria were eligible for inclusion: (1) studies concerning adult patients undergoing major elective resectional surgery of the pancreas, (2) studies describing an enhanced recovery program with at least four different perioperative elements, (3) studies reporting at least the following outcome measures: LOS, postoperative morbidity and mortality, and readmission rates. Excluded were: (1) studies describing a single intervention in perioperative care rather than a bundle of elements combined in an enhanced recovery program, (2) studies describing emergency/nonelective or transplantation surgery, and (3) reviews.

These criteria were chosen following internal discussion in our research group as well as in the international ERAS group and are in keeping with earlier systematic reviews on ERAS in colonic surgery^{15,16}. Practice was considered “ERAS” when at least four different items were included, covering the pre-, intra- and postoperative periods^{15,16}. Table 2.1 shows different items used in ERAS protocols for pancreatic resections. The items are supported by varying levels of evidence.

Systematic review and meta-analysis

Systematic review was performed for articles on the implementation of an ERAS program for all pancreatic resections: distal pancreatectomy (DP), total pancreatectomy (TP), and PD. Subsequent meta-analysis was performed only on studies focusing on PD.

Table 2.1 Items in an ERAS protocol for pancreatic resection

Preoperative elements
Pre-operative counseling
No oral bowel prep
Preoperative feeding: CHO loading up to 2h before surgery
Anti-thrombotic prophylaxis
Intra-operative elements
No pre-anesthetic medication
Single dose antibiotics
Prevention of Postoperative Nausea and Vomiting (PONV)
Avoiding hypothermia
Perioperative glycemic control (below 10 mmol/l)
Epidural analgesia
No postoperative nasogastric intubation
Good fluid balance
Postoperative elements
Early and scheduled mobilization
Normal food at will after surgery from day 1, increasing intake according to tolerance over 3-4 days
Removal of urinary catheter on day 1 or 2
Perianastomotic drain removal < 72h
Stimulation of bowel movement with laxatives
Somatostatin analogues
Audit

Outcome measures

The primary outcome measure of this systematic review was postoperative length of stay. Secondary outcome measures were time to recovery of normal function (criteria for functional recovery are: good pain control with oral analgesia, only taking solid food, no intravenous fluids, passage of stool and being independently mobile at preoperative level), overall postoperative complication rates, readmissions, and mortality. Secondary outcome measures also included delayed gastric emptying (DGE) and pancreatic fistulas in patient groups undergoing pancreaticoduodenectomy. Pancreatic fistula and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgery (ISGPS)^{17,18}. Additionally, total hospital costs were analyzed if available.

Study selection and data selection

The two researchers identified and selected citations from the search independently. In case of doubt about inclusion, a third reviewer was consulted (RvD) until consensus was reached. Data from included studies were extracted independently by the two researchers. Randomized as well as nonrandomized studies were eligible as long as they met the inclusion criteria. Methodological quality of the articles was assessed using the MINORS checklist (Methodological Index for Non-Randomized Studies)¹⁹. This instrument scores 8 methodological items for noncomparative studies and an additional 4 criteria for comparative studies with a maximum score of 24 points for

comparative and a maximum score of 16 points for noncomparative studies. Missing data were obtained by contacting the authors of the respective studies.

The following variables were extracted from the articles: number and age of patients in the study group and historical control groups if available, type of surgery, discharge criteria, and data on recovery to normal function (if available), duration of follow-up, postoperative length of hospital stay, complications, mortality, readmissions, and adherence to protocol. Furthermore, for each included article an assessment was made of the different ERAS program interventions. If available, hospital costs also were extracted from the articles.

Statistical analysis

Because searching the available literature produced no randomized, controlled trials, but only historical comparative studies, the MOOSE checklist for meta-analysis of observational studies was used to assess the possibility for conducting a meta-analysis²⁰. When studies focusing on PD were considered sufficiently clinically homogeneous according to the MOOSE consensus statement checklist, data were pooled and meta-analyzed using the statistical software package StatsDirect²¹. Meta-analysis of four comparative studies with historical controls that focused on PD was performed for morbidity, mortality, and readmissions. Meta-analysis of the incidence of complications, including pancreatic fistula and delayed gastric emptying, was performed in three studies addressing pancreaticoduodenectomy. For binary end points, risk differences and 95% confidence intervals were calculated using random effects models (Der-Simonian-Laird). Pooled risk differences were tested for statistical significance using Chi-square tests and a significance level of 0.05. Heterogeneity was expressed in terms of I^2 . Results were presented graphically using Forest plots. To assess the impact of the different studies on the results, a sensitivity analysis was performed. In this sensitivity analysis, two different factors were explored: methodological quality of the studies and number of ERAS items used in a study protocol. Potential publication bias was explored using a funnel plot and Egger's test for risk of bias²².

RESULTS

Selected articles and characteristics

The results of the literature search and study selection are summarized in Figure 2.1. No randomized, controlled trials were available for inclusion. Full-text versions could not be retrieved of two articles despite contact with the authors of both articles. One relevant abstract was never published as a full paper and the original data could not be obtained through the author²³.

Figure 2.1 Study selection

The author of the second article could not provide us with the original article published in *Rozhledy V Chirurgii*²⁴, but mentioned that the same data were published in German elsewhere²⁵. Subsequently, we excluded this article because not all outcome parameters were reported, there was no clear description of the pathway, and the study group was limited to 12 patients with no control group. Eight studies were finally included in this review: five comparative studies with historical controls studies, two retrospective case series, and one prospective case series. Characteristics of these seven studies are shown in Table 2.2. Five studies included only patients undergoing pancreaticoduodenectomy^{26,39-42}, one study included only patients undergoing distal pancreatectomy⁴³, and two studies included patients undergoing different forms of pancreatectomy (distal, central or total pancreatectomy, pylorus-pre-serving pancreatic head resections, segmental resections, or pancreatico-duodenectomy)^{44,45}. All studies included a consecutive series of patients with a follow-up of 30 days. The MINORS score of the comparative studies was on average 13.4, and the two retrospective case studies and one prospective case series were rated with scores of 12, 13, and 14 respectively (Table 2.2).

Six studies contained clear descriptions of an ERAS program with at least four different protocol elements. Study protocols of the two articles that did not describe the full ERAS program were retrieved from the authors. An assessment of the different protocol elements was made for each study (Supplementary Table S2.1). The number of protocol elements used in these study programs ranged from 9 to 14 with an average of 13 elements. All studies described pre-, peri-, and postoperative interventions, but study protocols differed slightly.

Primary and secondary outcome measures

Systematic review

For patients managed in an ERAS program, postoperative length of hospital stay (LOS) decreased significantly in four studies with a comparative design (Table 2.3). These studies included PDs as well as total pancreatectomies and distal pancreatectomies. Vanounou et al.²⁶ did not find a difference between the study group and the control group in LOS. Three studies reported predefined discharge criteria and data on recovery to normal function^{39,42,44}. However, only one of them reported exactly when the predefined discharge criteria were met or if there were any discrepancies between achieving functional recovery and actual discharge⁴².

A summary of total hospital costs calculated in four different studies is shown in Table 2.4^{26,40,41,43}. Three of these studies included PDs; one study included distal pancreatectomies. All studies reported a decrease in total hospital costs after implementing a clinical pathway, and this decrease was significant in the three studies focusing on PD^{26,40,41}.

Table 2.2 Study characteristics and quality assessment

Study	Type of surgery	Study design	No of patients in study/control group	Consecutive series of patients	Follow-up (days)	Mean age (years)		MINORS score
						ERAS	control	
Balzano et al. 2008 ³⁹	PPPD	Comparative study with historical controls	252/252	Yes	30	64	63	13/24
Porter et al. 2000 ⁴⁰	PD, TP	Comparative study with historical controls	80/68	Yes	30	60	62	12/24
Kennedy et al. 2009 ⁴³	DP	Comparative study with historical controls	72/40	Yes	30	63.4	53.6	11/24
Vanounou et al. 2007 ²⁶	PD/PPPD	Comparative study with historical controls	145/64	Yes	30	64 (median)	64 (median)	15/24
Kennedy et al. 2007 ⁴¹	PD	Comparative study with historical controls	91/44	Yes	30	63.9	61.3	16/24
DiSebastiano et al. 2010 ⁴⁴	PD, TP, DP	Retrospective case series	145	Yes	30	65	-	12/16
Berberat et al. 2007 ⁴⁵	DP, PD, DPPHR, TP, SP	Retrospective case series	255	Yes	30	59	-	13/16
Robertson et al. 2012 ⁴²	PD, PPPD	Prospective case series	50	Yes	30	67 (median)	-	14/16

PPPD: pyloruspreserving pancreaticoduodenectomy, PD: pancreaticoduodenectomy, TP: total pancreatic-tomy, DP: distal pancreatectomy, SP: segmental pancreatectomy, DPPHR: duodenum preserving pancreatic head resection

Three studies described adherence to protocol for different protocol elements^{39,42,45}. In most patients, the nasogastric tube could be removed on the first postoperative day. However, it had to be reinserted in 11–15% of the patients^{39,45}. Normal intake was achieved on median days 4–5, and mobilization was achieved according to protocol in approximately 70–85% of the patients^{39,42,45}. Berberat et al. also performed uni- and multivariable analysis in which early removal of intra-abdominal drains, occurrence of first stool, normal food, and complete mobilization correlated significantly with early discharge. Furthermore, other patient specific predictors of early discharge were age <60 years, low ASA score, BMI <25, and presence of benign disease. Surgical factors contributing to early discharge were short operation time, blood loss <1,000 ml,

absence of blood transfusion, and early extubation. More extensive resections (Whipple, segmental resections) were negatively correlated with early discharge⁴⁵.

Table 2.3 Postoperative outcome after implementation of a clinical pathway

Study	Type of surgery	Length of hospital stay (days; study group vs control)	Morbidity (%; study group vs control)	Mortality (%; study group vs control)	Readmissions (%; study group vs control)
Balzano et al. 2008 ³⁹	PPPD	13 (7-110) vs 15 (7-102) (p<0.001)	47.2 vs 58.7 (p=0.014)	3.6 vs 2.8 (ns)	7.1 vs 6.3 (ns)
Porter et al. 2000 ⁴⁰	PD, TP	13.5 vs 16.4 (p=0.001)	24 vs 20 (ns)	1 vs 3 (ns)	9 vs 10 (ns)
Kennedy et al. 2009 ⁴³	DP	6.7 vs 10.2 (p=0.037)	15.7 vs 37.5 (ns)	1.1 vs 2.3 (ns)	7 vs 25 (p=0.027)
Vanounou et al. 2007 ²⁶	PD/PPPD	8 vs 8 (ns)	54 vs 62 (ns)	1.4 vs 1.6 (ns)	9 vs 6 (ns)
Kennedy et al. 2007 ⁴¹	PD	7 vs 13 (p<0.0001)	37 vs 44 (ns)	1.1 vs 2.3 (ns)	7.7 vs 7 (ns)
DiSebastiano et al. 2010 ⁴⁴	PD, TP, DP	10 (6-69)	38.6	2.7	6.2
Berberat et al. 2007 ⁴⁵	DP, PD, DPPHR, TP, SP	10 (4-115)	24.7	2	3.5
Robertson et al. 2012 ⁴²	PD, PPPD	10 (8-17)	46	4	4

PPPD: pyloruspreserving pancreaticoduodenectomy, PD: pancreaticoduodenectomy, TP: total pancreatectomy, DP: distal pancreatectomy, SP: segmental pancreatectomy, DPPHR: duodenum preserving pancreatic head resection, ns: no significant differences, p<0.05 is considered significant

Table 2.4 Total hospital costs

Study	Type of surgery	No of patients in control/study group	Costs pre-pathway	Costs post-pathway	P-value
Porter et al. 2000 ⁴⁰	PD, TP	68/80	\$ 47,515	\$ 36,627	0.003
Kennedy et al. 2009 ⁴³	DP	40/72	\$ 26,393± 4719	\$ 22,806 ± 1300	ns
Vanounou et al. 2007 ²⁶	PD/PPPD	64/145	\$ 28,886	\$ 23,344	<0.001
Kennedy et al. 2007 ⁴¹	PD	44/91	\$ 240,242 ± 32,490	\$ 126,566 ± 4883	<0.001

PPPD: pyloruspreserving pancreaticoduodenectomy, PD: pancreaticoduodenectomy, TP: total pancreatectomy, DP: distal pancreatectomy, SP: segmental pancreatectomy, DPPHR: duodenum preserving pancreatic head resection, ns: no significant differences, p<0.05 is considered significant

Meta-analysis

Meta-analysis was performed on four comparative studies focusing on PD. One study reported on 148 patients of whom 12 patients underwent TP and 136 PD⁴⁰. Because we were unable to obtain specific data of only the 136 PDs, despite repeated attempts to contact the author, we decided to perform the meta-analysis with these four articles on PD, including 984 PDs in total and 12 TPs (i.e. we assumed the 12 TPs would not affect the main outcome). Meta-analysis for mortality did not show a difference between the study group and the control group [risk difference (95% confidence interval (CI) 0.2% (-1.7 to 2.1) $I^2=0\%$, $p=0.83$; Figure 2.2]. For readmission rates, meta-analysis did not show a significant difference [risk difference (95% CI) 0.8% (-2.5 to 4.1) $I^2=0\%$, $p=0.64$; Figure 2.3]. Regarding overall morbidity, there was a consistent difference in favor of the ERAS group. The reported percentage of postoperative morbidity was lower in the ERAS group [absolute risk difference (95% CI) 8.2 (2–14.5) $I^2=0\%$, $p=0.008$]. The number needed to treat (NNT) was approximately 10 (Figure 2.4).

Figure 2.2 Forest plot of comparison: Mortality

Figure 2.3 Forest plot of comparison: Readmissions

Figure 2.4 Forest plot of comparison: Morbidity

Sensitivity analysis was performed to assess impact of methodological quality and number of ERAS protocol items on outcome. The overall relative risk was 0.83 (95% CI 0.73–0.95), indicating complications were consistently lower in the ERAS groups compared with controls. This result depends mainly on the studies of good

methodological quality (MINOR score of 13 or more)^{26,39,41}, as analysis of these studies only shows a comparable relative risk of 0.82 (95% CI 0.72–0.94). Also, when excluding studies with less than 13 protocol items^{39,40}, sensitivity analysis shows a relative risk comparable to the overall relative risk 0.85 (95% CI 0.69–1.06).

To assess the presence of bias in this meta-analysis, a funnel plot was constructed. Egger et al.²⁰ proposed a test for asymmetry of the funnel plot; the trials' effect estimate is set out against its sample size. Figure 2.5 shows a symmetrical deviation of the different studies. The calculated p value is 0.27, indicating the chance of bias in this meta-analysis, including only studies focusing on PD is low.

Complication rates of pancreatic fistula and DGE after PD ranged from 2 to 26% and 7-25% respectively in the included studies. Meta-analysis of three studies focusing on PDs and reporting incidence rates of PF and DGE showed that the incidence of pancreatic fistula and DGE was not significantly different between the intervention and control groups (data not shown)³⁹⁻⁴¹.

Figure 2.5 Funnel plot of 4 studies included in the meta-analysis

DISCUSSION

This systematic review shows that perioperative management based on an ERAS program in pancreatic resection may help shorten hospital length of stay without compromising morbidity and mortality. This seemed to apply to distal pancreatectomy, total pancreatectomy, and PD. Because these procedures differ considerably as to consequences for perioperative care, meta-analysis was only performed for those studies that focused on PD, as this is the most common pancreatic resection. This meta-analysis of four studies on ERAS programs in PD showed that morbidity rates were significantly lower for patients in the ERAS study group compared with those treated in a traditional care pathway. This effect remained unaltered when studies of lower methodological quality or studies, including less than 13 elements in the ERAS protocol, were excluded. After meta-analysis, readmission rates were not significantly higher in the ERAS group. One study reported a non-significant 1% higher mortality rate in the ERAS group³⁹. Also, on meta-analysis of the four studies addressing PDs, mortality was not significantly different. This is in keeping with another meta-analysis on ERAS programs in colonic surgery in which no higher mortality was found¹⁵. Additionally, hospital costs were significantly lower in three of the four studies that reported a cost-effectiveness analysis. Unfortunately, in most studies no data on functional recovery or predefined discharge criteria were available. Accordingly, no conclusion could be drawn on the assumed positive effects of an ERAS program on functional recovery.

A previous systematic review concluded that there is little evidence to support the benefits of ERAS programs for pancreatic surgery³⁶. This review included only three studies and concluded that an ERAS program in pancreatic surgery was safe but that morbidity rates were higher in the ERAS group. However, this conclusion was not in accordance with the results presented, because the source data from the studies showed an “equal morbidity” between study and control group.

A limitation of this review is that no randomized, controlled trials were available for inclusion. Only a limited number of randomized, controlled trials have been conducted comparing ERAS programs with traditional care^{15,46}, mostly in elective colorectal surgery. No such trials have been conducted in HPB surgery. This is probably due to the fact that randomized controlled trials are difficult to organize for multimodal recovery programs under greatly varying conditions. Problems are very likely to be encountered with blinding and various interventions and professionals are involved. Several protocol elements of an ERAS program already have become standard practice in many hospitals during the last decade (e.g. thromboprophylaxis, prevention of hypothermia with Bair Huggers, early mobilization). This raises ethical concerns with respect to randomization, because patients in the control group may not receive specific evidence-based interventions.

It must be noted that the introduction of an ERAS program in the two included studies by Kennedy et al. took place after two experienced pancreatic surgeons moved in from

a different hospital. In parallel with the implementation of the ERAS program, surgical volume per month almost tripled. These facts may have contributed to improved outcome regardless of the implementation of the ERAS program.

In line with this, one could argue that any positive effects of ERAS implementation are not attributable to the ERAS program itself but to changing secular trends with respect to lowering LOS. However, a recent national implementation study in the Netherlands of colorectal surgery looking at the effects of ERAS implementation in more than 30 hospitals nationwide showed that hospital LOS decreased by 3 days in 1 year in addition to any such secular trends⁴⁷.

After a pancreaticoduodenectomy, the incidence of specific complications, such as DGE and pancreatic fistula, varies from 13 to 57%^{10,13,48,49} and from 2 to 15%, respectively^{10,13,50-52}. In the present review, the incidence of these complications tended to be lower in the ERAS group, but meta-analysis in patients undergoing pancreaticoduodenectomy did not show statistical significance.

The included studies were either retrospective or prospective case series or comparative studies based on historical controls. It is difficult to extract conclusive evidence from such studies. The use of historical controls also led to variable methodological quality of the different studies, as rated with the MINORS criteria.

Another topic of concern in the investigation of perioperative pathways is the fact that distinct studies use different study protocols incorporating a variety of elements and some protocols might include elements that are more conservative than others. For instance, postoperative feeding started from postoperative days 1–2 in some studies^{44,45}, whereas other studies started with liquid intake first with a gradual increase from clear to full liquids and solid food from days 3–4^{26,39,41-43}. Unfortunately, it is still unclear which element is most important in perioperative care in pancreatic resections and henceforth we cannot draw hard conclusions about that. However, in a recent paper a multivariable analysis of care elements influencing LOS in 2,485 patients undergoing colonic surgery⁴⁷, cessation of IV fluids, mobilization on post-operative day 1, and postoperative administration of laxatives (magnesium oxide) were associated with shortened LOS. In this way, ERAS programs may accelerate restoration of gut motility. In PD, this might help to lower the incidence of DGE, which also was shown in one of the included studies³⁹.

Most studies do not investigate adherence to the protocol, so it remains unclear what the actual clinical difference in perioperative treatment is between study and control group. Problems with protocol adherence have already been described in a large international study in ERAS colon surgery by Maessen et al.⁵³. Reporting of adherence to protocol should be a standard item in studies describing the ERAS implementation. Policies to improve postoperative protocol adherence in particular should be considered, for instance reorganization of surgical wards, continuous education of nurses and staff, and the introduction of self-reporting diaries⁵³. A study of Ahmed et al. showed that an overall protocol compliance of 77% compared with 88% compliance

in patients participating in a clinical trial does not negatively affect outcome⁵⁴. Particularly, low compliance to preoperative carbohydrate loading and early fluid and diet introduction postoperative was observed. This study shows that it is rather the combination of items that determines outcome and that a reasonable adherence is acceptable.

On a further note, the consistency between criteria defining minor and major complications after pancreatic surgery in the included studies is limited. Therefore, comparing morbidity between centers is difficult. Only one study reported complications according to a validated classification scheme (Clavien-Dindo classification), grading complications based on the use of therapeutic interventions²⁶. A suggestion would be to use a composite end point⁵⁵, which would reduce the required sample sizes for studies and would improve objectivity and comparability.

Clearly, the studies included in this review are all subject to different forms of bias and heterogeneity in study groups as well as ERAS programs. This implies that it is difficult to draw hard conclusions on the effectiveness of ERAS programs in pancreatic surgery. Therefore, the ERAS group recently conceived perioperative guidelines focused only on pancreaticoduodenectomy⁵⁶. The feasibility of implementing these guidelines will be studied in the ERAS group in a multicenter, prospective consecutive series of patients undergoing pancreaticoduodenectomy (www.erassociety.org).

In summary, although the available evidence is still limited, the present systematic review suggests that implementation of an ERAS program in pancreatic resections, particularly PD, is feasible and safe. Implementation of an ERAS program in pancreatic resections may contribute to a shorter hospital stay and does not seem to compromise outcome measures, such as morbidity, mortality, and readmissions. Future studies should report on predefined discharge criteria and time to functional recovery to assess whether actual postoperative recovery is in fact accelerated.

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CHAPTER 3

A systematic review of outcomes in patients
undergoing liver surgery in an enhanced recovery
after surgery pathway

MME Coolson, EM Wong-Lun-Hing, RM van Dam, AA van der Wilt, K Slim, K Lassen,
CHC Dejong

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ABSTRACT

Objectives

Enhanced recovery after surgery (ERAS) or fast-track protocols have been implemented in different fields of surgery to attenuate the surgical stress response and accelerate recovery. The objective of this study was to systematically review the literature on outcomes of ERAS protocols applied in liver surgery.

Methods

The MEDLINE, EMBASE, PubMed and Cochrane Library databases were searched for randomized controlled trials (RCTs), comparative studies with historical controls and case series published between January 1966 and October 2011 comparing adult patients undergoing elective liver surgery in an ERAS program with those treated in a conventional manner. The primary outcome measure was hospital length of stay (LOS). Secondary outcome measures were time to functional recovery, and complication, readmission and mortality rates.

Results

A total of 307 articles were found, six of which were included in the review. These comprised two RCTs, three comparative studies with historical controls and one retrospective case series. Median LOS ranged from 4 days in an ERAS group to 11 days in a control group. Morbidity, mortality and readmission rates did not differ significantly between the groups. Only two studies assessed time to functional recovery. Functional recovery in these studies was reached 2 days before discharge.

Conclusions

This systematic review suggests that ERAS protocols can be successfully implemented in liver surgery. Length of stay is reduced without compromising morbidity, mortality or readmission rates.

INTRODUCTION

Liver resection is the preferred treatment for a variety of primary and secondary liver tumors. Major abdominal surgical procedures such as hepatic resections cause a considerable surgical stress reaction and possible derangements in metabolic and pulmonary functions. Specific complications after hepatic resection include postoperative hemorrhage in the first hours to days after surgery, biliary leakage, intra-abdominal abscess and liver failure in a later postoperative stage¹. Improved operative techniques and insight into perioperative management have lowered mortality after liver resection to its current level of well below 5%, but morbidity rates remain high and range between 30% and 50%²⁻⁴.

In the past decade, multimodal enhanced recovery after surgery (ERAS) protocols or fast-track pathways have been applied in different forms of surgery. These pathways were developed to attenuate the surgical stress response and improve recovery, thereby decreasing postoperative complications and postoperative length of stay (LOS) in hospital⁵. ERAS protocols have gained territory quickly because of the associated cost efficiency derived from the reduction in LOS, an important issue in today's context of rapidly increasing health care costs and the consequent need for optimization. To date, studies that show ERAS protocols that reduce LOS and morbidity rates and improve patient satisfaction have been published in the contexts of vascular surgery^{6,7}, musculoskeletal surgery,⁸ breast surgery⁹ and different forms of abdominal surgery¹⁰⁻¹². Enhanced recovery after surgery protocols have also been implemented in liver surgery, but their effectiveness has not been studied extensively. The present systematic review was performed to evaluate the effects of ERAS protocols in liver surgery on time to recovery following surgery and postoperative hospital LOS, and to examine the effects of the implementation of such protocols on complication and readmission rates following liver surgery.

MATERIALS AND METHODS

Search strategy

A systematic search was performed in PubMed, the Cochrane Library, EMBASE and MEDLINE for studies published between January 1966 and October 2011. Languages were restricted to English, Dutch and German. The following search terms were applied using the Boolean operators 'AND' and 'OR': 'clinical pathway', 'critical pathway', 'enhanced recovery', 'accelerated', 'perioperative' and 'fast track', combined with 'liver', 'hepatic' and 'resection'. Synonyms of terms were also used in the search. The reference lists of selected papers were hand-searched for articles that were not

retrieved in the database search. If necessary, authors of relevant articles were contacted to obtain additional information.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they met all of the following inclusion criteria: (i) they reported on adult patients undergoing elective open or laparoscopic liver surgery; (ii) they described an enhanced recovery program with at least four different perioperative elements, and (iii) they reported outcomes including LOS, postoperative morbidity and mortality, and readmission rates. Studies were excluded if they: (i) described a single intervention in perioperative care rather than a group of interventions combined in an enhanced recovery program; (ii) reported on emergency, non-elective or transplantation surgery, and (iii) reported a non-systematic review. Table 3.1 lists a summary of ERAS items applicable to liver surgery. The items are supported by varying levels of evidence¹³. Perioperative care is considered to fall within an ERAS protocol when at least four different items are included, covering the pre-, intra- and postoperative periods¹⁴⁻¹⁵.

Table 3.1 Summary of elements in an enhanced recovery after surgery (ERAS) program applicable to liver surgery

Evidence-based factors	Probably useful factors
No oral bowel preparation	Preoperative counseling
Preoperative feeding: carbohydrate loading up to 2 h before surgery	Provision of i.v. analgesia
No pre-anesthetic medication	Stimulation of bowel movement with laxatives
Anti-thrombotic prophylaxis	Early and scheduled mobilization
Single-dose antibiotics	Audit
Epidural analgesia	
Prevention of postoperative nausea and vomiting	
Avoidance of hypothermia	
No routine drainage of peritoneal cavity	
No postoperative nasogastric intubation	
Good fluid balance	
Removal of urinary catheter on day 1	
Normal food at will after surgery from day 1	

Evidence-based factors: separate items are graded as being supported by level 1 or level 2 evidence (according to the guidelines of the Oxford Center for Evidence-Based Medicine¹³). Probably useful factors: evidence is less strong, but these factors are felt to be useful because the items are most probably quality-enhancing, are associated generally with a low incidence of adverse effects and low costs.

Outcome measures

The primary outcome measure of this systematic review was hospital LOS. Secondary outcome measures were time to functional recovery, complication rates, readmissions and mortality rates. Criteria for functional recovery were: good pain control with oral

analgesia only; tolerance for solid food; no requirement for i.v. fluids; passage of stool, and independent mobility at the preoperative level¹⁶.

Study selection and data selection

Abstracts and titles of studies identified by the search were read by two authors (MMEC and AAvdW), each of whom independently made a first selection of studies. These first selections were compared and, in the event that the inclusion of a study required discussion, a third reviewer (RMvD) was consulted. Second and final selections were made independently by each of the two authors after reading the full-text articles. Both randomized as well as non-randomized studies were eligible for inclusion as long as they met the inclusion criteria. The methodological quality of the included studies was assessed using the MINORS (*methodological index for non-randomized studies*) criteria¹⁷, a checklist scoring eight methodological items for non-comparative studies (maximum of 16 points) and an additional four items for comparative studies (maximum of 24 points). Missing data were obtained by contacting the authors of the relevant studies.

Data on the following factors were extracted from the included articles: postoperative LOS; number of patients included; patient ages; types of surgery; discharge criteria; functional recovery; mortality; morbidity; readmissions, and protocol adherence.

Statistical analysis

As the search strategy did not identify any randomized controlled trials (RCTs) evaluating the outcomes of ERAS protocols against those of traditional care, the MOOSE (*meta-analysis of observational studies in epidemiology*) checklist for meta-analysis of observational studies was used to assess the possibility of conducting a meta-analysis¹⁸. The included studies were considered to be too heterogeneous to support this and therefore no attempt at meta-analysis was made. Results are subsequently presented in tables and figures.

RESULTS

Selected articles and characteristics of the studies

The literature search produced 307 articles, of which 300 were excluded after their abstracts had been read in the first round of selection because they did not concern the evaluation of a fast-track program in liver surgery (Figure 3.1). After evaluation of the remaining seven papers, one was excluded because it was a non-systematic review¹⁹.

Figure 3.1 Study selection for systematic review

Finally, six papers were included in this systematic review. The details of the included studies are shown in Table 3.2. There were no reports of RCTs evaluating the outcomes of an ERAS program against those of traditional care. In two RCTs, both study groups were treated in an ERAS program. One of these RCTs evaluated the use of laxatives and oral nutritional supplements within an ERAS program²⁰ and one assessed different forms of postoperative analgesia in two groups managed in a fast-track program²¹. Three comparative studies with historical controls and one retrospective case series were also included^{16, 22-24}.

All studies included patients undergoing various forms of liver resection, including (extended) hemi-hepatectomy, metastasectomy, sectionectomy, central resection and repeat hepatectomy. One study did not include major hepatectomies; all patients in this study underwent laparoscopic liver resection²⁰. All studies included a consecutive series of patients. Follow-up was 30 days in four studies and 3–6 months in one study. One study did not report the duration of follow-up.

Table 3.2 Study characteristics and quality assessment

Study	Type of surgery	Study design	No of patients in study/control group, n	Consecutive series of patients	Length of follow-up	Age, years, median (range)		MINORS score
						ERAS group	Control group	
van Dam et al. 2008 ¹⁶	HE, EHE, ME, SE, CR, RHE	Comparative study with historical controls	61/100	Yes	30 days	62 (24-82)	60 (20-81)	18/24
Lin et al. 2000 ²²	SE, HE, EHE, CR	Comparative study with historical controls	56/61	Yes	30 days	57 (23-73)	55 (22-81)	17/24
Stoot et al. 2009 ²³	Laparoscopic: ME, SE, LLS	Comparative study with historical controls	13/13	Yes	3-6 months	55 (34-82)	45 (26-70)	19/24
Hendry et al. 2010 ²⁰	HE, ME, SE, CR	RCT	68 ^a	Yes	30 days	62 (53-69)	-	13/16
Koea et al. 2009 ²¹	HE, EHE, ME, SE	RCT	100 ^a	Yes	30 days	60 (23-83)	-	11/16
Mackay & O'Dwyer 2008 ²⁴	HE, SE	Retrospective case series	12	Yes	Unknown	60 (43-74)	-	9/16

^a Patients in the control and experimental arms were all treated according to ERAS protocols. ERAS, enhanced recovery after surgery; HE, hemi-hepatectomy; EHE, extended hemi-hepatectomy; ME, metastatectomy; SE, segmentectomy; CR, central resection; RHE, repeat hemo-hepatectomy; LLS, left lateral sectionectomy; RCT, randomized controlled trial

Age and other patient characteristics did not differ significantly among the patient groups described in the selected studies. Methodological quality assessed using the MINORS criteria was scored in the range of 17–19 points (of a maximum of 24 points) in comparative studies. Non-comparative studies achieved MINORS scores in the range of 8–13 points (of a maximum of 16 points).

Most studies described the enhanced recovery program in detail. A summary of the specific ERAS elements included in the different studies is shown in Table 3.3. Fourteen protocol elements were identified. Most studies included the majority of these elements; one study included only seven elements.

Primary and secondary outcome measures

Table 3.4 outlines postoperative outcomes after implementation of an ERAS program. Hospital LOS decreased significantly in the three comparative studies after ERAS implementation, in which median LOS was 5–7 days in the ERAS groups and 7–11 days in the traditional care groups.

Table 3.3 Summary of elements in an enhanced recovery after surgery (ERAS) programme included in each study

Study	Preoperative				Perioperative				Postoperative					
	Counselling	Feeding	No pre-med	Thromboembolic prophylaxis	No bowel prep	No drain	Epidural analgesia	Fluid restriction	Prevention of hypothermia	No NG tube	Early oral Feeding (from PoD 1)	Mobilization from PoD 1	Laxatives	Early removal of bladder catheter
van Dam <i>et al.</i> ¹⁶ 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin <i>et al.</i> ²² 2011	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes	Yes		Yes
Stoot <i>et al.</i> ²³ 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hendry <i>et al.</i> ²⁰ 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Koea <i>et al.</i> ²¹ 2009		Yes	Yes	Yes		Yes	Yes	Yes		Yes	Yes	Yes		Yes
Mackay & O'Dwyer ²⁴ 2008	Yes	Yes				Yes		Yes			Yes	Yes		Yes

PoD, postoperative day

Table 3.4 Postoperative outcome after implementation of a clinical pathway

Study	Type of surgery	Hospital LoS, days, study group versus control group	Morbidity, %, study group versus control group	Mortality, %, study group versus control group	Readmissions, %, study group versus control group
van Dam <i>et al.</i> 2008 ¹⁶	HE, EHE, ME, SE, CR, RHE	6 versus 8 (P=0.001)	41 versus 31 (NS)	0 versus 2 (NS)	13 versus 10 (NS)
Lin <i>et al.</i> 2011 ²²	SE, HE, EHE, CR	7 versus 11 (P=0.001)	46.4 versus 43.3 (NS)	1.8 versus 1.6 (NS)	7.1 versus 3.3 (NS)
Stoot <i>et al.</i> 2009 ²³	Laparoscopic: ME, SE, LLS	5 versus 7 (NS)	15.3 versus 15.3 (NS)	0 versus 0 (NS)	0 versus 0 (NS)
		Functional recovery: 3 versus 5 (P=0.04)			
Hendry <i>et al.</i> 2010 ²⁰	HE, ME, SE, CR	6	17	2	5
		Functional recovery: 4			
Koea <i>et al.</i> 2009 ²¹	HE, EHE, ME, SE	4.7±0.9 (intrathecal morphine) 6.8±1.2 (epidural)	19	0	4
Mackay & O'Dwyer 2008 ²⁴	HE, SE	4 (2-7)	16.6	0	0

LoS, length of stay; HE, hemi-hepatectomy; EHE; extended hemi-hepatectomy; ME, metastasectomy; SE, segmentectomy; CR, central resection; RHE; repeat hemi-hepatectomy; LLS; left lateral sectionectomy; NS, not significant

Table 3.5 Adherence to an enhanced recovery after surgery (ERAS) protocol

Protocol element	van Dam <i>et al.</i> 2008 ¹⁶ (ERAS vs. control)	Lin <i>et al.</i> 2011 ²² (ERAS vs. control)	Stoot <i>et al.</i> 2009 ²³ (ERAS vs. control)	Koea <i>et al.</i> 2009 ²¹ (ERAS, n=100)	Hendry <i>et al.</i> 2010 ²⁰ (ERAS, n=68)	Mackay & O'Dwyer 2008 ²⁴ (ERAS, n=12)
No NG tube or removed directly after surgery	92% vs. 0%	NA	0% vs. 38%	100%	100%	NA
NG tube reinserted	4% versus 0%	3.5% vs. 1.6%	0% vs. 15%	NA	NA	NA
Intra-abdominal drain	2% versus 66%	0% vs. 1.6%	0% vs. 46%	2%	13%	0%
Oral fluid intake PoD 0 (EAS), % or days, median (range)	92%	NA	1 (0-2) vs. 1 (0-6)	NA	94%	100%
Resumption of normal food, % or days, median (range)	1 (0-3) vs. 3 (0-14)	NA	1 (0-2) vs. 1 (0-6)	20% on day 1	37% on day 1	NA
Full mobilization (ERAS)	85% on day 3	NA	NA	20% on day 1	91% on day 2	NA
Functional recovery criteria met on day	NA	NA	3 vs. 5	NA	28% on day 1	NA
				4		NA

NG, nasogastric; PoD, postoperative day; NA, data not available; vs., versus

In the non-comparative studies, postoperative LOS after liver resection ranged between 4 days and 7 days. In the study by Stoot et al.²¹, all patients underwent laparoscopic liver resection. The median postoperative LOS was 5 days in the ERAS group and 7 days in the traditional care group; however, this difference was not statistically significant and the study did not include major liver resections. It is noteworthy that only two studies^{17,20} assessed time to functional recovery and the reasons for delayed discharge. In both studies time to functional recovery was achieved 2 days prior to actual discharge from hospital. The main reasons for later discharge were concern for complications or extensive surgery, low patient confidence, and transport-related or other social problems.

Table 3.5 shows the extent of protocol adherence. The level of adherence to protocol was moderate in the studies included. Generally, nasogastric tubes were either not used or were immediately removed after surgery. The proportion of patients requiring the reinsertion of a nasogastric tube was low. In the study groups, intra-abdominal drains were used in only 2–13% of patients. The majority of patients resumed oral fluid intake on the day of surgery and achieved a normal diet on days 1 or 2. The percentage of patients mobilized on the first postoperative day was low, with rates of 20–28% reported in only two studies²⁰⁻²¹. In one study full mobilization was achieved on day 3 by 85% of patients¹⁶.

DISCUSSION

This systematic review examined the use of ERAS protocols in liver surgery in three comparative studies with historical controls, two RCTs and one case series. The results suggest that an enhanced recovery protocol can be successfully implemented in liver surgery. Hospital LOS was reduced and functional recovery was accelerated without compromising morbidity or mortality rates, and readmission rates were not significantly increased. The present results are in line with a recent review describing the use of fast-track protocols in hepato-pancreatic resections²⁵.

At least four items in the pre-, peri- and postoperative periods must be included in an ERAS protocol for the protocol to be considered of value^{14,15}. The studies in this review incorporated an average of 12 of 14 items (range: 7–14 items). In large series of patients undergoing liver surgery, LOS varies between 8 days and 14 days.^{3,4} All of the studies included in this review reported a shorter LOS in the ERAS study group. Two studies assessed time to functional recovery, which was significantly lower than total LOS. In many studies, LOS is reported as a primary outcome parameter. However, the use of this outcome may not always be appropriate as discharge is often delayed by a variety of other factors that may be unrelated to the true outcomes of the procedure²⁶. The present authors therefore propose that time to functional recovery should be used as an outcome measure rather than LOS.

Morbidity rates reported in the literature vary from 38% to 45%^{4,27} and are comparable with the complication rates reported in the studies in the present review. However, it should be noted that complications in the studies included here were not always reported using a validated classification system (e.g. Dindo-Clavien or Accordion classification^{28,29}). This makes it more difficult to make meaningful comparisons of morbidity among the different centers.

The reporting of adherence to the various elements of the protocol was rather low in the included studies, especially as far as the introduction of normal diet and fluids was concerned. As Maessen et al.³⁰ have observed, the reporting of adherence to protocol seems to be problematic in a considerable number of international studies. This impedes comparisons among studies³⁰. The use of self-report patient diaries and continuous education of nurses and staff may represent strategies for overcoming this difficulty.

Overall, the methodological quality of the studies included in the present review, as assessed according to the MINORs criteria, was acceptable. However, this systematic review is limited by the fact that no RCTs comparing fast-track with standard care were available for inclusion (the RCTs included treated both the patient and control groups according to an ERAS protocol) and only case series and comparative studies using historical controls were included. The studies included were considered to be too heterogeneous to allow a meta-analysis. Another limitation of this review is that the individual studies used slightly different study protocols, with the result that the items incorporated in the various protocols are not identical and thus these studies are not fully comparable. However, a recent study by Ahmed et al.³¹ compared adherence to protocol in two groups of patients undergoing colorectal surgery and showed that outcome was unaltered in the study group in which adherence to some elements of the study protocol (e.g. preoperative carbohydrate loading and early fluid and diet introduction) was significantly lower. From this, it seems reasonable to conclude that not every item of an ERAS protocol makes an independent contribution to enhanced recovery, but, rather, it is the combination of different items in a structured care pathway that determines the outcome. This might also to some degree reflect a Hawthorne, or trial, effect, indicating a positive effect resulting from the implementation *per se* of a complex and comprehensive intervention.

Kehlet first introduced ERAS protocols in colon surgery in 1997³². Now, 15 years later, several items drawn from ERAS protocols are increasingly implemented in modern care worldwide. However, in many surgical fields, ERAS protocols have not yet been accepted as standard care. In the context of liver surgery, ERAS was first described in 2008²⁴, since when only five studies examining an ERAS protocol in this field have been published^{16,20-23} and three of these were performed by the same study group^{16,21,23}. This seems to illustrate a limited international implementation of ERAS protocols in liver surgery.

Although the methodology used in the studies included is not optimal, the results are consistent and seem to indicate clear advantages in terms of recovery. Although most centers today perform a proportion of resections laparoscopically, the present results serve to illustrate what can be achieved in open surgery and hence serve as a backdrop against which advances in technique and subsequent results can be compared.

In summary, this systematic review shows that it is feasible and safe to implement an ERAS protocol in hepatic surgery. The available evidence suggests that LOS is shortened without comprising morbidity, mortality or readmission rates. In view of the limited number of studies and the discrepancies in reporting among them, the present authors recommend the application of a standardized system of classifying complications, the accurate reporting of adherence to protocol, and the use of time to functional recovery as a primary outcome measure in future studies in order to enhance quality and comparability.

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CHAPTER 4

To drain or not to drain: a cumulative meta-analysis
of the use of routine abdominal drains after
pancreatic resection

AA van der Wilt, MME Coolen, IHJT de Hingh, GJ van der Wilt, H Groenewoud,
CHC Dejong, RM van Dam

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ABSTRACT

Background

To warrant the adoption or rejection of health care interventions in daily practice, it is important to establish the point at which the available evidence is considered sufficiently conclusive. This process must avoid bias resulting from multiple testing and take account of heterogeneity across studies. The present paper addresses the issue of whether the available evidence may be considered sufficiently conclusive to continue or discontinue the current practice of post-operative abdominal drainage after pancreatic resection.

Methods

A systematic review was conducted of randomized and non-randomized studies comparing outcomes after routine intra-abdominal drainage with those after no drainage after pancreatic resection. Studies were retrieved from the PubMed, Cochrane Central Trial Register and EMBASE databases and meta-analyzed cumulatively, adjusting for multiple testing and heterogeneity using the iterated logarithm method.

Results

Three reports, describing, respectively, one randomized and two non-randomized studies with a comparative design, met the inclusion criteria predefined for primary studies reporting on drain management and complications after pancreatic resection. These studies included 89, 179 and 226 patients, respectively. The absolute differences in rates of postoperative complications in these studies were -6.4%, -9.5% and -6.3%, respectively, in favor of the no-drain groups. The cumulative risk difference in major complications, adjusted for multiple testing and heterogeneity, was -7.8%, with a 95% confidence interval of -20.2% to 4.7% ($P=0.214$).

Conclusions

The routine use of abdominal drains after pancreatic resection may result in a higher risk for major complications, but the evidence is inconclusive.

INTRODUCTION

For several decades, the routine use of postoperative abdominal drains has been standard practice in abdominal surgery. The main rationale for this practice is the prevention of fluid collections in the abdomen and the detection of postoperative bleeding or anastomotic leakage¹. However, the routine use of postoperative drains in abdominal surgery can itself provoke complications. These include hemorrhage, inflammation, retrograde bacterial migration, drain occlusion or loss, pain, and loss of fluids and electrolytes². All such complications may delay recovery and prolong hospital stay. The standard use of drains is also interfering with attempts to accelerate recovery through enhanced recovery after surgery (ERAS) programs^{3,4}. Therefore, it is no longer self-evident that the benefits of the routine use of postoperative drains after abdominal surgery outweigh the associated risks.

Pancreatic resection may represent a special case in this respect because a postoperative leakage of the pancreaticojejunostomy is generally considered to pose an extra risk to the patient's recovery and health as a result of the autolytic properties of pancreatic juices⁵. However, as long ago as 1992, Jeekel questioned the routine use of postoperative drainage after pancreatic resection⁶. Since then, several randomized and non-randomized studies have addressed the subject.

As evidence on the safety and effectiveness of health care interventions accrues over time, a crucially important challenge is to decide when the evidence that has amassed on the benefit or harm of an intervention is clinically and statistically sufficient to warrant its adoption or rejection in clinical practice. For this purpose, the method of cumulative meta-analysis has been developed^{7,8}. In the present study, this method was used to assess whether there is currently sufficient evidence to omit post-operative drainage after pancreatic resection without undue complications.

MATERIALS AND METHODS

Literature search

A search of the PubMed, EMBASE and Cochrane Central Trial Register databases was performed to identify studies on routine peripancreatic drainage after pancreaticoduodenectomy (PD). Search terms included 'drainage', 'drain*', 'suction', 'pancreatectomy', 'pancreatic resection', 'pancreaticoduodenectomy', 'pancreat*', 'postoperative complications', 'complication*', 'fistula' and 'abscess'. The full search strategy is shown in Appendix S1.

Study selection and data extraction

Eligible studies were assessed on predefined inclusion criteria. In order to be considered as eligible, studies were required to: (i) report primary data; (ii) include a study population consisting of patients with suspected or histologically proven pancreatic or periampullary malignancy; (iii) include a population of patients undergoing pancreatic resection, including PD or distal resection, and (iv) compare routine peripancreatic postoperative drainage with no drainage. To make optimal use of the available evidence, randomized as well as non-randomized studies, conducted prospectively as well as retrospectively, were included taking into account any heterogeneity in the analysis.

Two reviewers independently assessed all titles and abstracts for inclusion. Disagreements were resolved by discussion. Full texts of studies eligible for inclusion were retrieved. The following data were extracted from the included studies: study design; inclusion and exclusion criteria; population size; baseline characteristics; duration of follow-up; statistical analysis; details of surgery and postoperative care, and outcome data. The methodological quality of studies was assessed using the MINORS (methodological index for *non*-randomized studies) score⁹. This score has been found to be a valid and reliable measure of the methodological quality of surgical trials and can be used for both randomized and non-randomized studies. It rates the appropriateness of enrolment of patients, endpoints and their mode of assessment, follow-up, control group, and statistical analysis, as well as comparability at baseline.

Cumulative meta-analysis

The primary outcome of this analysis was risk for major postoperative complications. Major complications were defined as postoperative complications severe enough to result in radiologic, endoscopic or surgical intervention. Secondary outcome parameters were mortality rate and hospital length of stay (LOS). When necessary, authors were contacted and asked to provide details on the definition of endpoints. Quantitative data were entered into a database using the statistical software package StatsDirect¹⁰. For each study included, a 2 x 2 table was constructed to show the number of events (major complications) and non-events in the treatment (drain) and control (no-drain) groups. Risk differences and associated cumulative Z-scores were calculated, both unadjusted and adjusted, using the iterated logarithm method described by Hu et al.¹¹. A random-effects model was used, with total variance consisting of within- and between-study variance. To control for type I error, an adjustment factor (I) of 1.5 was used, as recommended by Hu et al.¹¹.

RESULTS

Studies included and their characteristics

The search produced 206 hits in PubMed (1969 to August 2011). The 21 and 55 publications retrieved from the Cochrane Trial Register and EMBASE, respectively, did not identify further eligible studies (Figure 4.1). Three studies including a total of 494 patients met the predefined selection criteria.¹²⁻¹⁴ Characteristics of these studies are summarized in Table 4.1.

Figure 4.1 Flow-chart, showing number of studies retrieved from the literature databases and selection of studies on the basis of inclusion- and exclusion criteria

The study by Heslin et al.¹⁴ was a retrospective review of records of patients who underwent PD, with only little variation in surgery, including Roux-en-Y reconstruction and pylorus-preserving procedures. Patients in the drain group routinely received peripancreatic closed suction drains postoperatively. A total of 38 patients were not given drains; in 51 patients, closed suction drains were placed at the end of the procedure. Over 80% of the patients included had malignant disease. On histologic diagnosis, adenocarcinoma was found to be most prevalent. Locations of the tumor were the pancreas head (74%), ampulla of Vater (13%), duodenum (5%) and distal common bile duct (10%). Major complications were defined as death, reoperation, significant pancreatic leak, fascia dehiscence, re-intubation, pneumonia and intra-abdominal abscess. Major complications occurred in 27% [95% confidence interval (CI) 16–42%] of the drain group and 21% (95% CI 10–37%) of the no-drain group. Mean LOS was 12 days in both groups. Outcome measures are summarized in Table 4.2.

Table 4.1 Summary of key characteristics of included studies

Characteristics	Heslin et al, 1998	Conlon et al, 2001	Fisher et al, 2011
Country, time period when study was conducted	US, 1994 – 1996	US; time period when study was conducted not reported	US, 2004 – 2009 (drain group) and 2009 – 2010 (no drain group)
Design of study	Retrospective record review	Randomized Controlled Trial with two parallel groups	Prospective recording of data that were retrospectively reviewed
Patient population	Pancreaticoduodenectomy for presumed or histologically proven periampullary malignancy PD/ PPPD (n = 89)	Adult, peri-pancreatic tumor, considered for surgical resection	Consecutive patients undergoing pancreatic resection
Type of surgery		PD (n = 133), PPPD (n = 6), DP (n = 40)	Pancreaticoduodenectomy (n=153), distal pancreatectomy (n=73)
Drain vs. no drain	51 vs. 38	88 vs. 91	179 vs. 47
Follow-up period	Not reported	3 months	30 days
Primary and secondary end-points	Postoperative complications; operating room characteristics (duration of surgery, time in the operating room, blood loss, need for blood transfusion); pathology (presence of malignancy, presence of nodal metastasis, presence of positive margin)	Incidence of postoperative complications; mortality, re-intervention, hospital stay	Anastomotic failure, percutaneous abdominal drainage, delayed gastric emptying, infectious complications and organ failure, cardiovascular complications, length of stay, operative mortality.
Age drain vs. no drain	65 ± 2 vs. 65 ± 2 (mean and SEM)	69 (33 – 87) vs. 66 (23 – 81) (Median, range)	63 (53 – 72) vs. 59 (51 – 70) (Median, interquartile range)
MINORS score	12/24	16/24	15/24

SEM = Standard Error of the Mean

Table 4.2 Summary of outcomes of included studies

Outcome (No Drain vs. Drain)	Heslin et al, 1998	Conlon et al, 2001	Fisher et al, 2011
Operative mortality (% 95% CI)	Not reported	2% (0-8) vs. 2% (0-8)	2% (0-11) vs. 1% (0-3)
Major complications (% 95% CI)	21% (10-37) vs. 27% (16-42) ^a	12% (6-21) vs. 22% (14-32) ^b	15% (6-28) vs. 21% (15-28) ^c
Minor complications (% 95% CI)	24% (11-40) vs. 25% (14-40)	Not reported as separate category	11% (4-23) vs. 8% (4-13) ^d
Fistula (% 95% CI)	3% (0-14) vs. 6% (1-16)	0% (0-4) vs. 17% (10-27) ^e	11% (4-23) vs. 12% (7-17) ^f
Intra-abdominal abscess (% 95% CI)	0% (0-9) vs. 6% (1-16)	7% (2-14) vs. 7% (3-14)	4% (1-15) vs. 6% (3-10)
Intra-abdominal collection (% 95% CI)	Not reported	2% (0-8) vs. 7% (3-14)	Not reported
Reoperation (% 95% CI)	8% (2-21) vs. 2% (0-10)	4% (1-11) vs. 9% (4-17)	0% (0-8) vs. 4% (2-9)
CT-guided drainage (% 95% CI)	3% (0-14) vs. 4% (0-14)	8% (3-15) vs. 13% (6-21)	11% (4-23) vs. 2% (1-6)
Length of hospital stay (days)	12 ± 1 vs. 12 ± 1	9 vs. 9 (median)	7 (6-8) vs. 7 (7-10)
Readmission	Not reported	Not reported	17% (8-31) vs. 9% (6-15)

^a Definition of major complication: death, reoperation, significant leak/fistula, fascial dehiscence, re-intubation, pneumonia, intra-abdominal abscess, myocardial infarction, pulmonary embolus, cerebrovascular accident, multisystem organ failure (pers. comm., Dr. Heslin); ^b Complications requiring return to operating room or interventional radiology; ^c Grade 3 or higher, CTCAE classification; ^d Grade 1 or 2, CTCAE classification; ^e Includes enterocutaneous fistula and pancreatic fistula; ^f Clinically significant, Grade B or C, ISGPF classification

The study by Conlon et al.¹² was a randomized controlled trial (RCT). It included a total of 179 patients with peripancreatic tumors who were considered for surgical treatment and randomized to receive no drain ($n=91$) or a closed suction drain ($n=88$) placed at the end of the procedure. A total of 78% of the procedures were PDs and 22% were distal pancreatectomies (DPs). Because the authors did not classify the severity of complications, complications requiring interventional radiologic procedures or a return to the operating room were rated as major complications. Such complications were reported in 22% (95% CI 14-32%) of patients in the drain group and 12% (95% CI 6-21%) of those in the no-drain group. Mortality within 30 days after surgery was 2% in both groups. Hospital LOS did not differ between the two groups; overall median LOS was 9 days (range: 5-11 days). Twenty-nine patients were readmitted to hospital. Of these readmissions, 19 occurred in the drain group and 10 in the no-drain group ($P=0.07$). The median duration of readmission was significantly longer in the patients in the drain group (10 days versus 5 days; $P<0.05$).

Fisher et al.¹³ prospectively collected data for a total of 226 patients including 179 in whom postoperative drains were routinely placed after pancreatic resection (2004-2009) and 47 in whom no postoperative drains were placed after pancreatic resection (2009-2010). In this study, the Common Terminology Criteria for Adverse Events (CTCAE) index¹⁵ was used to record complications; events of grade 3 or greater were considered as major complications. Major complications occurred in 21% (95% CI 15-28%) of patients in the drain group and 15% (95% CI 6-28%) of patients without drains ($P=0.3$). No differences in median hospital stay (7 days) were observed between the two cohorts. The readmission rate was significantly higher in the no-drain cohort (17% versus 9%; $P=0.007$). Of eight patients in the no-drain cohort who required readmission, five underwent percutaneous drainage for pancreatic fistula and the other three required observation only.

Cumulative meta-analysis

The results of the meta-analysis are presented in Table 4.3 and Figures 4.2 and 4.3. The proportions of patients with major postoperative complications were consistently lower in the no-drain groups compared with the drain groups. The differences in risk for major complications in the three studies¹²⁻¹⁴ were -6.4% (95% CI -33.9% to 21.1%), -9.5% (95% CI -24.2% to 6.9%) and -6.3% (95% CI -20.2% to 4.7%), respectively. However, in none of the studies did this difference reach statistical significance. The unadjusted cumulative Z-score of the three studies¹²⁻¹⁴ was -2.13, just crossing the critical value of -1.96, which suggests that statistical significance was reached when the data from the study by Fisher et al.¹³ were combined with the data from the previous two studies¹²⁻¹⁴. However, after adjustment for multiple testing and heterogeneity using the iterated logarithm method, the cumulative Z-score was -1.24, indicating that the difference had not reached statistical significance. The adjusted cumulative difference in risk for major complications for the three studies¹²⁻¹⁴ was -7.8%, with a

95% CI of -20.2% (favoring no drainage) to 4.7% (favoring drainage).

Meta-analysis of the secondary endpoints (mortality and LOS) proved to be impossible because the requisite data on variance could not be extracted from the original studies¹²⁻¹⁴ nor obtained from the authors.

Table 4.3 Difference in risk of major postoperative complications, in patients who had not routinely placed postoperative drains after pancreatic resection, as compared to patients who had such drains placed routinely. Individual Z-statistics and cumulative Z-statistics, unadjusted and adjusted for multiple testing and heterogeneity across studies

Study	Risk difference	Z-statistic for each individual study	Cumulative Z-statistic, unadjusted	Cumulative Z-statistic adjusted (LIL-based) (Random effect model)
Heslin 1998	-0.064	-0.703	-0.703	-0.653
Conlon 2001	-0.095	-1.709	-1.889	-1.180
Fisher 2011	-0.063	-1.051	-2.128	-1.240

LIL = Law of Iterated Logarithm

Figure 4.2 Cumulative random effects meta-analysis using LIL of 3 studies of routine postoperative drainage after pancreatic resection. Risk differences and 95% confidence intervals. LIL = Law of Iterated Logarithm

Figure 4.3 Cumulative meta-analysis of routine postoperative drainage after pancreatic resection. Cumulative Z-statistic for effect of omitting drainage on major postoperative complications. Traditional cumulative Z-statistic and Z-statistic adjusted for multiple testing and heterogeneity. LIL = Law of Iterated Logarithm

DISCUSSION

There is a persuasive logic to the practice of routine drainage after pancreatic surgery because drainage is assumed to allow for the early identification and monitoring of fluid collections and subsequently to prevent their negative impact on the patient's recovery. It seems, however, that the available evidence does not support this practice. In this study, a traditional meta-analysis of the available evidence pointed to a significantly lower complication rate in the group without routine drainage. However, when a cumulative meta-analysis was performed with adjustment for repeated testing and heterogeneity, this difference was no longer statistically significant.

It is important to establish when the available evidence may be considered sufficiently conclusive to warrant the use of a particular intervention in daily practice. In this process, care should be taken to avoid bias resulting from multiple testing and heterogeneity across studies should be taken into account. Several methods have been developed to address this issue. Pogue and Yusuf¹⁶ proposed the alpha-spending approach for controlling type I error in cumulative meta-analysis. However, this approach is a closed sequential process, requiring the pre-specification of the final sample size, which is usually unknown¹¹. The approach used in this study was recently developed by Hu et al.¹¹.

The method proposed by Hu et al.¹¹ accounts for multiple testing and for heterogeneity across studies in a cumulative meta- analysis of trials with a binary endpoint. This method typically involves the performance of an updated meta-analysis every time that new evidence becomes available. Two challenges are encountered when using this method. Firstly, the procedure suffers from the problem of repeated testing and the associated inflated overall type I error (the unjustified acceptance of evidence of benefit or harm)¹⁷. Secondly, because data may be pooled from studies that are spread over a prolonged period of time, medical technology, supportive care and patient populations may differ across studies, introducing substantial heterogeneity. The method, based on the law of Z-statistics, is an open and therefore more flexible approach towards controlling for type I error compared with those mentioned earlier. Moreover, it allows for reliable estimation of the between-study variance component, which is challenging, especially in a context in which the number of studies is small¹¹.

In the studies¹²⁻¹⁴ included in the present analysis, substantial heterogeneity was found. This related to research design, definitions of endpoints, patient populations, types of interventions and supportive care. In particular, the definition of what constitutes a major complication differed among the studies, none of which used a standardized scale such as the Dindo-Clavien system of classification. An attempt was made to pool the different results as adequately as possible by comparing the different scoring systems. Such heterogeneity is likely to represent the rule rather than the exception, and therefore should be taken into account in any analysis in which studies are combined to make optimal use of the available evidence.

With respect to postoperative drains, several studies on other types of surgery, such as colon and liver surgery, have shown that the use of abdominal drains is not beneficial in terms of postoperative outcome and may even be harmful¹⁸. Pancreaticoduodenectomy is technically one of the most challenging surgical procedures and is associated with potential anastomotic break- down attributable to the activity of pancreatic enzymes; probably in response to this, surgeons tend to favor the conventional placement of abdominal drains. In order to avoid the risk for retrograde infection but to preserve the diagnostic safety drains are alleged to provide, some surgeons choose to place drains after every pancreatic resection and remove them after a short period of time. Kawai et al.¹⁹ assessed 104 consecutive patients undergoing pancreatic head resection and came to the conclusion that removing the drain on postoperative day 4 rather than day 8 reduced the incidence of complications. A soft pancreas is thought to result in a higher incidence of complications and therefore Kawai et al.¹⁹ also evaluated the impact of this clinical variable; however, the difference between groups in postoperative complication rates was not statistically significant. Bassi et al.²⁰ assessed 114 patients with a low prior probability of pancreatic fistula, including only patients with drain amylase levels of ≤ 5000 U/l. They concluded that the drain could safely be removed on postoperative day 3. Moreover, delayed removal of the drains (after postoperative day 5) led to a higher complication rate and increased

hospital LOS and costs. Therefore, if abdominal drains are placed, it seems that their removal within a short period of time is justified.

It is important to note that two^{12,14} of the three studies^{12,14} included in this review included patients undergoing DP as well as those scheduled for PD among their study samples (113 of 494 patients, 22%). Heslin et al.¹⁴ did not report the exact numbers of patients undergoing each type of resection. In the study by Conlon et al.¹² patients in the DP group were more likely to be allocated to the no-drain group than those in the PD group (DP group: drain group, $n=15$ versus no-drain group, $n=25$; PD group, drain group, $n=73$ versus no-drain group, $n=66$). In the study by Fisher et al.¹³, both PD and DP patients were equally divided between the drain and no-drain groups. Nonetheless, this potentially increases complication rates and makes adequate comparison more difficult because leak rates after DP have been reported to be 22%, whereas leak rates after PD have been reported to be 11%^{21,22}.

The reluctance of surgeons to abandon abdominal drainage is understandable given the well-known detrimental effects of leakage of the pancreatojejunostomy and the absence of sufficiently powered, high-level evidence on prophylactic drainage after pancreatic resection. However, the development of less invasive radiologic intervention techniques benefits the treatment of post-operative complications such as intra-abdominal abscesses²³. This may contribute to a reduction in surgeon anxiety in relation to the development of severe complications and eventually to the willingness to abandon abdominal drainage after pancreatic resection.

A recently published overview of the available evidence for the use of abdominal drains after pancreatic resection adopted a slightly different approach, using a standard Mantel-Haenszel random-effects model and separate evaluations of overall and specific complications, respectively²⁴. It was concluded that more evidence is required before any firm conclusions on the use of abdominal drains can be reached, which is in line with the present findings. This overview²⁴ also included studies comparing the early and late removal of abdominal drains, which resulted in the inclusion of a higher number of studies. However, the study by Fisher et al.¹³ had not been published at the time this earlier analysis²⁴ was conducted and as a consequence its results were not included in the analysis. Moreover, Diener et al.²⁴ did not correct for heterogeneity and multiple testing and thus their results should be interpreted with great caution. Unfortunately, studies suitable for meta-analysis remain scarce and this affects the results of the present study to a similar extent as it has previous meta-analyses. Moreover, two of the studies^{12,14} included in the present analysis were conducted at the same center in different timeframes, which may have introduced bias to the present study. Nonetheless, both of these studies (randomized and non-randomized) were included in order to facilitate the pooling of data for as many patients as possible. In addition, in the current analysis, MINORS scores were used to rate the studies for quality. These scores provided evidence that the non-randomized studies included in the present analysis were of sufficient quality. It is of interest that the results of the

non-randomized studies do not differ substantially from those of the RCT, which suggests that non-randomization did not introduce significant bias in the case of these two studies.

In conclusion, the current study shows the importance of taking into account multiple testing and heterogeneity within and between studies when conducting a meta-analysis. Without adjustment for the latter, the currently available evidence might be taken to imply that omitting drainage after pancreatic surgery leads to a statistically significant decrease in the risk for major complications. However, that conclusion is premature, as can be inferred from the present results when multiple testing and heterogeneity are taken into account. At present, an international, multicenter RCT intended to establish whether or not the prophylactic use of abdominal drains after PD can be abandoned is in preparation in the Netherlands. Until the results of such a trial become available, drain policy will depend on the surgeon's judgment. The available evidence suggests that it is reasonable to adopt a no-drain policy because not using a drain does not seem to increase postoperative complications.

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CHAPTER 5

Development of a composite endpoint for
randomized controlled trials in
pancreaticoduodenectomy

MME Coolsen, SHEMA Clermonts, RM van Dam, B Winkens, M Malagó, GK Fusai,
CHC Dejong, SWM Olde Damink

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ABSTRACT

Background

Few randomized controlled trials (RCTs) have been performed in patients undergoing pancreaticoduodenectomy (PD). An important factor contributing to this is the large number of patients needed to adequately power RCTs for relevant clinical single endpoints. A PD-specific composite endpoint (CEP) could solve this problem. The aim of the present study was to develop a PD-specific CEP, consisting of complications related to PD, allowing reduction in sample sizes and improving the ability to compare outcomes.

Methods

PD-specific CEP components were selected after a systematic review of the literature and consensus between 25 international pancreatic surgeons. Ultimately, prospective cohorts of patients who underwent PD in two high-volume HPB centers (London, UK, and Maastricht, NL) were used to assess the event rate and effect of implementing a PD-specific CEP.

Results

From a total of 18 single-component endpoints, intra-abdominal abscess, sepsis, post-PD hemorrhage, bile leakage, gastrojejunostomy leakage, leakage of the pancreatic anastomosis, delayed gastric emptying, and operative mortality within 90 days were selected to be included the PD-specific CEP. All eight components had consensus definitions and a Dindo–Clavien classification of 3 or more. The incidence of the PD-specific CEP was 24.7% in the Maastricht cohort and 23.3% in the London cohort. These incidence rates led to a twofold reduction in the theoretical calculated sample size for an adequately powered RCT on PD using this CEP as a primary endpoint.

Conclusion

The proposed PD-specific CEP enables clinical investigators to adequately power RCTs on PD and increases the feasibility, comparability, and utility in meta-analysis.

INTRODUCTION

In modern medicine, clinicians are obliged to practice evidence-based medicine. Meta-analyses and randomized controlled trials (RCTs) deliver the highest level of evidence regarding current practice. Conclusions of meta-analyses and large RCTs are incorporated in the latest guidelines and help to optimize care and outcome in surgical practice. In the field of pancreatic surgery, however, very few RCTs have been performed^{1,2}. Pancreaticoduodenectomy (PD) is the standard surgical procedure for patients with malignant and benign diseases of the pancreatic head and the periampullary region. With improved surgical techniques and perioperative management methods, PD has become increasingly safe. Mortality rates are relatively low (<5% in large series), and morbidity is in the range of 35–50%^{3,4}. Centralization of PDs in high-volume centers has also contributed to improved outcomes⁵. Nonetheless PD remains one of the most complex operations in gastrointestinal surgery. Complications, such as anastomotic leakage (in particular of the hepatojejunostomy and pancreaticojejunostomy) and the formation of pancreatic fistula, have serious consequences for the patient. Clinical outcomes, such as surgery-related mortality or specific PD-related morbidity, are important for evaluation of the efficacy of surgical interventions. However, in RCTs focusing on pancreatic surgery the usefulness of these outcomes as a primary endpoint is limited because they are dichotomous and individually have a relatively low incidence. Consequently, large sample sizes are needed to obtain adequate statistical power. The aforementioned reasons could account for the low number of RCTs in this field^{2,6}.

The use of a composite endpoint (CEP) that is specifically designed for PD could be a solution to the problem of the lack of RCTs in PD. In a CEP several individual, single-outcome parameters are combined into one CEP; every time an individual outcome parameter is positive, the CEP is positive, but if in a patient more individual outcome parameters are positive, the CEP is only positive once. The individual parameters should be dichotomous, highly specific for the given surgical procedure, and of clinical relevance^{7,8}. As the CEP combines individual outcome parameters (i.e. “individual, single endpoints”) into one CEP, scoring a CEP results in a higher incidence than the incidence of individual specific endpoints. Using CEP as a primary endpoint therefore increases statistical power and allows a lower sample size when performing RCTs. It must be noted that a CEP is dichotomous (it occurs or it does not occur) and can therefore only be scored once in a patient, even though a patient has more than one complication that is included in the CEP. Therefore, a CEP will not result in underpowering. CEPs are already widely used in cardiovascular and pulmonary research and have recently been developed for liver surgery⁸⁻¹³. In pancreatic surgery, however, CEPs have been applied in only a few trials¹⁴⁻¹⁶. Furthermore, the CEPs used in the studies on pancreatic surgery all included different components, making the results incomparable. A CEP can be viewed as a minimal set of endpoints, a core outcome set (COS), that

facilitates the conduct of future RCTs and meta-analyses and reduces the missing outcome parameters. The aim of the present study was to develop a standardized CEP specific for PD that can be used as a primary endpoint for future RCTs.

METHODS

The PD-specific CEP was developed according to a three-step method. First a systematic review of the literature was performed to identify all single-component clinical endpoints used in previous PD-related RCTs (development step 1). The systematic review was performed following the PRISMA statement. Second, a list of candidate components was defined and a web-based survey was used that allowed an international group of clinical experts in pancreatic survey to select the most relevant components for a CEP (development step 2). Consensus was reached between these experts and the study group to form a definitive CEP for PD. Third, validation of the CEP was conducted by assessing the event rate of the proposed CEP in two PD-patient cohorts at Maastricht University Medical Center (Maastricht, the Netherlands) and in the Royal Free Hospital London (London, United Kingdom). Both are tertiary referral centers for hepatopancreaticobiliary (HPB) surgery. Finally, the theoretical sample size was calculated of an RCT using the PD-specific CEP as a primary endpoint (development step 3).

Development step 1: identification of all single-component clinical endpoints in randomized trials on pancreaticoduodenectomy

Search strategy

Two researchers (M.C., S.C.) performed a review of the literature to identify all single-component clinical outcomes used as a primary or secondary endpoint in trials on PD. The databases of PubMed, Embase, and the Cochrane Library were searched for the following search terms: “pancreatic resection” OR “Whipple” OR “distal pancreatectomy” OR “PD” combined with “RCT.” Only English language articles published between January 2006 and August 2011 were included for further investigation.

Eligibility criteria

The following RCT eligibility criteria were used: (1) studies reporting on outcome after pancreatic surgery, (2) studies reporting on human subjects, and (3) studies using dichotomous clinical outcomes as primary or secondary endpoint. Exclusion criteria were studies reporting on non-pancreatic surgery-related outcomes, using only

surrogate outcomes as primary and secondary endpoints, describing a study protocol or studies that were published only in abstract form.

Study selection

One author (M.C.) screened all the retrieved abstracts and crosschecked the reference lists for additional eligible papers. Full texts of potentially eligible RCTs were retrieved via the databases or by contacting the corresponding author. Two authors (M.C., S.C.) performed the full-text examination and decided on inclusion for final analysis. Disagreements on inclusion or exclusion were resolved through discussion with a third author (S.O.D.). The data on study origin, design, sample size, study interval, type of intervention, primary and secondary endpoints, definitions of complications, and trial outcomes were recorded systematically in a database. Extra attention was given to dichotomous endpoints of different RCTs that were published by the same institute using data from overlapping time intervals. These were taken into account only once in order to prevent the use of duplicate data.

Development step 2: reaching consensus on definitions of complications after pancreaticoduodenectomy.

A web survey was used as a tool to reach consensus on which endpoints should be included in the CEP. This web-based survey was designed using free online software (<http://www.surveymonkey.com>). An example of the survey can be found in Appendix 1 (supporting information). All endpoints used in the included RCTs were systematically registered in a database. The most frequently used endpoints formed the basis of the web survey. The survey consisted of two parts. The aim of Part I was to obtain a first selection of single endpoints to be included in a CEP for PD. Directors of HPB surgery units worldwide were personally contacted by email and invited to participate in the survey. Multiple email reminders were sent in order to acquire a maximum of reactions, comments and opinions. In this part the participants were explicitly asked whether they preferred the use of the Accordion severity grading scale described by Strasberg et al.^{17,18} or the Dindo–Clavien classification as standard complication-grading system. Initial analysis of the survey results revealed a negative opinion toward the adoption of the Accordion grading scale. Thus the Dindo–Clavien severity grading system was used onwards. This system grades complications according to the interventions needed to treat the complication. Second the selected single components were defined (if possible using already existing definitions of known study groups such as the International Study Group of Pancreatic Surgery (ISGPS)^{19,20} and International Study Group of Pancreatic Fistula (ISGPF)²¹). The used definitions can be found in Appendix 2 (supporting information). After collection of all replies, the proposed definitions were adjusted according to the suggestions of the responders and selected when a minimum of two thirds of the responders agreed upon the proposed

definition. Finally, during multiple meetings by the research group a CEP for PD was defined.

Development step 3: selection of components of the pancreaticoduodenectomy-specific endpoint

The second part of the survey covered the components of the PD-specific CEP. These were selected after receiving the responses from part I of the survey. Only complications with a Dindo–Clavien severity grade of 3 or more, and on which more than 75 % of the responders agreed, were included. An agreement percentage of 75 % is commonly used in surveys using the Delphi technique²². In part II of the survey this final combination of components was proposed to the respondents as a final endpoint on which agreement should be reached. Again, the final CEP for PD was accepted when more than 75 % of the respondents agreed.

Evaluation of the incidence of the pancreaticoduodenectomy-specific composite endpoint

The incidence of the individual components and the proposed PD-specific CEP was determined using two prospectively collected databases containing a consecutive series of patients having undergone a PD operation in Maastricht University Medical Center between 1 January 2000 and 1 October 2012, and in the Royal Free Hospital London between 1 July 2010 and 30 June 2012. Complications occurring within 90 days of the initial PD operation were recorded and graded according to the Dindo–Clavien classification.

Statistical analysis

The incidence of the individual components and the proposed PD-specific CEP was determined using two prospectively collected databases containing a consecutive series of patients having undergone a PD operation in Maastricht University Medical Center between 1 January 2000 and 1 October 2012, and in the Royal Free Hospital London between 1 July 2010 and 30 June 2012. Complications occurring within 90 days of the initial PD operation were recorded and graded according to the Dindo–Clavien classification⁸.

RESULTS

Identification of single-component clinical endpoints in randomized trials in pancreatic surgery

A total of 307 abstracts of RCTs that fulfilled the search terms were identified with the electronic search. The main reasons for exclusion are shown in Figure 5.1. Characteristics of the 33 RCTs included in the final analysis are summarized in Table 5.1. The mean sample size of the included RCTs was 123 patients (range 22–450 patients). Table 5.1 shows more detailed information about (1) which single-component clinical endpoints were used most frequently as the primary or secondary endpoint and (2) how many times they were used in the selected RCTs.

Figure 5.1 Flow chart of study selection

Table 5.1 Characteristics and single-component clinical endpoints of 33 randomized controlled trials in pancreaticoduodenectomy published between January 2006 and August 2011.

	No. of trials
Continent of origin	
Asia	15
Europe	13
North America	5
Type of intervention	
Drug	5
Nutrition	4
Surgical technique	17
Other	7
Multicenter trial	10
Clinical dichotomous primary endpoint	27
Composite Endpoint	3
Surrogate continuous primary endpoint	6
Single-component clinical outcome used as primary or secondary endpoint	
Operative, 30-day, in-hospital mortality	23
Biliary leakage	19
Requirement for blood transfusion	7
Intra-abdominal abscess	18
Wound infection, wound dehiscence	20
Intra-abdominal hemorrhage, bleeding, hemoperitoneum	19
Pneumonia	12
Ascites	5
Pleural effusion	7
Sepsis	7
Gastrojejunostomy leakage	11
Pancreaticojejunostomy leakage	25
Pancreatic fistula	28
Delayed gastric emptying	25
Body weight gain within 3 months (kg)	3
Pancreatic dysfunction	9
Quality of life	4

Consensus on definitions of complications after pancreaticoduodenectomy

Fifty HPB surgeons were invited to participate in the survey. Twenty-five of those surgeons (50%) completed the survey. Participating surgeons were from Canada (5%), the United States (5%), the Netherlands (40%), and various other European countries (50%). According to the respondents, the following complications were considered PD-specific complications: intra-abdominal abscess (100%), bile leakage/hepaticojejunostomy leakage (80%), sepsis (95%), post-PD hemorrhage (95%), gastrojejunostomy leakage (80%), pancreatic fistula formation (95%), delayed gastric emptying (90%), and operative mortality (100%). Eight complications were considered not to be PD specific (Table 5.2). The participating surgeons agreed with the proposed definitions (Appendix 2). Several respondents recommended changing the term

“pancreatic fistula” into “leakage of the pancreatic anastomosis”. This covers leakage of both the pancreaticojejunostomy and the pancreaticogastrostomy. Following suggestions made by some respondents ($n=3$), the mortality registration period was changed from 30 to 90 days by consensus.

Table 5.2 Selection of components of the pancreatic surgery-specific composite endpoint

	No. of respondents indicating that the component should be included in the pancreatic surgery-specific CEP ($n=25$)
Intra-abdominal abscess	25 (100)
Sepsis	24 (96)
Gastrojejunostomy leakage	24 (96)
Post pancreatic surgery hemorrhage	24 (96)
DGE	23 (92)
Bile leakage/ hepaticojejunostomy leakage	21 (84)
Pancreatic fistula (pancreaticojejunostomy-, pancreaticogastrostomy leakage)	25 (100)
Mortality	25 (100)
Wound infection	10 (40)
Pleural effusion	1 (4)
Ascites	1 (4)
Pneumonia	8 (32)
Renal failure	4 (16)
Blood transfusion	8 (32)
Cost	3 (14)
Quality of life	9 (36)

Values in parentheses are percentages; DGE delayed gastric emptying

Selection of components of the pancreaticoduodenectomy-specific composite endpoint

Twenty-five (100%) experts who completed part I of the survey also completed part II. Their preferences for components to be included in the PD-specific CEP are summarized in Table 5.2. Final analysis of part II resulted in selection of eight complications with a Dindo–Clavien grade of 3 or higher. All respondents agreed with this proposal, and each respondent indicated that he or she would be interested in using a PD-specific CEP as a primary endpoint of a RCT.

Evaluation of the incidence of the pancreaticoduodenectomy-specific endpoint

Between 1 January 2000 and 1 October 2012, 387 patients underwent a pancreatic resection at Maastricht University Medical Center, and between 1 July 2010 and 30 June 2012, 178 patients underwent resection at the Royal Free Hospital London. Of these patients, 178 and 120 underwent a PD at the respective institutions.

The characteristics of the procedures and their postoperative complications are displayed in Table 5.3. At the Maastricht University Medical Center the incidence of individual complications as combined in the CEP and with a Dindo–Clavien grade of 3 or higher within 90 days after PD, varied between 0.5% for delayed gastric emptying (DGE) and 15.7% for intra-abdominal abscess. The incidence of the PD-specific CEP was 24.7% (44 patients). The incidence of the individual components of the CEP at the Royal Free Hospital London ranged from 1.7 to 8.3% for operative mortality and post-pancreatic surgery intra-abdominal hemorrhage, respectively. The incidence of the PD-specific CEP in this group was 23.3% (28 patients).

Table 5.3 Patient characteristics and incidence of complications after pancreatic surgery

	Maastricht University Medical Center (<i>n</i> =178 resections)	Royal Free Hospital London (<i>n</i> =120 resections)
Sex (F:M)	29:111	57:63
Age (Years)*	67	62
Pancreaticoduodenectomy (PPPD)	145 (81.5)	20 (16.7)
Pancreaticoduodenectomy (Whipple's procedure)	33 (18.5)	100 (83.3)
Complication grade 1-2 (Dindo-Clavien)		
Intra-abdominal abscess	4 (2.2)	6 (5.0)
Sepsis	1 (0.5)	4 (3.3)
Gastrojejunostomy leakage	-	-
Post pancreaticoduodenectomy hemorrhage	-	7 (5.8)
Bile leakage/hepaticojejunostomy leakage	2 (1.1)	2 (1.7)
Pancreatic anastomosis leakage	5 (2.8)	12 (10.0)
Delayed gastric emptying	16 (8.9)	19 (15.8)
Complication grade 3-5 (Dindo-Clavien)		
Intra-abdominal abscess	28 (15.7)	4 (3.3)
Sepsis	9 (5.0)	6 (5.0)
Gastrojejunostomy leakage	1 (0.5)	4 (3.3)
Post pancreaticoduodenectomy hemorrhage	7 (3.9)	10 (8.3)
Bile leakage/hepaticojejunostomy leakage	7 (3.9)	4 (3.3)
Pancreatic anastomosis leakage	24 (13.4)	7 (5.8)
Delayed gastric emptying	1 (0.5)	5 (4.1)
Operative mortality 90 days	10 (5.6)	2 (1.7)
Pancreaticoduodenectomy specific CEP	44 (24.7)	28 (23.3)

Values in parentheses are in percentages unless indicated otherwise; * values are in mean

Subsequently, taking only complications with Dindo–Clavien grade 3 or higher in the present data set into account, the theoretical sample size for a RCT was calculated with the goal of showing a relative reduction in the individual complication or the PD-specific CEP by one third, one half, or two thirds (Table 5.4). To show a risk reduction of 33, 50, and 66%, the sample size of an RCT powered on the incidence of the PD-specific CEP reached a number of 386, 154, and 80, respectively, based on the Maastricht University Medical Center patient cohort. Calculation of the relative risk reduction based on the Royal Free Hospital London data set showed PD-specific CEP sample sizes of 414, 165, 86, respectively.

Table 5.4 Sample size of each arm of an adequately powered randomized controlled trial aiming to show a one-third, one-half or two-thirds relative reduction in the primary endpoint

	Relative reduction in primary endpoint					
	Maastricht University Medical Center			Royal Free Hospital London		
	33%	50%	66%	33%	50%	66%
Intra-abdominal abscess	665	264	136	3546	1391	714
Sepsis	2306	906	466	2306	906	466
Gastrojejunostomy leakage	23976	9384	4813	3546	1391	714
Post-pancreaticoduodenectomy hemorrhage	2985	1171	602	1344	529	273
Bile leakage/ hepatico-jejunostomy leakage	2985	1171	602	3546	1391	714
Pancreatic anastomosis leakage	2985	315	163	1974	776	399
Delayed gastric emptying	23976	9384	4813	2785	1093	562
Operative mortality	2048	805	414	7107	2784	1429
Pancreaticoduodenectomy specific CEP	386	154	80	414	165	86

Assumptions: $\alpha = 0.05$, $\beta = 0.20$ and two-sided testing. CEP, composite endpoint

DISCUSSION

The aim of the present study was to design a consensus-based CEP for PD that can be used as a primary endpoint in RCTs on PD in order to reach adequate power and to improve comparability between studies. The PD-specific CEP developed in this study consists of 8 components: intra-abdominal abscess, sepsis, gastrojejunostomy leakage, bile leakage, leakage of the pancreatic anastomosis, delayed gastric emptying, post-PD hemorrhage, and mortality occurring within 90 days postoperatively. Additionally, the aforementioned complications need to have a Dindo–Clavien grade of 3 or more. The PD-specific CEP was evaluated in two cohorts of patients undergoing PD in two tertiary referral centers in Europe, Maastricht and London. The incidence of the CEP in both cohorts was considerably higher than the incidence of the individual components. As a result, the theoretical sample size of a RCT in PD decreased substantially and will result in a higher statistical precision and efficiency.

CEPs have been used commonly in cardiovascular trials and pharmacological trials^{12,23}. Publication of these trials has resulted in criticism of the drawbacks of CEPs. For example, individual components of a CEP may be ill defined, may differ in severity or incidence, and might not be affected in the same manner by the intervention. For these reasons, study groups have set up recommendations for the use of composite outcomes^{7,24–26}.

In the present study an attempt was made to address these issues in a systematic way. To gain international consensus regarding definitions of most of the individual components, the use of definitions already developed by international study groups

such as the ISGPS/ISGPF was suggested¹⁹⁻²¹. After evaluation and adjustments, international consensus was reached regarding individual components that had not been defined previously (Appendix 2). Furthermore, in order to include components of similar severity and clinical relevance, only components with a Dindo–Clavien score of grade 3 or more were used in the PD-specific CEP. The Dindo–Clavien classification aims to objectively group different complications with respect to the severity of therapeutic interventions. Importantly, the use of a standardized complication classification system like the Dindo–Clavien system increases comparability between studies.

In the present study, experts were asked whether quality of life (QoL) should be included in the CEP, but QoL was not considered to be sufficiently PD-specific. Hence, patient perceptions were not included in this CEP. Nevertheless, they may be of importance, as certain complications can have serious implications for patients, and patients may view the consequences of these complications (e.g. pain, fatigue, confusion) as more critical. The OMERACT initiative (Outcome Measures in Rheumatoid Arthritis Clinical Trial) introduced the development of a COS, which also includes patient perception²⁷. More recently, the COMET initiative (Core Outcome Measures in Effectiveness Trials) extended this approach in order to develop COSs that are applicable to other disciplines as well, such as pediatrics and bariatric surgery^{11,28}. At present, the senior author's group is developing a COS for pancreatic surgery in collaboration with the COMET initiative.

The mean sample size of RCTs involving pancreatic surgery was found to be 123 after a systematic literature search. However, sample sizes calculated for single-component primary outcomes, as used in the included studies, should be much higher. This was shown in a previous publication where sample sizes were calculated for a single-component primary endpoint for liver surgery (range 826–6250 patients) having complication incidences comparable to those associated with pancreatic surgery²⁹. As a consequence, the studies included in this systematic review were most likely underpowered. Also, only a few of the included studies, those that were large and multicenter, using a dichotomous primary endpoint showed a statistical significant difference in outcome. This present study also shows that it is almost impossible to perform future studies on PD that are adequately powered on a single primary outcome as it would need sample sizes that are too large to be reached for a single institution.

Only three of the included studies used a CEP as primary endpoint, and two of them defined the CEP as “overall and pancreas-specific postoperative complications” or “serious complications”^{15,16}. However “overall complications” as a CEP should be avoided, because complications with less clinical relevance may contribute strongly to the incidence of the CEP²⁵. For this reason, it is important to explicitly define each of the CEP components and assess their severity.

A limitation of our study is the selection bias introduced by inviting specific surgeons to the web survey. The majority of respondents came from Europe. This means that the CEP to be used in RCTs is mainly based on the view of European pancreatic surgeons.

In this study a CEP is developed specifically for PD instead of a CEP for pancreatic surgery in general. PD is a procedure that differs considerably from other types of pancreatic surgery because it involves the construction of multiple anastomoses. This is not necessary, for example, for a distal pancreatectomy. The anastomoses are the primary cause of specific PD complications, such as anastomotic leakage and post-PD hemorrhage, and PD therefore should not be lumped together with other surgical procedures of the pancreas.

It may be necessary to develop CEPs for other forms of pancreatic surgery, as well as for drug-related pancreatic research. Furthermore, weighing of specific components of a CEP, not only by clinicians but also by patients, might be considered in future work. This issue will also be addressed in the development of the COS for pancreatic surgery by the present authors' group.

In this study a CEP for PD was developed in a systematic fashion, taking into account the definition of individual components as well as the clinical relevance of included components. Given the positive results of this study, a prospective validation of the PD-specific CEP for RCTs worldwide may be the appropriate next step.

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PART II

Development of ERAS guidelines and a multicenter trial for pancreaticoduodenectomy

CHAPTER 6

Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS[®]) Society recommendations

K Lassen, MME Coolen, K Slim, F Carli, JE de Aguilar-Nascimento, M Schäfer, RW Parks, KCH Fearon, DN Lobo, N Demartines, M Braga, O Ljungqvist and CHC Dejong, on behalf of the ERAS[®] Society, the European Society for Clinical Nutrition and Metabolism and the International Association for Surgical Nutrition and Metabolism

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ABSTRACT

Background & aims

Protocols for enhanced recovery provide comprehensive and evidence-based guidelines for best perioperative care. Protocol implementation may reduce complication rates and enhance functional recovery and, as a result of this, also reduce length-of-stay in hospital. There is no comprehensive framework available for pancreaticoduodenectomy.

Methods

An international working group constructed within the Enhanced Recovery After Surgery (ERAS®) Society constructed a comprehensive and evidence-based framework for best perioperative care for pancreaticoduodenectomy patients. Data were retrieved from standard databases and personal archives. Evidence and recommendations were classified according to the GRADE system and reached through consensus in the group. The quality of evidence was rated “high”, “moderate”, “low” or “very low”. Recommendations were graded as “strong” or “weak”.

Results

Comprehensive guidelines are presented. Available evidence is summarized and recommendations given for 27 care items. The quality of evidence varies substantially and further research is needed for many issues to improve the strength of evidence and grade of recommendations.

Conclusions

The present evidence-based guidelines provide the necessary platform upon which to base a unified protocol for perioperative care for pancreaticoduodenectomy. A unified protocol allows for comparison between centers and across national borders. It facilitates multi-institutional prospective cohort registries and adequately powered randomized trials.

INTRODUCTION

Enhanced Recovery After Surgery (ERAS), Fast-Track or Clinical Pathway programs are multimodal strategies that aim to attenuate the loss of, and improve the restoration of, functional capacity after surgery. Morbidity is reduced¹ and recovery enhanced by reducing surgical stress, by optimal control of pain, early oral diet and early mobilization. As a consequence, length-of-stay in hospital (LOSH) and costs are also reduced. The ERAS group has published evidence-based consensus recommendations for colorectal surgery^{2,3}. Beneficial experiences with clinical pathway programs after pancreaticoduodenectomy (PD, Whipple's procedure) have been published⁴⁻⁹, but the reported series employed different protocols, or no prospective protocol at all⁶. A comprehensive consensus framework is presented on which to base a future protocol for optimal perioperative care after PD. Such a recommendation will allow for a unified protocol to be developed and validated prospectively across different institutions and healthcare systems. This guideline framework has been formulated and endorsed by the ERAS Society, European Society for Clinical Nutrition and Metabolism (ESPEN) and the International Association for Surgical Metabolism and Nutrition (IASMEN).

METHODS

Literature search

The authors met in April 2011 and the topics to be included were agreed and allocated. A principal literature search up to June 2011 was undertaken. Comprehensive drafts were circulated for discussion and reviewed in a group conference in November 2011. Additional relevant literature published after June 2011 was considered by members of the group at meetings in November 2011 and May 2012.

Study selection

All co-authors screened web-based databases and personal archives for relevant articles. Non-systematic emphasis was given to more recent publications and publications of better quality (moderate- and high-quality randomized controlled trials and high-quality, large cohort studies; and systematic reviews and meta-analyses of these). Retrospective series were considered only if data of better quality could not be identified.

Quality assessment and grading

The strength of evidence and conclusive recommendations were assessed and agreed by all authors in May 2012. Quality of evidence and recommendations were evaluated

according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system¹⁰⁻¹². Quoting from the GRADE guidelines,¹² the recommendations are: “Strong recommendations indicate that the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects”. “Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident”. Recommendations are based on quality of evidence (high, moderate, low, very low) but also on the balance between desirable and undesirable effects; and on values and preferences¹². The latter implies that, in some cases, strong recommendations may be reached from low-quality data and vice versa. A summary of the guidelines is shown in Table 6.1.

EVIDENCE AND RECOMMENDATIONS

Preoperative counseling

Preoperative counseling targeting expectations about surgical and anesthetic procedures may diminish fear and anxiety and enhance postoperative recovery and discharge.¹³⁻¹⁵ Personal counseling, leaflets or multimedia information containing explanations of the procedure along with tasks that the patient should be encouraged to fulfill may improve perioperative feeding, early postoperative mobilization, pain control, and respiratory physiotherapy; and hence reduce the risk of complications¹⁶⁻¹⁸. Ideally, the patient should meet with the surgeon, anesthetist and nurse.

Summary and recommendation: Patients should receive dedicated preoperative counseling routinely.

Evidence level: Low.

Recommendation grade: Strong.

Preoperative biliary drainage

Five meta-analyses¹⁹⁻²³, and two articles from a randomized controlled trial (RCT) not included in the meta-analyses^{24,25}, assessed the role of biliary drainage before PD. The first meta-analysis from 2002¹⁹, included randomized (n=5) and non-randomized trials (n=18). A Cochrane review²¹ included 5 randomized trials, but considered all 5 trials to have a risk of bias, thereby weakening the conclusions reached. Of the trials included, 4 evaluated percutaneous drainage and 1 evaluated endoscopic drainage. The Cochrane review concluded that preoperative biliary drainage did not decrease mortality in patients with obstructive jaundice.

Table 6.1 Summary of key characteristics of included studies

Item	Summary and recommendations	Evidence level	Recommendation grade
Preoperative counseling	Patients should receive dedicated preoperative counselling routinely.	Low	Strong
Perioperative biliary drainage	Preoperative endoscopic biliary drainage should not be undertaken routinely in patients with a serum bilirubin concentration <250 mmol/l.	Moderate	Weak
Preoperative smoking and alcohol consumption	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted.	Alcohol abstinence: Low Smoking cessation: Moderate	Strong
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition preoperatively.	Very low	Weak
Perioperative oral immunonutrition (IN)	The balance of evidence suggests that IN for 5e7 days perioperatively should be considered because it may reduce the rate of infectious complications in patients undergoing major open abdominal surgery.	Moderate	Weak
Oral bowel preparation	Extrapolation of data from studies on colonic surgery and retrospective studies in PD show that MBP has no proven benefit. MBP should not be used.	Moderate	Strong
Preoperative fasting and preoperative treatment with carbohydrates	Intake of clear fluids up to 2 h before anesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anesthesia. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given in patients without diabetes.	Fluid intake: High Solid intake: Low Carbohydrate loading: Low	Fasting: Strong Carbohydrate loading: Strong
Preanesthetic medication	Data from studies on abdominal surgery show no evidence of clinical benefit from pre-operative use of long-acting sedatives, and they should not be used routinely. Short-acting anxiolytics may be used for procedures such as insertion of epidural catheters.	No long-acting sedatives: Moderate	Weak
Anti-thrombotic prophylaxis	LMWH reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines.	High	Strong
Antimicrobial prophylaxis and skin preparation	Mechanical measures should probably be added for patients at high risk. Antimicrobial prophylaxis prevents surgical-site infections, and should be used in a single-dose manner initiated 30e60 min before skin incision. Repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of procedure.	High	Strong

Table 6.1 (continued)

Item	Summary and recommendations	Evidence level	Recommendation grade
Epidural analgesia	Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with intravenous opioids.	Pain: High Reduced respiratory complications: Moderate	Weak
Intravenous analgesia	Some evidence supports the use of PCA or intravenous lidocaine analgesic methods. There is insufficient information on outcome after PD.	Overall Morbidity: Low PCA: Very Low I.V. Lidocaine: Moderate	Weak
Wound catheters and transversus abdominis plane block	Some evidence supports the use of wound catheters or TAP blocks in abdominal surgery. Results are conflicting and variable, and mostly from studies on lower gastrointestinal surgery.	Wound catheters: Moderate	Weak
Postoperative nausea and vomiting (PONV)	Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's PONV history, type of surgery and type of anesthesia. Multimodal intervention during and after surgery is indicated.	TAP blocks: Moderate Low	Strong
Incision	The choice of incision is at the surgeon's discretion, and should be of a length sufficient to ensure good exposure.	Very low	Strong
Avoiding hypothermia	Intraoperative hypothermia should be avoided by using cutaneous warming, i.e., forced-air or circulating-water garment systems.	High	Strong
Postoperative glycaemic control	Insulin resistance and hyperglycemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycemia with intravenous insulin in the ICU setting improves outcomes but hypoglycemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycemic control without the risk of hypoglycemia. Hyperglycaemia should be avoided as far as possible without introducing the risk of hypoglycemia.	Low	Strong
Nasogastric intubation	Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely.	Moderate	Strong

Table 6.1 (continued)

Item	Summary and recommendations	Evidence level	Recommendation grade
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes. Perioperative monitoring of stroke volume with transesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9% saline.	Fluid balance: High Esophageal Doppler: Moderate Balanced crystalloids vs. 0.9% saline: Moderate	Strong
Perianastomotic drain	Early removal of drains after 72 h may be advisable in patients at low risk (i.e., amylase content in drain <5000 U/l) for developing a pancreatic fistula. There is insufficient evidence to recommend routine use of drains, but their use is based only on low-level evidence.	Early removal: High	Early removal: Strong
Somatostatin analogues	Somatostatin and its analogues have no beneficial effects on outcome after PD. In general, their use is not warranted. Subgroup analyses for variability in the texture and duct size of the pancreas are not available.	Moderate	Strong
Urinary drainage	Suprapubic catheterization is superior to transurethral catheterization if used for >4 days. Transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated.	High	For suprapubic: Weak Transurethral catheter out: Strong
Delayed gastric emptying (DGE)	There are no acknowledged strategies to avoid DGE. Artificial nutrition should be considered selectively in patients with DGE of long duration.	Very low	Strong
Stimulation of bowel movement	A multimodal approach with epidural and near-zero fluid balance is recommended. Oral laxatives and chewing gum given postoperatively are safe, and may accelerate gastrointestinal transit.	Laxatives: Very low Chewing gum: Low	Weak
Postoperative artificial nutrition	Patients should be allowed a normal diet after surgery without restrictions. They should be cautioned to begin carefully and increase intake according to tolerance over 3e4 days. Enteral tube feeding should be given only on specific indications and parenteral nutrition should not be employed routinely.	Early diet at will: Moderate	Strong
Early and scheduled mobilization	Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet daily targets for mobilization.	Very low	Strong
Audit	Systematic improves compliance and clinical outcomes.	Low	Strong

Although there was a trend towards decreased postoperative morbidity, the increased risk of procedure-related complications counterbalanced this possible benefit (especially for percutaneous drainage). The findings of the Cochrane review were in accordance with those of the other meta-analyses, suggesting that preoperative drainage confers neither benefit nor harm. One recent RCT not included in the meta-analyses²⁴ (and which included patients with serum bilirubin concentrations <250 mmol/l) showed increased morbidity in patients undergoing preoperative biliary drainage (endoscopic primarily; percutaneous as rescue option), but the delay in surgery did not affect overall survival²⁵.

Summary and recommendation: Preoperative endoscopic biliary drainage should not be carried out routinely in patients with a serum bilirubin concentration <250 mmol/l.

Evidence level: Moderate.

Recommendation grade: Weak.

Preoperative smoking and alcohol consumption

Overall postoperative morbidity is increased by two- to three-fold in alcohol abusers²⁶. Also, 1 month of preoperative abstinence has been shown to significantly improve outcome in a group who took “five or more drinks (60 g of ethanol) a day without clinical or historical evidence of alcohol related illness”²⁷.

Daily smokers (>2 cigarettes daily for ≥1 year) have an increased risk of pulmonary and wound complications^{28,29}. RCTs have demonstrated reductions in the rates of both types of complications 1 month after cessation of smoking^{29,30}.

Summary and recommendation: For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted.

For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted.

Evidence level: Alcohol abstention: Low.

Smoking cessation: Moderate.

Recommendation grade: Strong.

Preoperative nutrition

In western countries, patients scheduled for PD are, in general, not malnourished, and usually present with <7% weight loss³¹. In such cases, preoperative artificial nutrition is not warranted. The situation may be different in other regions. It is widely accepted that significantly malnourished patients suffer increased postoperative morbidity after major surgery³²⁻³⁴. Preoperative supplements with oral sip feeds or enteral tube feeds are usually administered in these cases, but scientific evidence to support this routine

(as opposed to no nutritional support) is lacking. Extrapolating data from studies in the postoperative setting suggests that parenteral nutrition should be used only if the enteral route is inaccessible.

Summary and recommendation: Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition preoperatively.

Evidence level: Very low.

Recommendation grade: Weak.

Perioperative oral immunonutrition (IN)

The role of IN has been investigated thoroughly over many years. Few studies specifically address IN for PD patients, and the variation in active immune-modulating nutrients administered makes interpretation difficult. A reduction in the prevalence of infectious complications is a consistent finding in patients with gastrointestinal cancer, as are beneficial effects on surrogate endpoints (levels of interleukins and C-reactive protein (CRP)) or LOSH. A reduction in mortality has not been shown. Several recently published reviews and meta-analyses³⁵⁻⁴¹ conclude that there is a benefit from perioperative and postoperative IN in patients undergoing major gastrointestinal surgery, but results remain inconsistent⁴²⁻⁴⁴. Beneficial outcomes have been shown in a systematic review of 35 trials in patients undergoing elective surgery, in which arginine-supplemented diets were associated with a significantly reduced prevalence of infectious complications and LOSH⁴⁵. There is also evidence to suggest that immune-modulating nutrition may be more beneficial in undernourished rather than in normally nourished patients. However, IN could be detrimental in patients with sepsis⁴⁶. There are no trials investigating IN within ERAS care pathways.

Summary and recommendation: The balance of evidence suggests that IN for 5-7 days perioperatively should be considered because it may reduce the prevalence of infectious complications in patients undergoing major open abdominal surgery.

Evidence level: Moderate.

Recommendation grade: Weak.

Oral bowel preparation

Mechanical bowel preparation (MBP) may lead to dehydration and offset fluid and electrolyte balance, particularly in the elderly⁴⁷. Meta-analyses from colonic surgery have not shown clinical benefit from MBP^{48,49}. A large and recent retrospective analysis of 200 consecutive patients undergoing PD did not find any benefit of MBP to a clear

liquid diet the day before surgery⁵⁰. No trial has compared MBP to a regimen without MBP and an unrestricted diet until midnight before surgery.

Summary and recommendation: Extrapolation of data from colonic surgery and retrospective studies in PD show that MBP has no proven benefit. MBP should not be used.

Evidence level: Moderate.

Recommendation grade: Strong.

Preoperative fasting and preoperative treatment with carbohydrates

Fasting from midnight has been standard practice in elective surgery, but is not supported by evidence⁵¹. Overnight fasting increases insulin resistance and discomfort after abdominal surgery^{52,53}. Guidelines recommend the intake of clear fluids ≤ 2 h before the induction of anesthesia as well as a fasting period of 6 h for solids⁵⁴. The latter recommendation has a weak scientific basis⁵⁵. Intake of a complex clear carbohydrate-rich drink designed for preoperative use ≤ 2 h before the induction of anesthesia has been shown to reduce hunger, thirst and anxiety, and to decrease postoperative insulin resistance⁵⁶⁻⁵⁸. Earlier resumption of gut function after colorectal surgery has also been suggested⁵⁹, and an RCT including some PD patients concluded that oral carbohydrate treatment may preserve skeletal muscle mass⁶⁰. An RCT conducted in patients undergoing cholecystectomy did not show any benefit⁶¹. Data on the safety and clinical benefit of preoperative carbohydrate in patients with diabetes are sparse^{62,63}, and further research is warranted in this group.

Summary and recommendation: Intake of clear fluids up to 2 h before anesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anesthesia. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given in patients without diabetes.

Evidence level: Fluid intake: High.

Solid intake: Low.

Carbohydrate loading: Low.

Recommendation grade: Fasting: Strong.

Carbohydrate loading: Strong.

Pre-anesthetic medication

Anxiety makes postoperative pain more difficult to control. Pre-emptive treatment of anxiety could lower pain scores and reduce the demand for opiates⁶⁴. However, pre-induction anxiolytic medication increases postoperative sedation⁶⁵, and a meta-analysis did not demonstrate reduced postoperative pain with pre-emptive use of analgesics⁶⁶.

Short-acting anxiolytics may be helpful in some patients during placement of an epidural catheter, and experiences from day surgery suggest that cognitive function is not significantly impaired⁶⁷. Additionally, oral fluids and a carbohydrate-rich beverage have been shown to reduce preoperative anxiety⁵⁷. Medications for chronic pain need to be continued on the morning of surgery, and should be prescribed in the postoperative period.

Summary and recommendation: Data from studies on abdominal surgery show no evidence of clinical benefit from preoperative use of long-acting sedatives, and they should not be used routinely. Short-acting anxiolytics may be used for procedures such as insertion of epidural catheters.

Evidence level: No long-acting sedatives: Moderate.

Recommendation grade: Weak.

Anti-thrombotic prophylaxis

Malignant disease and major surgery increase the risk of venous thromboembolism (VTE)⁶⁸. Unfractionated and fractionated low- dose heparins are effective at preventing VTE⁶⁹. Fractionated low- molecular-weight heparin (LMWH) is preferable in view of compliance (once-daily administration)⁷⁰. Treatment is usually initiated 2-12 h before surgery and continued until patients are fully mobile. A meta-analysis supports continued treatment for 4 weeks after hospital discharge⁷². Concomitant use of LMWH and epidural catheters is controversial⁷²⁻⁷⁵. It has, therefore, been recommended that the catheter be inserted ≥ 12 h after a dose of LMWH, and removed ≥ 12 h after administration of LMWH⁷⁶. The risk of an epidural or spinal hematoma is increased in patients who are also on anti-platelet drugs or oral anticoagulants⁷³. Combined prophylactic modalities have been shown to be superior to pharmacological measures only in preventing VTE⁷⁷. Mechanical intermittent pneumatic leg compression⁷⁷, and elastic stockings may be used as adjuncts in patients who are at moderate or high risk for VTE⁷⁸.

Summary and recommendation: LMWH reduces the risk of thromboembolic complications. Administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk.

Evidence level: High.

Recommendation grade: Strong.

Antimicrobial prophylaxis and skin preparation

There is ample evidence favoring the prescription of antimicrobial prophylaxis for major abdominal procedures^{79,80}. Trials specifically targeting patients undergoing PD were not identified. Recently published studies reported or recommended prescription in a single-dose manner⁸⁰. However, an extra dose should be provided every 3-4 h during the procedure if drugs with a short half-life are chosen⁸¹. Initial administration should be as near as possible to the skin incision and ≤ 1 h before the incision^{79,82}. The choice of antibiotic is dependent upon local guidelines, and should be different from the drug of choice for treatment of established infections. Skin preparation with a scrub of chlorhexidine-alcohol has recently been claimed to be superior to povidone-iodine in preventing surgical-site infections⁸³. However, the difference is likely to be very small because excellent results are obtained with povidone-iodine⁸⁴. Alcohol-based scrubs have been reported to be used in fire-based and burn injuries⁸⁵.

Summary and recommendation: Antimicrobial prophylaxis prevents surgical-site infections and should be used in a single- dose manner initiated 30-60 min before skin incision. Repeated intraoperative doses may be necessary depending on the half- life of the drug and duration of the procedure.

Evidence level: High.

Recommendation grade: Strong.

Epidural analgesia

A meta-analysis showed that continuous epidural analgesia with or without opioids provided significant improvement in postoperative pain control compared with parenteral opioids in open abdominal surgery⁸⁶. Moreover, a Cochrane review demonstrated that continuous epidural analgesia is superior to patient-controlled intravenous opioid analgesia in relieving pain ≤ 72 h after open abdominal surgery⁸⁷. A decreased prevalence of ileus was found for epidural administration of local anesthetic after laparotomy compared with systemic or epidural opioids in one Cochrane review⁸⁸. With respect to complications after abdominal or thoracic surgery, a meta-analysis⁸⁹ concluded that epidural analgesia was associated with a significantly decreased risk of postoperative pneumonia, as well as an improvement in pulmonary function and arterial oxygenation. Also, the use of epidurals has been shown to reduce insulin resistance⁹⁰. Despite the widespread use of epidural analgesia after pancreatic surgery⁹¹, RCTs that specifically examine the outcomes of epidural analgesia after pancreatic surgery are lacking. A retrospective study comparing epidural analgesia with intravenous analgesia after PD found that patients with epidural analgesia had lower pain scores but significantly higher rates of major complications⁹². It has been suggested that thoracic epidural analgesia after PD is associated with hemodynamic instability, which might compromise enteric anastomoses, intestinal perfusion and

recovery of gastrointestinal function⁹². In experimental acute pancreatitis and in sepsis, however, thoracic epidurals improved perfusion in gastrointestinal mucosal capillaries⁹³. The adverse perfusion effects of epidural analgesia appear to be related to the prolonged and extended sympathetic block. This would imply that the beneficial effects of epidural analgesia can be preserved as long as the hemodynamic consequences are adequately controlled with vasopressors⁹⁴. Concerns about anastomoses have been raised after colorectal surgery, but one meta-analysis did not detect differences in rates of anastomotic leaks between patients receiving postoperative local anesthetic epidurals and those receiving systemic or epidural opioids⁹⁵.

A potential drawback with epidurals is that as many as one-third of epidurals may not function satisfactorily in some centers⁹⁶⁻⁹⁷. Possible reasons may be that: catheters are not located in the epidural space; the insertion level does not cover the surgical incision; the dosage of local anesthetic and opioid are insufficient; or pump failure. For upper transverse incisions, epidural catheters should be inserted between T5 and T8 root levels. Sensory block should be tested (cold and pinprick) before induction of general anesthesia. Efforts should be made to check the sensory block on a daily (or more frequent) basis, and the infusion should be adjusted to provide sufficient analgesia to allow mobilization out of bed. It has been suggested that epidural analgesia should continue for ≥ 48 h and, after a successful stop-test, oral multimodal analgesia with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)/cyclooxygenase (COX)-2 inhibitors should be commenced together with oral opioids as required. Functioning epidural catheters may be used for a longer duration if needed. Further studies are warranted to evaluate specifically the potential risks and benefits of epidural analgesia after pancreatic surgery. The use of epidurals has not been investigated for laparoscopic pancreatic resections.

Summary and recommendation: Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with intravenous opioids.

Evidence level: Pain: High.

Reduced respiratory complications: Moderate.

Overall Morbidity: Low.

Recommendation grade: Weak.

Intravenous analgesia

Thoracic epidural anesthesia remains the 'gold standard' method for major open abdominal surgery, but there are situations in which it cannot be employed. Patient-controlled analgesia (PCA) with opioids is the most common modality used as an alternative to an epidural. In a clinical trial on the implementation of a critical pathway

for distal pancreatic surgery, PCA was the only analgesic modality used, but no comments were made on the impact of systemic analgesia on accelerating recovery⁹⁸. Intravenous infusion of lidocaine has analgesic, anti-inflammatory and antihyperalgesic properties, and has been evaluated as an analgesic modality for abdominal surgery. A systematic review of 8 trials (161 patients) in which the continuous infusion of lidocaine was compared with PCA morphine for abdominal surgery, showed a decrease in the duration of ileus, LOSH, postoperative pain intensity and side effects⁹⁹. A recent RCT in patients undergoing laparoscopic colorectal resection using the ERAS program showed no difference in return of gastrointestinal function and LOSH between continuous infusion of lidocaine and thoracic epidural anesthesia¹⁰⁰.

Summary and recommendation: Some evidence supports the use of PCA or intravenous lidocaine analgesic methods. There is insufficient information on outcome after PD.

Evidence level: PCA: Very Low.

I.V. Lidocaine: Moderate.

Recommendation grade: Weak.

Wound catheters and transversus abdominis plane (TAP) block

The efficacy of wound infusion with local anesthetic agents as a postoperative analgesic method has been proven in a meta-analysis of different surgical procedures¹⁰¹. Conversely, a more recent meta-analysis showed that wound catheters provided no significant reduction in pain intensity (at rest or with activity) or in morphine consumption at any time after laparotomy¹⁰². No significant differences in the prevalence of infectious complications were found. These inconsistent results might be due to factors such as the type, concentration and dose of local anesthetic, type of catheter, mode of delivery, or catheter location (subcutaneous or subfascial)¹⁰². In patients undergoing colorectal surgery, a significant opioid-sparing effect and reduction of LOSH were demonstrated when local anesthetic was infused through a catheter positioned between the fascia and the peritoneum¹⁰⁴. No significant increase in wound infections was found with the insertion of a catheter and infusion of local anesthetics. No comparison has been made with other modalities (e.g. epidural analgesia) or in enhanced recovery program.

TAP blocks anesthetize the thoracolumbar nerves (intercostal, subcostal and first lumbar), which provide sensory innervation to the anterolateral abdominal wall. The ultrasonography-guided technique for TAP blocks has been used for postoperative analgesia after abdominal surgery. A systematic analysis of 7 studies (360 patients) showed significant opioid-sparing in the post-operative period¹⁰⁵. A meta-analysis of 5 RCTs (176 patients) confirmed previous results showing improved pain relief and reduced opioid-associated side effects¹⁰⁶. However, no studies have compared TAP block with other analgesic methods such as epidural analgesia or infiltration of local

anesthetic into the abdominal wound. Furthermore, no studies have used an enhanced recovery program¹⁰⁷ and no studies have been conducted in patients undergoing pancreatic surgery.

The marked heterogeneity observed between studies included in the meta-analyses mentioned above would imply that further trials are needed to evaluate the potential use of wound catheters and TAP blocks in pancreatic surgery.

Summary and recommendation: Some evidence supports the use of wound catheters or TAP blocks in abdominal surgery. Results are conflicting and variable and mostly from studies in lower gastrointestinal surgery.

Evidence level: Wound catheters: Moderate.

TAP blocks: Moderate.

Recommendation grade: Weak.

Postoperative nausea and vomiting (PONV)

Data specifically addressing PONV after PD specifically have not been identified. One comparative (non-randomized) study⁷ showed that an ERAS protocol with early mobilization, metoclopramide and removal of nasogastric tube on day 1 or day 2 decreased the rate of postoperative nausea and vomiting. Until further documentation becomes available, the suggestions for patients undergoing colorectal surgery³ should be applicable to those undergoing PD:

Patients with two risk factors (female sex, non-smoking status, history of motion sickness (or PONV) and postoperative administration of opioids^{108,109}) should receive prophylaxis with dexamethasone at induction or a serotonin receptor antagonist (e.g. ondansetron, tropisetron) at the end of surgery¹¹⁰. High-risk individuals (three factors) should receive general anesthesia with propofol and remifentanyl and no volatile anesthetics; and dexamethasone 4-8 mg at the beginning of surgery, supplemented with serotonin receptor antagonists or droperidol¹¹⁰, or 25-50 mg metoclopramide 30-60 min before the end of surgery¹¹¹. Ondansetron can be used for prophylaxis and treatment. A possible risk of impaired anastomotic healing caused by single-dose dexamethasone or other steroids perioperatively has been addressed clinically and experimentally, but remains unclear¹¹²⁻¹¹⁵.

Summary and recommendation: Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's PONV history, type of surgery and type of anesthesia. Multimodal intervention, during and after surgery is indicated.

Evidence level: Low.

Recommendation grade: Strong.

Incision

There are no data comparing the types of incisions for patients undergoing PD. The authors of these recommendations are comfortable with straight transverse, curved transverse and chevron incisions, indicating that all are practical. Laparoscopic resection of the pancreatic head has been reported to be feasible,¹¹⁶ but its future role is uncertain.

Summary and recommendation: The choice of incision is at the surgeon's discretion, and should be of a length sufficient to ensure good exposure.

Evidence level: Very low.

Recommendation grade: Strong.

Avoiding hypothermia

Several meta-analyses and RCTs have demonstrated that preventing inadvertent hypothermia during major abdominal surgery (such as PD) reduces the prevalence of wound infections^{117,118}, cardiac complications¹¹⁸⁻¹²⁰, bleeding and transfusion requirements¹¹⁸⁻¹²¹, as well as the duration of post-anesthetic recovery¹²². Furthermore, extending systemic warming in the perioperative period (2 h before and after surgery) has additional benefits¹²³. Hence, the use of active cutaneous warming is highly recommended to reduce post-operative morbidity and enhance recovery. There is even evidence to suggest that circulating-water garments offer better temperature control than forced-air warming systems¹²⁴⁻¹²⁶.

Summary and recommendation: Intraoperative hypothermia should be avoided by using cutaneous warming, i.e. forced-air or circulating-water garment systems.

Evidence level: High.

Recommendation grade: Strong.

Postoperative glycemic control

Postoperative hyperglycaemia in patients without diabetes is a result of acquired insulin resistance. Morbidity and mortality after major abdominal surgery have been associated with increasing levels of insulin resistance¹²⁷ and plasma glucose¹²⁸. Such an association has also been demonstrated in pancreatic surgery.¹²⁹ Data from patients subjected to colorectal surgery within an ERAS regimen indicate that higher preoperative levels of glycated hemoglobin (HbA1c) and higher postoperative levels of glucose also predict postoperative morbidity¹³⁰.

Core elements of ERAS protocols attenuate postoperative insulin resistance and thus also lower glucose levels^{131,132}. The most obvious (of several) protocols are avoidance of preoperative fasting and oral bowel preparation; use of oral carbohydrate treatment and stimulation of early resumption of gut function by optimal fluid balance and

avoidance of systemic opioids; and the reduction of the stress response by use of epidural anesthesia.

Reducing the rate of hyperglycemia in surgical patients in intensive-care settings has been documented to reduce the rate of complications^{133,136}. Similar trials in ward settings in patients treated with modern care regimens are wanting. The target concentration for plasma glucose is controversial¹³⁷, but it seems fair to advocate that hyperglycemia should be avoided and that this will improve outcome irrespective of the baseline level. Achieving tight glycemic control with intravenous insulin is challenging in the ward setting because of the risk of hypoglycemia. Glucosuria with the risk of hypovolemia will ensue when the renal threshold is passed at >12 mmol/l¹³⁷. This levels been used as the control regimen in seminal trials^{133,138} and should probably be regarded as a limit irrespective of settings to avoid additional disturbances in fluid balance.

Summary and recommendation: Insulin resistance and hyperglycemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycemia with intravenous insulin in the intensive-care setting improves outcomes but hypoglycemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycemic control without the risk of hypoglycemia. Hyperglycemia should be avoided as far as possible without introducing the risk of hypoglycemia.

Evidence level: Low.

Recommendation grade: Strong.

Nasogastric intubation

There is strong evidence that routine nasogastric decompression after elective laparotomy should be avoided¹³⁹. Fever, atelectasis and pneumonia occur more frequently in patients with a nasogastric tube than in those without^{139,140}. Bowel function returns earlier in patients if nasogastric decompression is avoided¹³⁹. Gastroesophageal reflux is increased during laparotomy if nasogastric tubes are inserted¹⁴¹. The role of nasogastric tubes has not been investigated prospectively in pancreatic surgery. However, the abundant high-level evidence in other fields of abdominal surgery, including gastroduodenal surgery¹³⁹, should allow for an extrapolation to patients undergoing PD and justify a 'no decompressive nasogastric tube' policy. This is also supported by some series with historic controls^{142,143}. A large Norwegian RCT in patients after upper gastrointestinal and hepatopancreaticobiliary surgery (and including >80 patients who had undergone PD and were treated without routine use of a nasogastric tube) found that early oral feeding was safe and feasible¹⁴⁴. This has also been corroborated by other non-randomized, fast-track implementation series in this field^{5-7,9}. In keeping with data in other areas of gastrointestinal surgery, nasogastric decompression tubes had to be replaced in $\leq 15\%$ of patients^{6,7,9}. Nasogastric tubes

placed during surgery (to evacuate air) should be removed before the reversal of anesthesia. Delayed gastric emptying is a specific problem in $\approx 10\text{--}25\%$ of patients after PD^{6,7,9} and it may be necessary to insert a decompression tube in a minority of patients postoperatively.

Summary and recommendation: Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes and their use is not warranted routinely.

Evidence level: Moderate.

Recommendation grade: Strong.

Fluid balance

Patients undergoing abdominal surgery often receive excessive volumes of intravenous fluids during and in the days after surgery. This frequently exceeds actual fluid losses, resulting in a weight gain of 3-6 kg¹⁴⁵⁻¹⁴⁶. Excessive overload of salt and water in the perioperative period increases postoperative complication rates and delays the return of gastrointestinal function¹⁴⁶⁻¹⁴⁹. This strongly suggests that near-zero fluid balance must be achieved perioperatively. Identifying the correct amount needed is a challenge that is also complicated by the use of epidural analgesia, which causes vasodilatation and intravascular hypovolemia with hypotension, which is often interpreted and treated as fluid depletion. The result is copious volumes of fluid administration when a vasopressor would be preferable¹⁵⁰. In a meta-analysis of elective colorectal patients, intraoperative flow-guided fluid therapy with trans- esophageal Doppler (TOD) ultrasonography to accurately assess and monitor fluid status in relation to cardiac output reduced complications and LOSH¹⁵¹. Other methods, such as lithium dilution (LiDCO) are evolving and may prove to be equivalent to TOD.

Hyperchloremic acidosis results from infusion of 0.9% saline. Recent studies have shown that excessive use of 0.9% saline leads to renal edema, reduced flow velocity in the renal artery, renal cortical tissue perfusion¹⁵², and an overall increase in postoperative complications when compared with balanced crystalloids¹⁵³. A recent meta-analysis¹⁵⁴ has suggested that postoperative complications and LOSH are significantly reduced if patients undergoing major abdominal surgery are maintained in fluid balance rather than fluid imbalance. The meta-analysis concluded that too much and too little fluid is detrimental to outcome. Although colloids produce better blood volume expansion and less interstitial space overload than crystalloids¹⁵⁵, there is no evidence from clinical trials and meta-analyses that colloids result in better clinical outcome than crystalloids¹⁵⁶. To avoid unnecessary fluid overload, vasopressors should be considered for intra- and postoperative management of epidural-induced hypotension.

Summary and recommendation: Near-zero fluid balance as well as avoiding overload of salt and water results in improved outcomes. Perioperative monitoring

of stroke volume with trans-esophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9% saline.

Evidence level: Fluid balance: High.

Esophageal Doppler: Moderate.

Balanced crystalloids vs. 0.9 % saline: Moderate.

Recommendation grade: Strong.

Perianastomotic drains

Perianastomotic drains are believed to ameliorate the consequences of minor leaks and allow them to be treated as controlled fistulas. One RCT comparing suction drain to no drain after pancreatic cancer resection did not show significant differences in terms of mortality or overall complication rate¹⁵⁷. Moreover, patients who used these drains had a significantly greater incidence of intra-abdominal collections or fistulas (pancreatic and entero-cutaneous)¹⁵⁷. A series with historic controls failed to identify any increased risk after a no-drain regimen, but this design is prone to selection bias¹⁵⁸. Evaluation of early (post- operative day 3) versus late (postoperative day 5 and beyond) drain removal has been examined in an RCT¹⁵⁹. Early removal of the drain in patients at low risk of pancreatic fistula (amylase value in drains <5000 U/l at postoperative day 3) was associated with a significantly decreased rate of pancreatic fistula, abdominal and pulmonary complications. Until further data are available, a conservative approach with systematic postoperative drainage and early removal in patients at low risk of pancreatic fistula (firm pancreas, wide pancreatic duct¹⁵⁹⁻¹⁶¹) is recommended. In accordance with this notion, it would seem wise to place a drain in patients with a soft pancreas and narrow duct, and leave this drain in situ slightly longer.

Summary and recommendation: Early drain removal after 72h may be advisable in patients at low risk (i.e., amylase content in drain <5000 U/l) for developing a pancreatic fistula. There is insufficient evidence to recommend no routine use of drains routinely, but their use is based only on low-level evidence.

Evidence level: Early removal: High.

Recommendation grade: Early removal: Strong.

Somatostatin analogues

Somatostatin and its synthetic analogues (e.g. octreotide) reduce splanchnic blood flow and the release of pancreatic exocrine secretion¹⁶². The rationale for its use is to reduce the risk of pancreatic anastomotic fistulas by decreasing the volume of pancreatic exocrine secretions. Several RCTs have resulted in four systemic reviews and meta-analyses that assessed the possible role of a protective effect in pancreatic surgery¹⁶³⁻¹⁶⁶. The most recent meta-analysis involved 17 trials with 1457 patients

undergoing PD and 686 undergoing distal or other resections¹⁶⁶. The authors concluded that the use of somatostatin analogues reduced the crude rate of pancreatic fistulas, but that the rate of clinically significant fistulas as well as the overall major morbidity and mortality remained unchanged¹⁶⁶. Subgroup analyses of the PD patients showed no significant effect of somatostatin/octreotide on any of the reported outcomes¹⁶⁶. The beneficial effect of somatostatin commonly believed to be present in cases with acknowledged risk factors (soft pancreas, small pancreatic duct) is not substantiated by the available evidence.

Summary and recommendation: Somatostatin and its analogues have no beneficial effects on outcome after PD. In general, their use is not warranted. Subgroup analyses for the variability in the texture and duct size of the pancreas are not available.

Evidence level: Moderate.

Recommendation grade: Strong.

Urinary drainage

A meta-analysis of RCTs on urinary drainage after surgery showed that suprapubic catheterization was superior to transurethral catheterization¹⁶⁷. Patients found suprapubic catheters more acceptable, and morbidity was reduced¹⁶⁷. Most trials in the meta-analysis evaluated urinary drainage for 4-7 days. The only trial in the meta-analysis focusing specifically on hepatopancreaticobiliary surgery¹⁶⁸ included 82 such patients out of a total of 146. The number of patients undergoing PD was not stated. The authors found no difference in outcomes, but argued that suprapubic catheterization is probably superior; however, the difference is likely to be small. A recent RCT with a large number of patients undergoing major surgery with thoracic epidurals found removal of transurethral catheter on postoperative day 1 to be superior in terms of infection rates and did not lead to an increased rate of re-catheterization when compared with removal on day 3-5¹⁶⁹.

Summary and recommendation: Suprapubic catheterization is superior to transurethral catheterization if used for >4 days. Transurethral catheters can be removed safely on postoperative day 1 or 2 unless otherwise indicated.

Evidence level: High.

Recommendation grade: For suprapubic: Weak.

Transurethral catheter out postoperative day 1-2: Strong.

Delayed gastric emptying (DGE)

DGE is a specific problem after PD occurring in ≈10-25% of patients^{6,7,9,170}. It may be necessary to insert a nasojejunal feeding tube in a minority of patients. DGE is as

common after pylorus- preserving PD as after a classic Whipple's procedure¹⁷¹. In this context, DGE was less common in a fast-track group compared with a traditional care group in one study⁷. For pylorus-preserving PDs, it has been shown that constructing the duodenojejunostomy in an ante-colic (as opposed to a retro-colic) fashion results in less DGE¹⁷². Occasionally, DGE persists and may necessitate enteral feeding delivered beyond the gastrojejunostomy (or even parenteral nutrition). The available definition of DGE¹⁷⁰ is based on the assessed need for nasogastric tubes. The entity is susceptible to being over- diagnosed, and care should be taken to ensure that it does not encourage the insertion of nasogastric tubes as routine practice.

Summary and recommendation: There are no acknowledged strategies to avoid DGE. Artificial nutrition should be considered selectively in patients with DGE of long duration.

Evidence level: Very low.

Recommendation grade: Strong.

Stimulation of bowel movement

There is no high-level evidence to support a specific motility-enhancing drug. A multimodal approach involving the use of oral laxatives such as magnesium sulphate or bisacodyl may induce early gastrointestinal transit after colonic resections^{173,174}. Some protocols for fast-track pancreatic surgery have recommended the use of laxatives postoperatively¹⁷⁵. In a series of 255 pancreatic resections (almost 60% PDs), oral administration of magnesium (200 mg/day) and lactulose in addition to metoclopramide on postoperative day 1 to support early start of normal bowel function was advocated⁶. Along with other multimodal prescriptions, the authors concluded that this protocol was associated with a low prevalence of re-admission to hospital, mortality, and morbidity rates⁶. However, no randomized trial has investigated the use of oral laxatives, so further studies are necessary. As noted above, the appropriate use of epidurals and maintaining a near-zero fluid balance are associated with an enhanced return of bowel activity after abdominal surgery^{88,146}. Chewing gum has been shown to be safe and beneficial in restoring gut activity after colorectal surgery¹⁷⁶⁻¹⁷⁸.

Summary and recommendation: A multimodal approach with epidural and near-zero fluid balance is recommended. Oral laxatives and chewing gum given postoperatively are safe and may accelerate gastrointestinal transit.

Evidence level: Laxatives: Very low.

Chewing gum: Low.

Recommendation grade: Weak.

Postoperative artificial nutrition

Most patients tolerate normal oral intake soon after elective PD. Early oral intake in this patient group has been shown to be feasible and safe.^{6,144} A recent large multicenter RCT in patients undergoing only major upper gastrointestinal and hepato-pancreaticobiliary surgery (including >80 patients undergoing PD) investigated this issue and concluded that allowing early diet is safe for these patients and that enteral tube feeding did not confer benefit¹⁴⁴. This is in keeping with other reports¹⁷⁹, including enteral tube feeding after other major abdominal surgery¹⁸⁰. There are no data to support the idea that a surgeon-controlled stepwise increase from spoonfuls of water to a normal diet is safer than a patient-controlled routine as long as patients are informed about the potential of impaired gut function in the early postoperative period. Enteral or parenteral nutritional support will often be necessary if major complications develop. Parenteral nutrition is indicated only in those patients who cannot eat and drink normally, and who in addition cannot tolerate enteral nutrition¹⁸¹. Parenteral nutrition should be reduced as the tolerance of enteral nutritional intake increases.

Enteral tube feeding delivers artificial nutrients, but is a non-volitional intervention that bypasses the cephalic-vagal digestive reflex and carries significant risks^{182,183}. Traditionally, benefit has been shown compared with parenteral nutrition and is based on an assumption that an early- or patient-controlled oral diet is unacceptable³¹. The superiority of enteral tube feeding over an early oral diet after major abdominal surgery (including after PD), has not been documented and the opposite might well be the case (as outlined above). Oral nutritional supplementation post-hospital discharge seems appealing in a patient group known to struggle to achieve dietary goals, but evidence for a benefit is lacking¹⁸⁴.

Summary and recommendation: Patients should be allowed a normal diet after surgery without restrictions. They should be cautioned to begin carefully and increase intake according to tolerance over 3-4 days. Enteral tube feeding should be given only on specific indications and parenteral nutrition should not be employed routinely.

Evidence level: Early diet at will: Moderate.

Recommendation grade: Strong.

Early and scheduled mobilization

The relatively slow resumption of function in the stomach and gut together with significant surgical trauma leads to a prolonged recovery period in PD patients compared with many other laparotomy patients even in the absence of major complications. Extended bed rest is associated with several unwanted effects^{185,186}. Scientific data are lacking, but the authors have observed the feasibility of written

instructions for patients with detailed day-to-day targets postoperatively. This ensures autonomy and cooperation from patients. Daily progress can be monitored with diaries or with simple monitoring devices for patient activity. Analgesia must be adequate not only for rest, but also for early mobilization.

Summary and recommendation: Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet the daily targets for mobilization.

Evidence level: Very low.

Recommendation grade: Strong.

Audit

Systematic audit is essential to determine clinical outcome and to establish the successful implementation and continued use of a care protocol. There are also indications that audit per se improves clinical results through feedback¹⁸⁷. It is vital to distinguish between unsuccessful implementation and lack of desired effect from an implemented protocol if results are short of the desired quality standards. Comparison with other centers using similar protocols via identical tools of registration and identical definitions of key factors is needed.

Summary and recommendation: Systematic audit improves compliance and clinical outcomes.

Evidence level: Low.

Recommendation grade: Strong.

Conclusion

ERAS® programs have been strongly associated with reduced LOSH but this may not be the best indicator of the quality of functional recovery. An awareness of goals that improve safety and clinical outcomes is of greater importance. Emphasis must be placed on reducing morbidity with the introduction of standardized and appropriate enhanced recovery programs based on best available scientific evidence.

Multimodal ERAS programs are complex interventions that pose significant challenges to evaluation by conventional RCTs^{175,188}. The most obvious of these challenges are standardization of the intervention and a rapidly closing window of opportunity from ethical and practical concerns¹⁸⁹. This may, to some extent, explain the relative paucity of RCTs evaluating ERAS programs and the somewhat limited effect that has been shown on endpoints other than LOSH. In addition, interventions like these pathways are prone to show significant Hawthorne or Trial effects¹⁹⁰⁻¹⁹¹. This implies that the collateral effect on the infra-structure and management culture to implement such a comprehensive program will have beneficial consequences in addition to those caused

by the protocol items themselves or their synergistic effect. As has also been pointed out for this patient group¹⁷⁵, this is nevertheless a benefit related to the use of these programs. For these reasons it may be argued that a randomized evaluation of an evidence-based ERAS protocol against traditional care may not be the way forward. Furthermore, it seems reasonable to propose that, if RCTs have proven the benefit (item by item) of two wheels, two pedals, a frame, a chain and a handle bar, then a bicycle is highly likely to be a valuable tool. Feasibility, however, must be ensured. Hence, multicenter and multinational prospective validation of a unified and comprehensive perioperative care protocol in consecutive cohorts of patients undergoing PD is warranted.

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CHAPTER 7

Study protocol PANDA trial:

PAncreaticoduodeNectomy and Drainage After surgery: *Multicenter randomized controlled trial of prophylactic abdominal drain versus no drain policy after pancreaticoduodenectomy, within an enhanced recovery after surgery pathway*

MME Coolen, V van Woerden, RM van Dam, G van Breukelen, K Lassen, MG Besselink, CHC Dejong

ABSTRACT

Background

Prophylactic abdominal drainage after pancreaticoduodenectomy has been standard care for many years. However, recent studies assessing the efficacy of prophylactic abdominal drains suggest these drains have no advantage over avoiding prophylactic postoperative drainage. In fact, some studies show that abdominal drains may even be harmful in terms of an increased risk of infection. This study was designed to assess the feasibility and safety of omitting prophylactic abdominal drainage after pancreaticoduodenectomy.

Methods and design

Trail design: A multicenter, randomized controlled trial with stratification for center, and two treatment arms: prophylactic abdominal postoperative drainage versus a no drain policy within an enhanced recovery after surgery pathway.

Participants: The patients included in this study are patients above the age of 18, who require elective pancreaticoduodenectomy, such as a Pylorus Preserving Pancreaticoduodenectomy (PPPD) or a classical Whipple's procedure, who have an ASA score of I through III and are able to give informed consent. Patients undergoing double bypass surgery are analyzed as a separate group. Intervention: Omitting prophylactic postoperative abdominal drain.

Comparison: Prophylactic abdominal postoperative drain versus a no drain policy within an Enhanced Recovery After Surgery pathway.

Outcome: The primary outcome is the need for (re-)interventions, which are defined as drain related complications. Re-interventions are defined as the administration of antibiotics, endovascular coiling or stenting, ultrasound or CT guided drainage or relaparotomy. Secondary outcomes of interest are overall complications, a composite endpoint for pancreaticoduodenectomy, functional recovery and delay in discharge, readmissions, mortality and total length of hospital stay.

Discussion

This randomized controlled trial will shed light on whether prophylactic drainage after pancreaticoduodenectomy can be abandoned.

INTRODUCTION

Pancreaticoduodenectomy (PD) is a surgical procedure with morbidity rates nowadays varying from 30 to 65%, with leakage of the pancreaticojejunostomy being the most feared complication. Recent advances in surgical techniques have decreased the mortality rate for pancreatic surgery to less than 5%¹.

Intra-abdominal prophylactic drainage after surgery has been standard clinical practice for many decades. Many surgeons believe that postoperative drainage allows for the early detection of anastomotic leakage of the pancreaticojejunostomy, gastrojejunostomy or hepatojejunostomy as well as postoperative hemorrhage and that it may prevent fluid collections^{2-4,6,10}. However, recent studies assessing the efficacy of postoperative drains in abdominal surgery show that placement of a postoperative drain might not be advantageous over omitting a postoperative drain³⁻⁶. Kawai et al. already established that short term post-operative drainage in pancreatic surgery has favorable effects over long term drainage⁶. Other studies suggest that routine placement of drains after pancreatic surgery is unnecessary and may be harmful to the patient^{3,5}. There is sufficient evidence that prophylactic abdominal postoperative drains do not always drain fluid or hemorrhagic collections. It is therefore questionable whether drainage is useful if fluids are not adequately drained and can still become infected^{2,3}. In several studies the feasibility of early drain removal was assessed, and these studies suggested early drain removal did not result in an increase in mortality or morbidity but actually reduced the rate of pancreatic fistula and intra-abdominal infections^{6,8,9,11}.

Postoperative drains are uncomfortable, can cause pain and interfere with mobilization and therefore may delay recovery. An Enhanced Recovery After Surgery (ERAS) pathway aims for an accelerated recovery in which early mobilization is one of the main items^{8,9,11}.

Information about prophylactic postoperative drainage after pancreatic resection remains sparse and controversial. This study was designed to gather conclusive information regarding the use of postoperative prophylactic abdominal drainage after PD.

METHODS/DESIGN

Study Design

The PANDA-Trial is a multicenter, international, randomized controlled trial, conducted after elective PD in adult patients for a pancreatic neoplasm. Prophylactic postoperative drainage versus a no drain policy within an enhanced recovery after

surgery pathway will be assessed. Within each center, patients will be randomly allocated to receive a prophylactic abdominal drain after surgery versus no drain.

Objective

The objective of this study is to assess the feasibility and safety of omitting prophylactic abdominal postoperative drainage after pancreatic surgery.

Outcome

Primary study parameter

Primary outcome: rate of patients undergoing radiologic and/or surgical complications. All radiological and/or surgical interventions (Dindo 3a and above) for complications are documented and categorized (Table 7.1). Interventions are defined as image guided percutaneous drainage, endovascular coiling or stenting, or relaparotomy.

Table 7.1 Dindo-Clavien classification

Grade	Definition
Grade I	Any deviation from the normal post-operative course, without the need for intervention of any kind. Allowed therapeutic regimens are: anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This also includes wound infections treated at bedside.
Grade II	Requiring pharmacological treatment with drugs other than described for Grade I. This includes blood transfusions and total parenteral nutrition.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia.
Grade IIIb	Intervention under general anesthesia.
Grade IV	Life-threatening complication requiring ICU management (including CNS complications)*
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multi organ dysfunction
Grade V	Death of a patient
Suffix "d" (disability)	This is added if the patient still suffers from the complication at the time of discharge

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Secondary study parameters

- 1) Overall post-operative complications
Complication rates in both groups are documented, analyzed and compared.
- 2) Composite Endpoint for Pancreaticoduodenectomy¹²
Also, the incidence of the following composite endpoint is reported and analyzed.
The composite endpoint consists of:
 - Intra-abdominal abscess

- Sepsis
- Gastro-jejunostomy leakage
- Hepatojejunostomy/bile leakage
- Pancreatic Fistula (pancreaticojejunostomy-, pancreaticogastrostomy leakage)
- Post-pancreatic surgery hemorrhage
- Delayed Gastric Emptying
- 90 day- mortality

3) Functional recovery

Functional recovery is considered a secondary outcome of the study and is registered in order to determine whether or not there is a delay in discharge.

Therefore recovery criteria are defined as follows:

- Adequate pain control with oral analgesia only
- Tolerance of solid food
- No intravenous fluids
- Independently mobile or same level as prior to admission

The rates of functional recovery and the cause of delay of discharge will be analyzed and compared between the drainage and no-drainage group. Functional recovery criteria are equal to discharge criteria. In practice, patients often meet recovery criteria but are not discharged from the hospital. Reasons for this delay in discharge after recovery can be due to practical or logistical problems.

4) Discharge criteria

When functional recovery criteria have been met, the patient can be discharged if he or she is willing to go home. Therefore discharge criteria are defined as follows: adequate pain control with oral analgesia only, tolerance of solid food, no intravenous fluids, independently mobile or same level as prior to admission, all of the above and willing to go home.

5) Length of Hospital Stay (LOS)

To assess whether discontinuing postoperative abdominal drainage has an effect on postoperative length of hospital stay the difference in hospital stay between both groups will be assessed. LOS will be measured as days after surgery, with the day of operation as day 0. Next to delay in discharge and its causes, the total length of hospital stay is documented.

6) Mortality

Pancreatic surgery is commonly known for its high morbidity and mortality rates. Death is the most serious complication of pancreatic resections and in order to continuously assess the safety of the study this also is an outcome of interest and is considered a secondary outcome of the study. Causes of death will be analyzed to check for associations between death and surgery, drainage or disease. Mortality will be scored after 90 days of operation.

7) Readmissions

Readmission in this study is defined as re-hospitalization as a consequence of a complication of the primary operation. Readmission can be an important indication of complications or a result of early discharge and is therefore considered a secondary outcome of this study. The reason for readmission and the Dindo-classification of the cause of readmission will be analyzed.

Readmission for recurrent or progressive disease is not defined as a readmission. Abdominal wall herniation is a long-term complication and is not considered to be an endpoint of this study.

Hypothesis

Drains are typically placed as result of long standing practice without robust evidence. An abdominal drain does not always contribute to the patient's health and sometimes may even be harmful. We hypothesized that avoidance of prophylactic abdominal drainage after pancreaticoduodenectomy leads to fewer secondary interventions, fewer complications and a reduction in length of hospital stay.

Setting

The PANDA-Trial will be conducted as a multicenter international randomized controlled trial.

Inclusion

The baseline demographics for patients participating in the PANDA-trial are outlined in Table 7.2. The patients included in this study are patients above the age of 18 years who require elective PD such as PPPD and Whipple's procedure. Patients planned for undergoing PD but who turn out to receive a double bypass or no operation (e.g. in case of irresectability of the process) will be considered a subgroup within this study and will be analyzed separately.

For inclusion, all of the following inclusion criteria must be met: 1) the patient is diagnosed with a pancreas head tumor, 2) the patient will undergo elective PD, 3) the patient's age is more than 18 years, 4) the patient has ASA I, II, or III status 5) the patient has signed a written informed consent.

Exclusion criteria are: 1) patients undergoing emergency surgery, 2) patients with an ASA IV or V status, 3) patients who are pregnant, or 4) the impossibility to obtain informed consent.

Table 7.2 Baseline demographics for patients participating in the PANDA-trial

Age	Years	
Gender	Male / Female	
Classification tumor	1. Pancreas head Neoplasm	4. Chronic pancreatitis
	2. Duodenum Neoplasm	5. Peri-ampullary neoplasm
	3. Ampullary Neoplasm	6. Other
Co-morbidity	0. None	4. Portal hypertension
	1. Cardiovascular diseases	5. Cirrhosis
	2. Pulmonary diseases	6. Recent Alcohol abuse
	3. Diabetes Mellitus	7. Other
Body Mass Index	Weight (kg) / Height ² (m)	
Smoking	Yes / No	
Social environment	1. Single / Widow(er)	3. Single, with Children
	2. Cohabitation / Married	4. Cohabitation / Married with children
Actual performed surgery	1. Whipple	3. Double Bypass
	2. PPPD	4. Other
Duration of operation	Minutes	
ASA-classification	I / II / III	
Epidural	Yes / No	
Pre-operative Antibiotics	Yes / No	
Functional drain	Yes / No	

Number of participants

A RCT by Conlon et al.², randomizing between a drain or no drain, showed a reduction in radiologic or surgical interventions from about 21.5% to 12% in the no drain group. Our current intervention percentage is 25%. The sample size calculations were based on the premise of reducing the percentage of patients needing intervention from 25% to 12.5%. With a alpha set at 0.05 (two sided) and a β of 0.2 yielding an 80% power, data of 306 patients undergoing a Whipple or PPPD procedure need to be analyzed. Assuming there is a 10% withdrawal rate, a total of 340 patients need to be included in this study. Adjustment for center, by treatment effects and prognostic factors necessitates a further increase to 360 patients, which implies 180 per treatment arm.

Randomization procedure

Within each center, patients will be randomized in blocks of size 10 by equal allocation, meaning each participant has an equal likelihood to will be randomized in the drain or no drain group. Computerized randomization will be pre-stratified on center and in blocks of size 10 to ensure balanced allocation in every center. The patients will be divided into two groups: a control group receiving a prophylactic abdominal drain after PD (group A), and group receiving no drain (group B).

Computerized randomization will take place after the operation before closing the abdomen. If patients are randomized to receive a drain, the drain will be placed by the surgeon during the operation (PD) directly before closure of the abdomen. The drain will be removed at postoperative day 4.

Blinding

The study group will not receive a placebo drain of any kind because the effect of increased mobility on hospital stay will also be assessed, and because a placebo drain might, just like a real drain, increase the risk of infections and thereby reduce the contrast between both treatment arms with respect to the primary outcome, i.e. the need for (re-)intervention. Blinding of physicians or patients was not an option in this study. The possibility of adding a 'placebo' drain by attaching a drain to the abdominal wall, filling the container with a saline solution and covering up the container by a non-transparent plastic bag was considered. However, this was abandoned on practical and ethical grounds. As a placebo drain was not feasible, outcome assessment could not be blinded.

Interventions

Investigational treatment

Within each center, patients in this study will be randomized in a drain or a no-drain group (see flowchart) in blocks of size 10. The patients in the drain group constitute the control group, which will receive 1 or 2 drains according to routinely applied protocols. The no-drain group represents the study group and will undergo the exact same operation as the drain group. The only difference is that these patients will not receive a prophylactic postoperative abdominal drain.

Both the control group and the study group will undergo treatment within an Enhanced Recovery After Surgery program. The ERAS program especially designed for pancreatic surgery is shown in appendix 3 and 4. The program includes; clear liquids up to 2 hours before surgery, no pre-anesthetic medication, preoperative antibiotics, preoperative heparin, epidural anesthesia, no nasogastric drainage or removal of the nasogastric drainage directly after surgery, food at will postoperatively, early mobilization postoperatively, avoidance of long-term acting anesthetics, normothermia during surgery and adequate pain control¹³.

Patients are asked to keep a postoperative journal until their discharge in which can be described whether certain postoperative recovery goals are met (e.g. out of bed for 2 hours, drinking 0.5 l of water), also patients are asked to point out on a scale how much pain they experience and if they feel nauseous. Patients will not receive additional monitoring as part of the PANDA-Trial. They will be monitored on the recovery and the surgical ward twice daily according to normal healthcare standards.

Additional drainage

When additional drainage is required, irrespective of the cause or setting of the requirement, the drain should be placed as described by routinely applied protocols. Additional drainage is considered an intervention and is recorded accordingly.

Follow-up

Patients will not receive a separate follow up for this study. Readmissions and mortality are actively checked after 30, 60 and 90 days from discharge of each patient. They are registered if and when they occur within 90 days from surgery either in hospital or after discharge from the hospital or when readmission is a consequence of the pancreatic surgery.

Monitoring

All adverse events are reported and assessed by a Data Safety Monitoring Board and in case of serious adverse events such as death, this will be reported to the Medical Research Ethics Committee (MREC) as well. The investigator will inform the patients if serious adverse events occur, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. This also applies if the control group experiences more adverse effects than the study group. The study will be suspended pending further review by the accredited MREC. The investigator is in charge of keeping all patients informed.

Statistical analysis

Descriptive statistics

1) Baseline characteristics

The baseline characteristics of the participating patients will be summarized with descriptive statistics per treatment arm and overall in a table. Quantitative characteristics are summarized by their mean and standard deviation, categorical characteristics are summarized by percentages.

2) Interventions and complications

Interventions and complications are presented as frequencies per treatment arm per center and per treatment arm in total, using patients as units of analysis. Severity of interventions of complications (DINDO-classification) and the complications will likewise be summarized. Complications will also be registered as a Composite Endpoint, showing drain related complications as a positive outcome. Drain related complications are defined as; anastomotic leakage (defined according to International Study Group of Pancreatic Fistula, ISGPF)¹⁴, intra-abdominal collections and intra-abdominal hemorrhage (defined according to the International Study Group of Pancreatic Surgery, ISGPS classification)¹⁵.

3) Readmissions

The number of readmissions (shown in percentage of the population), the cause of readmission and interventions are registered.

4) Length of hospital stay

The length of hospital stay is measured in days and shown in mean and median number of days with standard deviation, per center and for the total sample. Length of hospital stay is defined as, days/nights in hospital, the day of operation being day 0.

5) Mortality

Mortality is defined as death within 90 days of surgery related to the surgery. Death due to recurrent or progressive disease is not defined as mortality in this study. Mortality is displayed as percentage of the study population, per center and for the total sample.

6) Functional recovery

Functional recovery is registered and analyzed to identify causes of delay in discharge. Furthermore, the number of days the patient resides in the hospital despite functional recovery is an outcome of interest.

7) Amylase concentration in drain fluids

Amylase can be measured in patients with a functional drain when one suspects the presence of an anastomotic leakage. Amylase is measured in Units / Liter and will be presented as mean value with standard deviation.

Inferential statistics

The primary efficacy analysis will be an intention-to-treat analysis, i.e. with patients grouped by treatment assignment (irrespective of actual treatment). The secondary analysis will be with grouping by actual treatment or “per protocol” (irrespective of assigned treatment). We note that this secondary analysis may suffer from hidden confounders, depending on the causes of, and reasons for, protocol deviation.

To correct for such confounding as much as possible, the reason for protocol deviation (e.g. a complication during surgery) will be documented, and information on the occurrence of such reasons/complications will be recorded for all patients in both arms to allow statistical corrections afterwards.

An interim analysis will be performed after 50% of the planned number of patients has been included, that is, after the first 180 patients. This analysis concerns efficacy as indicated by the primary outcome, and safety as indicated by mortality. The following stopping rules will be used:

Efficacy-stop: stop the trial if the primary outcome difference between both treatment arms (drain and no drain) is significant at $\alpha=0.005$ two-tailed, following the O’Brien and Fleming (1979) cut-off for a single interim analysis halfway a trial with a final $\alpha=0.05$ two-tailed. The significance test at interim has a power of 44% to detect an outcome difference of 25% with drain against 10% without drain, and a power of 71% for a difference of 25% versus 5%. The power at the final analysis is as described in the section with the sample size calculation.

Safety-stop: stop if at least one of the following two criteria is met:

- 1) Mortality is significantly higher in the no-drain arm (new treatment) than in the drain arm (standard treatment), using a one-tailed test with $\alpha=0.10$. This test has a power of 50% to detect a difference in mortality of 5% with drain against 10% without drain.
- 2) Mortality in the no-drain arm is significantly higher than 5%, following a one-tailed test with $\alpha=0.10$. The trial will thus stop if mortality in the no-drain arm equals or exceeds 8 of 90 patients (this applies with and without continuity correction). This test has a power of 82% to detect a true mortality of 10% in the no-drain arm.

Dichotomous outcomes will be analyzed with logistic regression, with a predictor's treatment, center, and possibly prognostic baseline variables like age, sex, general health status to increase power and precision for the treatment effect of interest. Continuous outcomes such as length of hospital stay will be analyzed with linear regression, possibly after data transformation in case of severe non-normality or outliers. The primary and secondary outcomes are univariate without correction for confounders, but with the pre-stratification variable center as covariate. Other prognostic variables are subsequently included to increase power for the test of the outcome difference between arms, and to increase precision of the effect estimate, by reducing unexplained variance. These other variables will be dropped from the model one-by-one if not significant at $\alpha=0.05$ two-tailed. Outcome results per center will be presented if treatment by center interaction is found.

Consent and ethical considerations

Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (October 2008) and with the Medical Research Involving Human Subjects Act.

Recruitment and consent

The surgeon sees patients eligible for PD in the out-patient clinic. He will inform the patients about the study from the moment patients are going to be planned for operation and will provide patients with written study information. Patients will be able to read the information about the study at home and will be given two weeks to reflect on their participation in the study. The investigator will contact the patient after 2 weeks to assess whether the patient is willing to participate. If a patient is willing to participate a written informed consent will be obtained by the investigator.

Individual withdrawal

Individuals can leave the study at any time without explanation and without any consequences. The investigator can decide to withdraw an individual from the study for

urgent medical reasons. If the operating physician decides to defer from the randomization this is documented and analyzed using an intention to treat analysis.

DISCUSSION

The use of surgically placed prophylactic abdominal drains after pancreaticoduodenectomy is still considered as routine in daily practice. The fear of major complications following a pancreatic leak or hemorrhage which might go unnoticed without a drain keeps surgeons from omitting abdominal drainage after surgery. Some surgeons have adopted an early drain removal policy to avoid the late drain-associated complications but to take advantage of the beneficial effects as a detector of early postoperative problems. However, some important leaks become only apparent later in the postoperative course, which would be after the early removal of a drain. Evidence for omitting drainage after pancreaticoduodenectomy currently presented is sparse and of low level. To change practice high level evidence needs to be gathered, hence a randomized controlled trials need to be conducted. With this multicenter international RCT in which we randomize between prophylactic drainage or no prophylactic drainage after pancreaticoduodenectomy with patients managed in an enhanced recovery after surgery pathway we hope to shed light on the risk and benefits of omitting a postoperative intra-abdominal drain.

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PART III

Evaluation of implementing an ERAS program in liver and pancreatic surgery

CHAPTER 8

Initial experience with a multimodal enhanced recovery program in patients undergoing liver resection

RM van Dam, PO Hendry, MME Coolen, MHA Bemelmans, K Lassen, A Revhaug, KCH Fearon, OJ Garden and CHC Dejong, on behalf of the Enhanced Recovery After Surgery (ERAS) Group

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ABSTRACT

Background

Accelerated recovery from surgery has been achieved when patients are managed within a multimodal Enhanced Recovery After Surgery (ERAS) protocol. This study evaluated the benefit of an ERAS program for patients undergoing liver resection.

Methods

The ERAS protocol of epidural analgesia, early oral intake and early mobilization was studied prospectively in a consecutive series of 61 patients. Outcomes were compared with those in a consecutive series of 100 patients who underwent liver resection before the start of the study. Endpoints were postoperative length of hospital stay, postoperative resumption of oral intake, readmissions, morbidity and mortality.

Results

Fifty-six patients (92%) in the ERAS group tolerated fluids within 4h of surgery and a normal diet on day 1 after surgery. Median hospital stay, including readmissions, was 6.0 days compared with 8.0 days in the control group ($P<0.001$). There were no significant differences in rates of readmission (13 and 10% respectively), morbidity (41 and 31%) and mortality (0 and 2%) between ERAS and control groups.

Conclusions

The ERAS fast-track protocol is safe and effective for patients undergoing liver resection. It allows early oral intake, promotes faster postoperative recovery and reduces hospital stay.

INTRODUCTION

In the past two decades, the application of multimodal perioperative care protocols, commonly referred to as fast-track or enhanced recovery programs, has achieved significant improvements in the outcome of a variety of surgical procedures. By targeting factors that delay postoperative recovery (pain, gut dysfunction and immobility), and combining a series of interventions to reduce perioperative stress and organ dysfunction, such programs have been shown to accelerate postoperative recovery and reduce length of hospital stay. This can be achieved with an unaltered or even reduced rate of postoperative complications¹. Protocols based on postoperative pain control through continuous mid- thoracic epidural anesthesia, stimulation of gut motility, early physical reactivation, and limited use of catheters, tubes and drains have resulted in improved convalescence for many surgical procedures, including colonic surgery, open aortic aneurysm repair and esophageal surgery²⁻⁷. In the past 5 years, the protocol in elective colonic surgery established by the Enhanced Recovery After Surgery (ERAS) Group has led to a reduction in median hospital stay from 9 to 5 days⁶.

Within a traditional perioperative care pathway median hospital stay following liver surgery ranges from 8 to 14 days⁸⁻¹¹. Morbidity is reasonably predictable, with hemorrhagic complications occurring predominantly during surgery or in the early postoperative phase, and biliary complications, intra-abdominal abscess or liver failure in the later postoperative phase^{12,13}. It was hypothesized that application of an enhanced recovery program for patients undergoing liver surgery would result in accelerated recovery and a shorter hospital stay. The main aim of the present study was to test the feasibility, safety and effectiveness of an ERAS protocol in patients undergoing liver surgery in two tertiary referral liver units in Europe.

METHODS

The ERAS liver study was initiated within the collaborative ERAS Group, and conducted in two units that perform high-volume liver surgery. The study was a prospective case series implementation study comparing outcomes with those in a historical control group.

The ERAS patient group comprised a consecutive series of 61 patients admitted to either the liver unit of Maastricht University Medical Center, The Netherlands, between 15 February 2005 and 31 August 2006, or the liver unit of the Royal Infirmary of Edinburgh, UK, where patient recruitment started on 1 February 2006. The control group consisted of a consecutive series of 100 patients who had liver resection in one of the two units between 1 July 2003 and 31 December 2004 (50 consecutive patients from each unit), when a more traditional care pathway was still in use. Patient and outcome data were derived from a prospectively collected database of all liver

resections performed since 1 January 2000 in both units. In both groups, patients undergoing elective liver resection for primary or secondary tumors were considered eligible for the study if they had normal underlying liver function. Patients were excluded if they required biliary reconstruction or had emergency surgery.

In both units, the same group of liver surgeons performed the liver resections in the ERAS group as well as in the control group. In Maastricht more fellows with hepatopancreatobiliary training operated in the ERAS group. Bilateral subcostal transverse abdominal incisions were used. The transection plane was determined by intraoperative ultrasonography. To avoid excessive blood loss central venous pressure was reduced to below 5 mmHg during transection using the Cavitron Ultrasonic Surgical Aspirator (CUSA®; Valleylab, Boulder, Colorado, USA) and argon beam coagulation. The portal pedicles supplying and veins draining the sectors to be resected were divided and ligated with a running polypropylene suture. After removal of the liver specimen, the raw surface of the liver remnant was subjected to argon beam coagulation and sealed with TachoSil® (Nycomed, Zurich, Switzerland). In accordance with the protocol, no abdominal drains were placed in the ERAS group and the abdomen was closed with a standard running suture.

Before the introduction of the ERAS program neither of the institutions had a written, agreed perioperative care pathway. There were no specific measures to avoid prolonged preoperative and postoperative fasting, nasogastric decompression, excessive use of intravenous fluids and systemic opioids, prophylactic abdominal drains and postoperative immobilization. This conventional postoperative care program emphasized prolonged rest for both the patient and the gastrointestinal tract.

The ERAS multimodal evidence-based recovery program protocol, which was designed originally for elective colonic surgery, was modified to cover all aspects of elective liver resection². Details of the ERAS liver protocol are given in Table 8.1.

In both groups, data were obtained prospectively during the hospital stay and for 90 days after surgery. Data recorded for each patient included morbidity, defined as complications related to the liver surgery, mortality, readmissions, postoperative hospital stay, use of preoperative chemotherapy, duration of surgical procedure, blood loss, anesthetic agents used and type of hepatectomy, defined according to the Brisbane 2000 terminology¹⁴. In the ERAS group, data on location of the epidural catheter, removal of the nasogastric tube if used, and time to resumption of oral intake and mobilization were also noted.

The primary endpoint of the study was total length of hospital stay, defined as the number of nights spent in hospital, including nights after readmission within 30 days after surgery. To facilitate objective assessment of clinical outcome and to prevent discharge too soon, predefined discharge criteria were used in the ERAS group (Table 8.2). Patients were informed about the protocol at a preadmission counseling session, where the importance of early mobilization and early oral intake were explained. Patients were discharged only if they met the discharge criteria and follow-up within

3 days was possible in the outpatient clinic. Patients were given the mobile telephone number of the operating consultant surgeon to allow direct communication and safe deployment of the protocol.

Table 8.1 Day to day care plan of patients undergoing liver resection in the ERAS program

Day before surgery:
Normal oral nutrition until midnight
No pre-anesthetic medication
Day of surgery
Carbohydrate drinks up to 2 hrs prior to surgery
Mid-thoracic epidural analgesia (local anesthetic+ low dose opioid)
Short-acting intravenous anesthetic agent
No nasogastric drainage; if used remove immediately after surgery
Warm i.v. fluids and upper and lower body air-warming device (Bair-Hugger)
Avoidance of excessive i.v. fluids (pre- and per-operative CVP <5 mmHg)
No routine drainage of the peritoneal cavity
Patient sent to recovery ward
Restart oral intake of water / nutrition ad libitum
Post Operative Day (POD) 1
Patient sent to surgical ward
Patient mobilizes a minimum of four times a day
Discontinuation of intravenous-fluids
Patient drinks at least 1.5 liters
Normal diet
Continue portable epidural analgesia (local anesthetic-low dose opioid)
1000 mg paracetamol 6 hourly
1000 mg magnesium oxide twice daily
Laboratory tests
POD 2
Continue portable epidural analgesia with local anesthetic
Stop low dose opioids
Continue mobilization a minimum of four times per day
1000 mg paracetamol 6 hourly
Normal diet
POD 3
Start NSAID's
Stop epidural analgesia
Remove urinary catheter
Continue mobilization
Normal diet
Laboratory tests
Check discharge criteria
Outpatient appointment made on postoperative day 10,11 or 12
POD 4
Check discharge criteria (Table 8.2)
Patient receives cellular phone number of operating HPB-surgeon
Discharge

Table 8.2 Discharge criteria ERAS liver protocol

Normal or decreasing serum bilirubin
Good pain control with oral analgesia only
Tolerance of solid food
No intravenous fluids
Independently mobile or at the preoperative level
All of the above and willing to go home

Patients in the control group were discharged without formal discharge criteria. The following secondary endpoints were evaluated: resumption of oral intake, defined as oral intake of water or normal food without discontinuation for at least 24h, readmissions, total morbidity, death and length of primary hospital stay, defined as the number of nights spent in hospital after surgery, excluding readmissions. Complications were registered during the primary admission or at subsequent outpatient clinic visits, after at least 6 and 30 days, using departmental liver registry databases.

Statistical analysis

Continuous data are expressed as median (range). Hospital stay, time to resumption of oral intake and postoperative duration of epidural analgesia were analyzed using the Mann–Whitney *U* test. Readmission, complication and mortality rates were analyzed using χ^2 test or Fisher's exact test. $P < 0.050$ was considered to be statistically significant. Data were analyzed using SPSS® version 13.0 for Windows® (SPSS, Chicago, Illinois, USA).

RESULTS

Patient characteristics were similar in the ERAS and control groups (Table 8.3). Types of liver resection are shown in Table 8.4. A higher proportion of patients in the ERAS group had repeat liver resections (11% versus 5.0% in control group; $P = 0.214$) and resections after intensive chemotherapy (62 versus 33.0%; $P < 0.001$).

The median (range) duration of surgery was 220 (60–420) min in the ERAS group and 270 (106–510) min in the control group ($P < 0.001$), and blood loss during surgery was 750 (0–5000) and 800 (0–6000) ml respectively ($P = 0.758$). Abdominal drains were used significantly less often in the ERAS group (2 versus 66.0%; $P < 0.001$).

In Edinburgh, the use of a nasogastric decompression tube in patients having partial liver resection had already been discontinued before 1 July 2003. In Maastricht, nasogastric decompression tubes were still used in most control patients. A nasogastric tube was inserted at induction in 37 of 47 patients in the ERAS group, significantly less frequently than in the control group (96%) ($P = 0.013$). In the ERAS group, the

nasogastric tube was removed at the end of surgery or in the recovery ward within 4 h of surgery.

Oral intake was resumed within 4 h after surgery in 56 patients (92%) in the ERAS group. Two patients required reinsertion of a nasogastric tube. The median (range) time to successful resumption of normal diet was 1 (0-3) day in the ERAS group, compared with 3 (0-14) days in controls ($P<0.001$). Three patients in the ERAS group (5%) became constipated after postoperative day 3, despite initial tolerance of normal food, but this resolved within 5 days by restricting intake.

Table 8.3 Patient demographics ERAS liver study

	ERAS N=61	CONTROLS N=100
Sex (male: female)	35:26	51:49
Age median (range)	62 years (24-82)	60 years (20-81)
ASA 1	9 (19%)	14 (14%)
ASA 2	31 (66%)	64 (64%)
ASA 3	7 (15%)	22 (22%)
Median blood loss (range)	750 mls (0-5000)	800 mls (0-6000)
Median duration of surgery (range)	220 min (60-420)	270 min (106-510)
Colorectal metastasis	51 (83.6%)	72 (72.0%)
Other metastasis	2 (3.3%)	4 (4.0%)
Hepatocellular / cholangiocarcinoma	4 (6.6%)	9 (9.0%)
Benign lesions	4 (6.6%)	14 (14%)
T4-invasive tumors in liver	0 (0%)	1 (1%)

ASA: American Society of Anesthesiologists, preoperative risk classification

Table 8.4 Type of liver resection

	ERAS N=61	Control N=100
Hemihepatectomy	20 (32.8%)	38 (38.0%)
Hemihepatectomy + ≥ 1 metastasectomies	6 (9.8%)	16 (16.0%)
Extended hemihepatectomy	7 (11.5%)	3 (3%)
Multiple (≥ 2) segmentectomy	17 (27.9%)	18 (18.0%)
Central resection / trisegmentectomy	1 (1.6%)	4 (4.0%)
Metastasectomy or mono-Segmentectomy	10 (16.4%)	21 (21.0%)
Repeat-hepatectomy %	7 (11.5%)	5 (5%)

Table 8.4b Specification of multiple (≥ 2) segmentectomies

	ERAS N=61	Control N=100
Left lateral sectionectomy	6 (9.8%)	9 (9.0%)
Posterior sectionectomy	1 (1.6%)	0
Left lateral sectionectomy + ≥ 1 metastasectomy	2 (3.3%)	0
Bisegmentectomy	4 (6.6%)	5 (5.0%)
≥ 3 segmentectomy	4 (6.6%)	4 (4.0%)

In the ERAS group, 58 patients (95%) followed the anesthetic protocol of mid-thoracic epidural analgesia commencing before surgery (0.1% bupivacaine + 2 g/ml fentanyl) with maintenance isoflurane or sevoflurane inhalation anesthesia, or intravenous propofol, as described previously¹⁵. After operation epidural analgesia comprising 0.1% bupivacaine and 2 µg/ml fentanyl was administered for at least 3 days via a portable patient-controlled device (GemStar[®] Infusion Systems; Hospira, Lake Forest, Illinois, UK) at a rate of 4-10 ml/h, combined with oral non-opioid analgesics. This differed from anesthesiological management in the control group, where 89 patients (89.0%) received epidural analgesia combined with isoflurane or sevoflurane inhalation anesthesia. In the postoperative period epidural analgesia consisting of 0.1% bupivacaine and 2 µg/ml fentanyl was administered without a specific time schedule at a daily fixed dose of 4-10 ml/h, combined with intramuscular opioids (mainly piritramide) and oral analgesics. Postoperative epidural analgesia was continued for a median (range) of 3 (1-5) days in the ERAS group and 2 (0-6) days in the control group ($P<0.001$). Epidural analgesia was discontinued earlier in the control group, and intramuscular or intravenous opioids (piritramide) were used more widely.

Outcome data are summarized in Table 8.5. There were no deaths in the ERAS group and one patient died within 30 days in the control group. A further control patient died after 62 days. Overall morbidity rates (percentage of patients with at least one complication) were 41 and 31.0% in the ERAS and control groups respectively ($P=0.197$) (Table 8.6). All complications in the ERAS group were managed by non-surgical means. Readmission rates in ERAS and control groups were similar (13 versus 10.0% respectively; $P=0.610$).

Table 8.5 Outcome of enhanced recovery program in liver surgery

	ERAS	Control	<i>P</i>
MAASTRICHT ONLY*	N=47	N=50	
Nasogastric tube (NGT)*	37 (78.7%)*	50 (100%)*	$P<0.013^*$
Removal of NGT on day of surgery	34/37 (91.9%)*	0 (0%)*	$P<0.0001^*$
MAASTRICHT & EDINBURGH	N=61	N=100	
Epidural analgesia	58 (95.1%)	89 (89%)	$P=0.253$
Abdominal drain	1 (1.6%)	66 (66%)	$P<0.0001$
Complication rate	25 (41.0%)	31 (31.0%)	$P=0.233$
Mortality	0 (0%)	2 (2.0%)	$P=0.526$
Readmission rate	8 (13.1%)	10 (10.0%)	$P=0.610$
Total length of stay (median, range), readmissions included)	6 days (3-82)	8 days (4-68)	$P<0.001$
Primary Hospital length of stay (median, range)	6 days (3-82)	8 days (4-55)	$P<0.0001$

* Maastricht only, in Edinburgh nasogastric tubes were not used in both patient groups.

Table 8.6 Complications of enhanced recovery program in liver surgery

	ERAS N=61	Control N=100	P-Value
Complications	41.0 % of patients	31.0 of patients	$P=0.197$
Bile leak	4 (6.6%)	4 (4.0%)	$P=0.479$
Liver failure	3 (4.9%)	1 (1.0%)	$P=0.121$
Sepsis	0 (0.0%)	1 (1.0%)	$P=0.433$
Abdominal abscess	5 (8.2%)	7 (7.0%)	$P=0.779$
Delayed GI function (<7 days)	3 (4.9%)	1 (2.5%)	$P=0.153$
Pneumonia	3 (4.9 %)	2 (2.0%)	$P=0.368$
Pleural Effusion	2 (3.3%)	2 (2.0%)	$P=0.634$
Pulmonary Embolism	0 (0%)	1 (1.0%)	$P=0.433$
Myocardial Infarction	2 (3.3%)	3 (3.0%)	$P=0.921$
Wound infection	9 (14.8%)	5 (5.0%)	$P<0.044$
Other minor	3 (4.9%)	16 (20.0%)	$P<0.018$

Fifty-two (85%) of 61 patients in the ERAS group were completely mobile on the third day after operation and 29 (48%) were discharged from hospital within 5 days. Median (range) total postoperative hospital stay, including readmissions, was 6.0 (3-82) days in the ERAS group and 8.0 (4-68) days in the control group ($P<0.001$) (Figure 8.1).

Figure 8.1 Total hospital length of stay (tLOS), readmissions included. Arrows = median tLOS in days, $P<0.001$, ERAS vs. control.

DISCUSSION

The present study showed that use of an evidence- based multimodal enhanced recovery program after liver resection accelerated postoperative recovery and led to a significantly shorter hospital stay. Patients managed according to the ERAS protocol were able to drink fluids within 4 h of liver resection and eat normal food on the day

after surgery. Most patients were completely mobile after 3 days and, as a consequence, almost half of the patients were discharged from hospital within 5 days. Median total hospital stay (including readmissions) was reduced from 8 to 6 days, which is considerably shorter than the 8–14 days reported by other European centers^{8–10}. Application of the ERAS protocol did not have any detrimental effect on safety in liver resection.

Based on previous experience of enhanced recovery implementation studies within these units, and attempts to randomize between fast-track and traditional care in a multicenter abdominal surgery trial^{6,16}, a randomized clinical trial comparing fast-track and traditional care was considered impractical. Both units had implemented ERAS protocols over the previous few years and, in view of the growing evidence base for such programs, a traditional perioperative protocol was felt to represent suboptimal care. More importantly, it would have been necessary for nursing and surgical staff to return to traditional perioperative care pathways. Therefore, this feasibility study was designed as a prospective case series with a historical control group.

Several important issues have become apparent from this study. Importantly, adverse outcomes, assessed in terms of readmissions, complications and deaths, were similar in the ERAS and control groups. The complication rate in the ERAS group is in keeping with recently published rates of 23–52%^{10,17–20}. Although the morbidity rate appeared to be higher in the ERAS group, the study was not sufficiently powered to determine statistical differences in the incidence of complications. Moreover, complications directly related to liver surgery, such as bleeding, bile leakage or temporary liver failure, are unlikely to be influenced by postoperative care. Avoidance of abdominal drains in this study might arguably have influenced the complication rate, but the authors consider this unlikely because the incidence of bile leak and intra-abdominal abscess was similar in the two groups. Prophylactic drains are employed in many centers to detect early complications such as postoperative hemorrhage or bile leakage, to remove intra-peritoneal fluids and to prevent abscess formation. However, there is evidence that abdominal drainage after liver resection does not reduce the incidence of re-interventions for these complications^{21–23}. Some studies have even noted higher rates of infected collections when drainage was used^{13,21,24}. This suggests that drains might be detrimental to clinical outcome by providing a route for ascending infections. Another disadvantage of drains within an enhanced recovery setting is that they represent a significant impediment to achieving early mobilization.

A few elements have proven difficult to implement universally. The use of carbohydrate drinks before surgery reduces thirst, hunger and anxiety, and is safe up to 2 h before abdominal surgery²⁵. However, a preoperative fasting policy of ‘nil by mouth from midnight’ is still common. Owing to tradition in the anesthesia department nasogastric decompression tubes were still used extensively during surgery in both groups in Maastricht, but were removed immediately after surgery in the ERAS group. This practice meant a major change in clinical routines, and did not appear to result in more

pulmonary complications in the present study. In general, nasogastric decompression is still used widely following abdominal surgery²⁶, despite evidence that it is unnecessary and can result in more pulmonary complications. Further support for avoidance of nasogastric tubes specifically in liver surgery has been published recently¹¹.

Early postoperative enteral nutrition compared with 'nil by mouth' improves clinical outcome²⁷. In the present study, oral intake of water within 4 h after surgery and institution of normal nutrition on the day after operation were well tolerated in the ERAS group. Early resumption of normal diet in combination with other elements of the enhanced recovery program is designed to reduce the occurrence of delayed gastrointestinal function after surgery and even promote appetite. Therefore, the ability of the patient to tolerate normal food is an outcome in itself. A period of delayed gastrointestinal functioning after operation, observed in a few patients, was registered as a complication. It might also be argued that a delay in gastrointestinal functioning is a physiological phenomenon that occurs after abdominal surgery in many patients. A restrictive perioperative intravenous fluid regimen may help to reduce the occurrence of delayed gastrointestinal functioning²⁸. Fluid restriction may well be an important issue in hepatic surgery and is the subject of ongoing research in the authors' units.

It is important that surgical patients are treated in an environment that encourages early mobilization⁴. Mobilization on the day of surgery was possible in Edinburgh, but was not achieved in Maastricht because the recovery unit did not contain the appropriate facilities. Adequate pain control and a substantial effort by nursing staff are required to achieve early mobilization.

In conclusion, a multimodal enhanced recovery program for patients undergoing liver resection for primary and secondary tumors, but with otherwise normal hepatic function, is feasible and effective. Patients were able to drink within 4 h of surgery, eat on the following day and were usually mobile by the third day after operation. This is indicative of earlier recovery and was accompanied by a 25% reduction in postoperative hospital stay. The fact that only half of the patients were discharged within 5 days indicates that there is further room for improvement.

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CHAPTER 9

Improving outcome after pancreaticoduodenectomy –
experiences with implementing an enhanced recovery
after surgery program

MME Coolsen, RM van Dam, A Chigharoe, SWM Olde Damink, CHC Dejong

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Abstract

Background

Pancreaticoduodenectomies (PDs) are complex surgical procedures that require high standard perioperative care. The objective of this study was to evaluate the effects on patient outcome of implementing an Enhanced Recovery After Surgery (ERAS) program for PD on patient outcome.

Methods

230 patients undergoing PD in Maastricht University Medical Center between January 1995 and January 2012 were included. Group 1 (1995-2005) received traditional care. From January 2006 several elements of an ERAS pathway for pancreatic surgery were implemented (group 2: 'ERAS-like'). From 2009 onwards the ERAS pathway was fully implemented (group 3: ERAS). Mortality, complications, readmissions and length of hospital stay (LOS) were evaluated in the subgroups and compared.

Results

Median LOS was significantly reduced from 20 days in group 1, to 13 days in group 2 and 14 days in group 3 ($P=0.001$). Median LOS of patients without complications was 16, 10 and 9 days, respectively, in group 1, 2 and 3 ($P<0.0001$). Over time, the average age of patients undergoing PD increased significantly. Complication rates as well as mortality and readmission rates did not change over time.

Conclusion

Implementing an ERAS program contributed to a decrease of LOS without compromising other outcomes. Mortality, morbidity and readmission rates stayed unchanged and more complications were managed non-operatively.

INTRODUCTION

Pancreaticoduodenectomy (PD) is a technically challenging surgical procedure and is currently the only curative treatment for malignancy in the periampullary region. In Whipple's original report on 41 pancreaticoduodenectomies, a mortality rate of 29% was recorded¹. Nowadays, centralization of PD patients in specialized centers and advances in perioperative care have resulted in mortality rates of less than 5%². Morbidity rates, however, have remained as high as 40-60%^{3,4}.

In order to further improve short-term outcome, enhanced recovery after surgery (ERAS) programs (also called "Fast Track") have been developed. These multimodal perioperative programs involving close collaboration between nurses, surgeons, anesthetists and other paramedic caregivers have received increasing interest over the last decades. The ERAS concept was initiated by Kehlet⁵ in the early 1990s for colonic surgery. Several other fields of surgery have since adopted the ERAS program achieving better postoperative outcome and decreasing length of postoperative hospitalization⁶⁻¹². In pancreatic surgery, a recent systematic review and meta-analysis suggested that an ERAS program reduces hospital stay and morbidity for PD¹³. Also, in another study of 145 patients undergoing pancreatic surgery implementing an ERAS program appeared to be feasible and safe¹⁴. An independent factor associated with early discharge in this study was early resumption of a normal diet and the lack of jaundice. In the Maastricht University Medical Center (MUMC), the ERAS program for colonic surgery was implemented from 2000 onwards¹⁵. In 2005, a pilot began in Maastricht resulting in the successful implementation of the ERAS program in liver surgery¹⁶. The impact of the ERAS liver program became more evident at the end of the 2006 pilot. Several ERAS elements were also implemented in pancreatic surgery but a standardized protocol was not available at that time. In 2009 a concept protocol was established and has been used ever since. The ERAS pancreas collaborative group, in which MUMC also participates, recently developed a consensus protocol for ERAS in pancreaticoduodenectomy¹⁷. This consensus protocol will be implemented from 2013 onwards and will be evaluated in a multicenter international prospective trial. The objective of the present study was to examine patient characteristics, indications and outcome after PD in the period from 1995 to 2011 and also to evaluate the effects of implementing the concept ERAS protocol for pancreaticoduodenectomy.

PATIENTS AND METHODS

All patients undergoing pancreaticoduodenectomy in MUMC between January 1995 and January 2012 were reviewed retrospectively by two authors (MC and AC). Four experienced surgeons carried out the surgical procedures. The procedure most commonly performed was pylorus-preserving PD with end-to-side pancreatico-

jejunostomy, end-to-side hepaticojejunostomy and retrocolic duodenojejunostomy. In case of distal stomach involvement or proximal duodenum a classical Whipple's procedure was performed. All anastomoses were hand-sewn. Until 2006 two drains were placed at the end of the procedure in the foramen of Winslow and near the pancreaticojejunostomy. From 2006, the left-sided drain was omitted and only one drain was placed near the pancreaticojejunostomy. Jejunostomy catheters were used until 2007. Octreotide was not given routinely.

From January 2006, a subset of ERAS protocol elements was implemented for all patients undergoing PD (epidural analgesia, early mobilization, use of laxatives, earlier removal of NG tube and resumption of intake). However, patients were not managed in an official care pathway. From January 2009, a protocol for ERAS pancreatic surgery was more rigorously implemented for all patients undergoing PD. The total population was therefore divided into three groups defined by these periods: Group 1 (1995-2005) "no ERAS", group 2 (2006-2008) "ERAS-like" and group 3 (2009-2011) "ERAS". Table 9.1 shows the elements of the ERAS program for pancreaticoduodenectomy applied to all patients in group 3 (ERAS). Patients managed in this ERAS program were discharged when medically fit for discharge, when functional recovery criteria were met, and if they were willing to go home. The functional recovery criteria included were good pain control with oral analgesia only, tolerance for solid food, no intravenous fluids, passage of stool, and being independently mobile at the pre-operative level.

All patients were entered into a database retrospectively from 1995 and from 2006 prospectively. The following data were extracted from the database: patient age, sex, co-morbidity, indication and type of surgery (classical Whipple's procedure or Pylorus Preserving Pancreaticoduodenectomy (PPPD)).

Postoperative outcomes were length of hospital stay (LOS), mortality, readmissions and complications. Definitions used for specific complications were according to literature standards (Appendix 5)¹⁸⁻²³. Data on postoperative interventions (radiological or surgical) were also extracted from the database. From 1995 until 2000 complications were registered once a week on paper. Since 2000 a national digital complication registration system for surgery was implemented and complications were registered prospectively. Complications were registered on paper on a daily basis and then entered into the national digital complication system by a secretary. As of 2009 this national registration system was linked to the electronic patient dossier and complications were completely registered digitally. Complications were classified using the Dindo-Clavien severity grading system²⁴. Mortality, readmissions and all complications were crosschecked with our complication registration office and adjusted when necessary.

Table 9.1 Protocol for the enhanced recovery after surgery (ERAS) program for PD

Preoperative outpatient visit
Pre-admission counseling
Give consent form and patient information
Day before surgery / Admission
Normal oral nutrition until midnight
No pre-anesthetic medication
Day of surgery
Carbohydrate drinks up to 2 hours prior to surgery
Start anti-thrombotic prophylaxis
Preoperative anti-microbial prophylaxis
Mid-thoracic epidural anesthesia
Short-acting I.V. anesthetic agent
Preferably no nasogastric drainage or removal of NG tube after surgery
Warm I.V. fluids and upper and lower body bear hugger
Jugular catheter (till resumption of oral intake)
Avoidance of excessive I.V. fluids
Patient send to recovery ward (ICU setting)
Restart oral intake of water or iced-chips
POD 1 Patient sent to surgical ward
Patient mobilizes out of bed
Free drinking up to 1,5L
Continue portable epidural analgesia
Antiemetics if based on nausea score
1000 mg Paracetamol every 6 hours
1000 mg Magnesiumoxide twice daily
POD 2 If patient is capable resumption of regular diet
Continue mobilization
Remove urinary catheter
Continuation epidural analgesia
Stop low dose opioids
POD 3 Stop epidural analgesia
Discontinue I.V. fluids
Start NSAIDs based on pain score
Continue mobilization
Regular diet
POD 4 Drain removal if amylase < less than 3-fold serum or < 50ml/d production
Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 5 Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 6-7 Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 8-10 Continue analgesics based on pain score
Continue mobilization
Regular diet
Check functional recovery criteria
Make outpatient appointment for after discharge
Discharge from hospital

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 19. Patient age was analyzed within two groups using an unpaired t-test while the overall significance within all three groups was analyzed using a one-way ANOVA test. All other baseline characteristics and results except LOS were analyzed using a Chi-square or Fisher's exact test. LOS was analyzed between two groups using the Mann-Whitney *U* test, whereas overall significance between all three groups was analyzed using the Kruskal-Wallis test. LOS in various time periods was compared with multivariable linear regression. Logarithmic transformation of length of stay was necessary as this variable was not normally distributed. Baseline characteristics were entered into the multivariable regression model. The clinically relevant interaction term time period $\times$ age was added to the regression model and removed if not statistically significantly associated with length of stay. Multicollinearity and influential outliers were checked using variance inflation factors and Cook's distance. A *P*-value <0.05 was considered significant.

RESULTS

Patient and operative characteristics

Demographic patient data and operative characteristics are shown in Table 9.2. Mean patient age was significantly higher in the most recently operated group (from 62 ± 13 to 61 ± 11 to 67 ± 11 , $P=0.003$). There were no differences in male-female distribution between the three groups. Co-morbidity did not differ significantly between groups. Fewer patients were operated on for distal cholangiocarcinoma in the last group ($P=0.04$). The ratio between classical Whipple procedure and PPPD was around 1:3 in the first two groups, with a ratio of approximately 1:4 in the last group (not significant). The PD resection volume in MUMC from 1995-2011 increased from an average of 8 PDs/year in the period of 1995-2000 to 29 PDs/year in the period 2009- 2011.

Clinical outcomes and complications

In groups 2 and 3, all patients received epidural analgesia and NG tubes were removed at the end of the procedure. Patients in groups 2 and 3 were structurally encouraged to mobilize with the help of a physiotherapist from postoperative day (POD) 1. In group 3 patients structurally received sips of water in the recovery ward on the day of surgery and were encouraged to resume and gradually increase their normal diet from POD 1. Clinical postoperative outcomes and complications are shown in Table 9.3. LOS decreased from 20 days in group 1 to 13 days in group 2 and 14 days in group 3 ($P=0.001$). LOS including readmissions was 22, 14 and 16 days in the 3 groups

respectively ($p=0.003$). Table 9.4 shows that patients without complications had a LOS of 16, 10 and 9 days respectively ($P<0.001$). Reasons for delayed discharge despite fulfilling functional recovery criteria were mainly of logistic nature (e.g. no discharge in weekends and home care not yet being arranged). Separate analysis of LOS for patients with complications demonstrated that patients with a Dindo-Clavien grade <3 complication had a significantly longer LOS in group 1 compared to group 2 and 3 ($P=0.01$). LOS of patients with a Dindo-Clavien grade ≥ 3 did not differ significantly between groups. Mortality did not differ significantly between the groups, nor did the readmission rate. The incidence of complications such as pancreatic fistula, delayed gastric emptying (DGE), intra-abdominal abscesses, post pancreaticoduodenectomy hemorrhage, gastrojejunostomy and hepaticojejunostomy leakage and sepsis did not change significantly as time passed. The incidence of complications classified according to Dindo-Clavien also did not show any differences between the groups. Wound infections were significantly more common in the patients of group 3 ($P=0.008$). Incidences of specific complications were calculated for PPPD and the classical Whipple procedure separately. There were no significant differences in occurrence of any of the complications between these two procedures (Appendix 6).

Table 9.2 Patient and operative characteristics

	No ERAS 1995-2005 Population 1 (n=97)	'ERAS-like' 2006-2008 Population 2 (n=47)	ERAS 2009-2011 Population 3 (n=86)
Age (mean)*	62 $\pm$ 13	61 $\pm$ 11	67 $\pm$ 11 †
Sex			
Male	58 (59.8)	30 (63.8)	44 (51.2)
Female	39 (40.2)	17 (36.2)	42 (48.8)
Co-morbidity			
DM	19 (19.6)	5 (10.6)	17 (19.8)
Cardiovascular	32 (33.0)	18 (38.3)	27 (31.4)
Indication			
Pancreatic carcinoma	38 (39.2)	22 (46.8)	45 (52.3)
Ampullary carcinoma	16 (16.5)	6 (12.8)	19 (22.1)
Duodenum carcinoma	5 (5.2)	3 (6.4)	4 (4.7)
Distal cholangiocarcinoma	12 (12.4)	2 (4.3)	3 (3.5) ‡
Pancreatic pseudo cyst	1 (1.0)	0 (0)	0 (0)
Peri-ampullary adenoma	3 (3.1)	3 (6.4)	1 (1.2)
Neuro-endocrine tumor	0 (0)	0 (0)	1 (1.2)
Benign pancreatic tumor	5 (5.2)	5 (10.6)	4 (4.7)
Pancreatitis			
Chronic	4 (4.1)	2 (4.2)	1 (1.2)
Other	13 (13.4)	4 (8.5)	8 (9.3)
Surgical technique			
Whipple	24 (24.7)	11 (23.4)	18 (20.9)
PPPD	73 (75.3)	36 (76.6)	68 (79.1)

Values in parentheses are in percentages unless indicated otherwise. * $\pm$ SD. † $P<0.05$ vs. group 1. ‡ $P<0.05$ vs. group 1,2

Table 9.3 Postoperative outcomes and complication

	No ERAS 1995-2005 Population 1 (n=97)	'ERAS-like' 2006-2008 Population 2 (n=47)	ERAS 2009-2011 Population 3 (n=86)
Complications			
Minor (<i>Dindo-Clavien grade I-II</i>)	17 (17.5)	13 (27.7)	20 (23.3)
Moderate (<i>Dindo-Clavien grade IIIa/b</i>)	24 (24.7)	10 (21.3)	21 (24.4)
Severe (<i>Dindo-Clavien grade IVa/b</i>)	7 (7.2)	2 (4.3)	5 (5.8)
Intra abdominal abscess	15 (15.5)	6 (12.8)	14 (16.3)
Pancreatic fistula	12 (12.4)	6 (12.8)	11 (12.3)
Grade A	1 (1.0)	1 (2.1)	1 (1.2)
Grade B	2 (2.1)	1 (2.1)	2 (2.3)
Grade C	9 (9.3)	4 (8.5)	8 (9.3)
DGE	7 (7.2)	4 (8.5)	11 (12.8)
Grade A	1 (1.0)	1 (2.1)	1 (1.2)
Grade B	0 (0)	0 (0)	1 (1.2)
Grade C	6 (6.2)	4 (8.5)	8 (9.3)
Biliodigestive anastomosis leakage	5 (5.2)	4 (8.5)	4 (4.7)
Post-pancreatectomy hemorrhage	3 (3.1)	1 (2.1)	7 (8.1)
Gastrojejunostomy leakage	2 (2.1)	0 (0)	2 (2.3)
Sepsis/MOF	4 (4.1)	2 (4.3)	5 (5.8)
Wound infection	5 (5.2)	10 (21.3) [†]	15 (17.4) [‡]
General complications	19 (19.6)	12 (25.5)	29 (33.7)
Interventions			
Percutaneous drainage	13 (13.4)	8 (17.0)	16 (18.6)
Relaparotomy	13 (13.4)	5 (10.6)	7 (8.1)
LOS (median) *	20 (9-132)	13 (7-62) [†]	14 (7-83) [‡]
LOS incl readmission (median) *	22 (9-132)	14 (7-62) [†]	16 (7-83) [‡]
Mortality	6 (6.2)	1 (2.1)	4 (4.7)
Readmissions	14 (14.4)	7 (14.8)	11 (12.8)

Values in parentheses are in percentages unless indicated otherwise. *range. [†] $P < 0.05$ vs. group 1. [‡] $P < 0.05$ vs. group 1,2\

Table 9.4 LOS of patients with and without complications, graded with the *Dindo-Clavien* classification

LOS, median (range)	1995-2005 No ERAS (n=97)	2006-2008 'ERAS like' (n=47)	2009-2011 ERAS (n=86)
No complication	16 [9-44]	10 [7-18] [†]	9 [7-16] [‡]
Complication grade <i>Dindo-Clavien</i> <3	26 [10-70]	12 [8-23] [†]	16 [8-49] [‡]
Complication grade <i>Dindo-Clavien</i> ≥3	32 [12-133]	37 [11-62]	36 [12-83]

[†] $P < 0.05$ vs group 1. [‡] $P < 0.05$ vs group 1,2

ERAS outcomes for group 3: “ERAS group” versus group 1: “no ERAS”

Patients in group 1 (n=97) all received a NG tube and it was removed several days to weeks after surgery when no gastric retention was present. In the ERAS group NG tubes were not routinely placed. If a nasogastric tube was placed during surgery, it was removed directly after surgery in all patients. Patients were allowed to take sips of water on the day of surgery in the recovery ward. In 11 patients in the ERAS group (12.8%) a NG tube had to be reinserted in the postoperative period to relieve symptoms of DGE.

All patients in the ERAS group (n=86, 100%) received epidural analgesia and it was stopped on POD 3 in 78% of the patients (n=67). In the ‘no ERAS’ group intravenous analgesia was mainly used.

All patients received an intra-abdominal drain located at the pancreatico-jejunostomy at the end of the procedure. Intra-abdominal drain removal was at the discretion of the surgeon in the ‘no ERAS’ group. In the ERAS group drain removal criteria were used (Table 9.1). Drains were removed on day 4 in 53% of the patients in the ERAS group. Reasons for not removing the drain on POD 4 were not fulfilling drain removal criteria or logistic problems (POD 4 was on a weekend day and drain removal was overlooked or laboratory results came back after the weekend).

In the ERAS group resumption of a solid diet on POD 2 could be achieved in 60% of the patients (n=52), 75% of the patients tolerated a solid diet on day POD 4 in the ERAS group (n=65). In the ‘no ERAS group’ patients started with intake of liquids after the NG tube was removed and started with a solid diet in the days thereafter, when liquids were tolerated.

63% of the patients in the ERAS group (n=54) were mobilized out of bed on POD 1. In the ‘no ERAS’ group there was no structured mobilization.

Multivariable linear regression

The following characteristics were entered into a multivariable linear regression model: time period, age, sex, co-morbidity, indication, resection type (PPPD or classical Whipple procedure) and the presence of a complication. Multivariable regression analysis showed that the earlier time period without ERAS and the presence of complications were independent predictors of longer postoperative LOS ($P=0.003$ and $P<0.001$, respectively).

DISCUSSION

The present study shows that postoperative LOS after PD decreased significantly in the last 16 years in our institution, while morbidity, mortality and readmission rate remained unchanged. More elderly patients were selected for PD in the most recent

period and there was an increasing trend towards operations performed for malignant disease. The improved outcomes after PD over the last decade might be attributed to the streamlining of patient care and surgical techniques. However, the implementation of an ERAS program after PD may have influenced the results, since LOS decreased dramatically from 2006 onwards. This was the time period when perioperative PD management in Maastricht was increasingly performed within an ERAS environment. The present results are in line with a previous report of Balcom et al. introducing case management and implementation of a clinical pathway in 733 cases of various types of pancreatic resection. For PD this study reported a decrease in mean LOS of 6.6 days, very similar to the reduction of LOS by 6-7 days observed for patients both with and without complications in the present study²⁵.

Complication rates remained unchanged during the study period, except for the incidence of wound infections, which increased over the study period. However, this finding may be confounded by information bias due to the better and prospective complication registration during the final years of the study. In particular, the recording of minor complications such as wound infections received more attention. Other reports on ERAS and PD also did not show an increase in morbidity after implementing an ERAS programme²⁶⁻²⁸ and one report even showed a decrease in morbidity²⁹. The rates of PD specific complications such as DGE, pancreatic fistula and post PD hemorrhage observed in this study were comparable with other reports on fast track and PD^{29,30}. Balzano et al. described a decrease in DGE after the institution of a fast track protocol for PD from 24.6% to 13.9%²⁹. In the present study, DGE did not change significantly after the implementation of an ERAS protocol (incidence of 12.8% in the ERAS group). One study reported a decrease in DGE after a clinical pathway was adopted but attributed this to the fact that more classical Whipple's procedures were performed in their clinic in the final years instead of pylorus-preserving PDs²⁵. In the present study PPPDs were performed increasingly over the years but no significant difference was noted between the incidences of DGE in the classical Whipple-group as compared to the PPPD-group. This observation is in line with a previous report by Tran et al.³¹.

Over time, there was a trend for complications to be increasingly managed by percutaneous drainage instead of relaparotomy. This is probably explained by the increasing use of CT and advances in CT-guided percutaneous interventions. Relaparotomy rates decreased from 13% to 8%, which corresponds with other reports²⁹⁻³¹. Readmission rates in the present study did not change significantly, which implies that earlier discharge in the years after implementation of the ERAS protocol did not affect patient morbidity.

It could be argued that improved outcomes in terms of reduced LOS are not the result of an ERAS protocol but instead the result of secular trends such as advanced surgical techniques and increased experience of surgeons. However, a recent report after implementation of an ERAS program in colonic surgery in over 30 hospitals in the

Netherlands in 1 year demonstrated that LOS can be decreased by 3 days in addition to secular trends³².

Multivariable regression analysis showed that the presence of a complication was an independent predictor of increased LOS. This was expected as in these patients the ERAS program can only be followed to certain extent. Brooks et al. reviewed a case series of 215 patients undergoing PD and found that complications and also age and operative year were independently associated with postoperative LOS using multivariable analysis³³. This is in accordance with the present results showing that a later time period (ERAS) was correlated with a lower LOS. In the current study the whole cohort was divided into three time periods reflecting the implementation of some ERAS elements ('ERAS-like') and the implementation of the ERAS protocol for PD (ERAS). There was no significant difference in LOS between the ERAS group and the 'ERAS like' group. This suggests that the introduction of several ERAS elements as compared to the introduction of a full ERAS protocol might be equivalent in terms of improving LOS. Ahmed et al. have shown that in colonic surgery that an ERAS protocol compliance of 77% does not worsen outcome when compared to a compliance of 88% in the trial group³⁴. Thus, the protocol elements may not all be equally important. Supporting the aforementioned finding, another study in colonic surgery analyzing individual ERAS elements showed that early cessation of i.v. fluids, the use of laxatives and mobilization from day 1 were associated with a lower LOS³². However, the previous study was performed in patients undergoing colonic surgery and these results might not be extrapolatable to pancreatic surgery.

Furthermore, a recent retrospective study comparing fast track recovery with traditional care in patients undergoing PD without complications also showed that fast track recovery was associated with shorter LOS³⁵. LOS without complications in the aforementioned study was 8 days in the fast track group, compared to 9 days in the our study.

Apart from the implementation of an ERAS protocol, another factor that might have contributed to improved outcome in this study was the increase in resection volume over the years at MUMC. A large population-based study of 3736 patients undergoing pancreatic resections showed that a higher hospital volume was correlated with lower mortality³⁶. Also, the centralization of pancreatic resections, leading to an increase in hospital volume, has led to significant improvements in survival, mortality and complication rates^{2,3,37-39}.

Although complications were prospectively registered in the final few years of the study, it is clear that this retrospective study has several limitations. A randomized controlled trial comparing ERAS with traditional care in PD would be the strongest way to assess the true effect of ERAS. However, this brings up ethical questions since the majority of ERAS protocol elements have been separately proven to be effective in RCTs and meta-analyses and several ERAS protocol elements have now become standard care.

To conclude, the present study shows that in the authors' center LOS after PD was reduced significantly in the last 16 years without altering complication, mortality, and readmission rates, even though more elderly patients were operated on. Implementation of an ERAS protocol may have contributed to the improvement in LOS without compromising other outcomes.

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CHAPTER 10

Implementing an enhanced recovery program after pancreaticoduodenectomy in elderly patients - is it feasible?

MME Coolsen, M Bakens, RM van Dam, SWM Olde Damink, CHC Dejong

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ABSTRACT

Background

An enhanced recovery after surgery (ERAS) program aims to reduce the stress response to surgery and thereby accelerate recovery. It is unclear whether these programs can be safely implemented for elderly patients, especially in highly complex surgery such as pancreaticoduodenectomy (PD). The objective of this study was to evaluate the feasibility of an ERAS program in elderly patients undergoing PD.

Methods

Implementation of the ERAS protocol was studied prospectively in a consecutive series of patients undergoing PD between January 2009 and August 2013. Patients were divided into two groups: ≤ 65 years and ≥ 70 years. Endpoints were length of stay (LOS), readmissions, morbidity, mortality and compliance with ERAS targets.

Results

Of a total of 110 patients, 55 were ≤ 65 years (median 57) and 55 ≥ 70 years (median 77). Median LOS was 14 days in both groups. In patients without complications median LOS was 9 days. Both mortality and readmissions did not differ between groups (mortality $n=3$ (5.5%) in younger versus $n=6$ (10.9%) in older patients, $P=0.49$, readmissions: $n=11$ (20%) versus $n=7$ (12.7%), $P=0.44$). CT-drainage and relaparotomy-rates were not different between groups, nor was overall morbidity ($n=31$ (56.3%) in the older versus $n=35$ (63.3%) in the younger group, $P=0.44$). There were no differences in compliance with elements of the ERAS protocol between groups.

Conclusion

An ERAS program seems feasible and safe for patients ≥ 70 years of age undergoing PD. Improving protocol compliance may further reduce morbidity and mortality, especially in high-risk patients.

INTRODUCTION

In the Netherlands, approximately 2000 patients are affected by cancer of the pancreas and periampullary region each year. Without treatment median survival after diagnosis is only 4-6 months. Patients with potentially curable disease ($\pm 20\%$) may undergo surgery with curative intent, but after 'curative' resection the prognosis is still poor with 5-year survival rates of 10-20%¹. Pancreaticoduodenectomy (PD) remains the only curative option for the majority of pancreatic and periampullary tumors. With an increasingly aging population, more elderly people suffering from pancreatic cancer will be presented for PD. In the past, surgeons were reluctant to perform PD on elderly patients. Common reasons were a reduced physical fitness and increased co-morbidity. Recent reports, however, show that PD is feasible in the elderly population with acceptable mortality and morbidity rates²⁻⁶.

To diminish the surgical stress response and speed up recovery 'Enhanced Recovery After Surgery' (ERAS) or 'fast track' pathways have been implemented in several forms of surgery⁷⁻¹⁰. Avoidance of pre- and postoperative fasting, optimized analgesia and early mobilization are typical elements of the ERAS protocol, which accelerates recovery and reduces hospital costs without compromising postoperative morbidity and mortality¹¹⁻¹⁴. In PD, a complex surgical procedure with high postoperative morbidity rates, ERAS protocols have also been successfully implemented¹⁵⁻¹⁷. Recently, perioperative guidelines for PD have been published by the ERAS group¹⁸.

When postoperative complications do occur, the elderly in particular seem to have an increased 30-day mortality risk¹⁹. Interestingly, two recent meta-analyses on ERAS in PD and colonic surgery suggest that postoperative morbidity rates may be lower in patients managed in an ERAS program^{11,12}. Therefore, it might be beneficial to implement ERAS programs also for an older population. However, some authors raise doubts about subjecting the elderly to ERAS programs with immediate postoperative feeding and forced mobilization²⁰.

The aim of this study was to prospectively evaluate the feasibility and safety of implementing an ERAS program in elderly patients (>70 years) undergoing PD and compare compliance and outcome with patients below 65 years of age.

METHODS

Patients

Perioperative outcome data were retrieved from a database in which all patients undergoing PD in Maastricht University Medical Center in a period between January 2009 and Augustus 2013 were entered prospectively. Patients were divided into two groups: below 65 years of age and above 70 years of age. The 5-year gap was arbitrary

chosen to create a real difference between the older and younger group (e.g. otherwise two people who differ two days in age could be in different groups). From January 2009 onwards a multimodal ERAS program for PD was implemented in our institution and all patients undergoing PD from that date onwards were managed accordingly. There were no exclusion criteria.

Perioperative management

A detailed description of the ERAS protocol for PD is shown in Table 10.1. Pre-operatively, patients were informed at the out-patient clinic about the ERAS protocol and possible postoperative complications. Before the operation, an assessment was made of ASA classification and co-morbidity. All patients received antibiotic prophylaxis and mid-thoracic epidural analgesia.

Four surgeons, all with extensive experience in PD, performed the operative procedures. Bilateral subcostal transverse abdominal incisions were used. The biliodigestive anastomosis, gastrojejunostomy and pancreaticojejunostomy were hand sewn and a prophylactic abdominal silicon drain was placed near the pancreaticojejunostomy at the end of the procedure. NG tubes were not placed or were removed after the procedure directly before transportation to the recovery ward.

Patients were allowed to restart oral intake of water on the day of surgery, to drink freely up to 1.5 l on the first postoperative day (POD) and resume their normal diet on the second postoperative day. Furthermore, patients received magnesiumoxide 1000mg twice daily. Mobilization out of bed was started on POD 1. Epidural analgesia was stopped on POD 3 and replaced by NSAIDs. The prophylactic abdominal drain was removed on POD 4 if amylase was less than 3 times the serum amylase concentration or drain production was less than 50ml per day. Patients were discharged if functional recovery criteria were met (good pain control with oral analgesia only, tolerance for solid food, no intravenous fluids, passage of stool and being independently mobile at the pre-operative level) and if the patient was willing to go home.

Primary and secondary endpoints

The primary endpoint was postoperative length of stay (LOS), defined as nights spent in hospital after the operation. Secondary endpoints were postoperative complications, mortality, readmissions, postoperative interventions and compliance with various elements of the ERAS protocol. Complications were defined as any deviation from the normal postoperative course. Definitions used for specific complications were according to literature (Appendix 5)²¹⁻²⁶ and further classified according to the Dindo-Clavien classification²⁷. Data were recorded prospectively during hospital stay and the 30-day period after surgery in an electronic registration system (SAP) as well as in a database. For mortality the follow-up was 90 days. In the morning after discharge, complications were registered in SAP for each patient.

Table 10.1 ERAS protocol for pancreaticoduodenectomy

Preoperative outpatient visit
Pre-admission counseling
Give consent form and patient information
Day before surgery / Admission
Normal oral nutrition until midnight
No pre-anesthetic medication
Day of surgery
Carbohydrate drinks up to 2 hours prior to surgery
Start anti-thrombotic prophylaxis
Preoperative anti-microbial prophylaxis
Mid-thoracic epidural anesthesia
Short-acting I.V. anesthetic agent
Preferably no nasogastric drainage or removal of NG tube after surgery
Warm I.V. fluids and upper and lower body bear hugger
Jugular catheter (till resumption of oral intake)
Avoidance of excessive I.V. fluids
Patient sent to recovery ward (ICU setting)
Restart oral intake of water or iced-chips
POD 1 Patient sent to surgical ward
Patient mobilizes out of bed
Free drinking up to 1,5L
Continue portable epidural analgesia
Antiemetics if based on nausea score
1000mg Paracetamol every 6 hours
1000mg Magnesiumoxide twice daily
POD 2 If patient is capable resumption of regular diet
Continue mobilization
Remove urinary catheter
Continuation epidural analgesia
Stop low dose opioids
POD 3 Stop epidural analgesia
Discontinue I.V. fluids
Start NSAIDs based on pain score
Continue mobilization
Regular diet
POD 4 Drain removal if amylase < less than 3-fold serum or < 50ml/d production
Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 5 Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 6-7 Continue analgesics based on pain score
Continue mobilization
Regular diet
POD 8-10 Continue analgesics based on pain score
Continue mobilization
Regular diet
Check functional recovery criteria
Make outpatient appointment for after discharge
Discharge from hospital
POD: postoperative day

Postoperative data in SAP were also crosschecked with existing in-house databases containing prospectively collected complications. Readmissions were recorded if related to the index-operation within a time-period of 6 months.

Adherence to various ERAS protocol elements that were specifically reviewed included resumption of oral fluid and solid intake, mobilization from POD 1, drain removal on POD 4, urinary catheter removal on POD 2 and removal of epidural analgesia on POD 3.

Data analysis and statistics

Continuous data are given as median (range). Categorical variables were analyzed using the χ^2 test or Fisher's exact test, quantitative variables with Student's *t* test. Postoperative length of stay was analyzed using the non-parametric Mann-Whitney *U* test. A *p*-value <0.05 was considered significant. Statistical analysis was performed using SPSS for Windows, version 19.

RESULTS

Demographics and operative outcome

A consecutive series of 110 patients undergoing PD between January 2009 and August 2013 was included in this study. Of these, 55 patients were below 65 years of age and 55 patients were older than 70 years (Table 10.2). The median age for the ≤ 65 years group was 57 (range 45-65) and for the ≥ 70 years group 77 (range 71-86). There were significantly more patients with a higher ASA classification in the older group. Furthermore, cardiac and pulmonary co-morbidity was more frequently present in the older group ($P < 0.016$ and $P < 0.014$ respectively). BMI (Body Mass Index) and type of pancreatic pathology did not differ between groups. In both groups most resections were performed for malignancies and more PPPDs than classical Whipple procedures were performed (84% versus 16% in the younger group and 85% versus 15% in the older group). Mean operative time did not differ between groups.

Postoperative outcome

Postoperative outcomes parameters are shown in Table 10.3. Median LOS was not different between the two groups (both 14 days with ranges 6-100 and 6-65 respectively), nor was median LOS for younger and older patients discharged without complications (9 days with ranges 6-15 and 6-22 respectively). Readmissions within 6 months of the index-hospitalization were not significantly different between the two groups (18.1% and 12.7% respectively). The same holds true for mortality rates although a trend to an increased mortality rate in the older group was observed (5.5% and 10.9% respectively). There were no differences in postoperative intervention rate

(CT/US-drainage and relaparotomy) and in minor (Dindo-Clavien grade I and II), moderate (grade IIIa/b) or severe (grade IVa/IVb) complications between the groups. Median LOS was also calculated for Dindo-Clavien grades below and above III. Patients who suffered from complications in the elderly group had a longer median postoperative length of stay than those in the younger group for Dindo-Clavien grades <III ($P=0.028$).

Table 10.2 Patient demographics, pathology and operative data

	≤65 years of age (n=55)	≥70 years of age (n=55)	p-value
Age median (range)	57 (45-65)	77 (71-86)	
Sex			
Male/female	35/20	22/33	0.013
ASA class			
I	28 (51%)	1 (2%)	>0.001*
II	21 (38%)	34 (62%)	0.013
III	5 (9%)	20 (36%)	0.001*
IV	1 (2%)	0 (0%)	0.315*
Comorbidity			
Cardiovascular	13 (24%)	25 (45%)	0.016
Pulmonary	2 (4%)	10 (18%)	0.014*
Diabetes	6 (11%)	12 (21.8%)	0.122*
Renal disease	1 (2%)	6 (10.9%)	0.056*
BMI (range)	24.9 (18.0-36.1)	24.4 (18.6-36.8)	0.656
Pathology			
Pancreatic head carcinoma	34 (62%)	33 (60%)	0.845
Duodenal cancer	2 (4%)	3 (5%)	1.000*
Ampullary carcinoma	8 (15%)	12 (22%)	0.459*
Distal cholangiocarcinoma	5 (9%)	5 (9%)	1.000*
Metastasis in head of pancreas	1 (1.8%)	0 (0%)	1.000*
Chronic pancreatitis	2 (4%)	2 (4%)	1.000*
IPMN	1 (2%)	0 (0%)	1.000*
Neuro-endocrine tumor	2 (4%)	0 (0%)	0.495*
Operation type			
Whipple	9 (16%)	8 (15%)	1.000
PPPD	46 (84%)	47 (85%)	0.792
Duration of OR time (min)	345 (180-810)	340 (217-715)	0.986 [†]

ASA: American Society of Anesthesiologists, BMI: Body Mass Index, PPPD: pylorus preserving pancreaticoduodenectomy. All statistics were performed with Chi-square, marked * with the Fisher's exact test, marked [†] with T-test.

Table 10.3 Postoperative outcomes

	≤65 years of age (n=55)	≥70 years of age (n=55)	P-value
Dindo-Clavien classification			
Minor (I/II)	15 (27.2%)	20 (36.3%)	0.409
Moderate (IIIa/b)	15 (27.2%)	8 (14.5%)	0.159*
Severe (IVa en IVb)	0 (0%)	2 (3.6%)	0.495*
Mortality < 90days	3 (5.5%)	6 (10.9%)	0.489*
Readmissions < 6 months	11 (20%)	7 (12.7%)	0.440*
Median length of hospital stay (range)	14 (6-100)	14 (6-65)	0.186
Length of stay uncomplicated (median)	9 (6-15)	9 (6-22)	0.275
Median LOS Dindo-Clavien grade <III (range)	10 (6-100)	14 (7-59)	0.028
Median LOS Dindo-Clavien grade >III (range)	32 (11-83)	33 (14-65)	0.488
Interventions			
CT/US-drainage	10 (18.1%)	8 (14.5%)	0.797*
Re-operation	6 (10.9%)	4 (7.2%)	0.742*

LOS: Mann Whitney U. *Fisher exact, all other statistics: Chi Square

Morbidity

Table 10.4 summarizes the overall and specific complications in both groups. Overall morbidity was 56.3% in the ≤65 years group and 63.3% in the ≥70 years group ($P=ns$). The incidence of specific complications did not differ between groups.

Table 10.4 Complications specified

	≤65 years of age (n=55)	≥70 years of age (n=55)	P-value
Overall complications	31 (56.3%)	35 (63.3%)	0.436*
Intra abdominal abscess	7 (13%)	7 (13%)	1.000
Wound infection	7 (13%)	7 (13%)	1.000
Pancreatic fistula	9 (16%)	5 (9%)	0.392
Pneumonia	2 (3,6%)	2 (3,6%)	1.000
Delayed gastric emptying grade	5 (9%)	5 (9%)	1.000
Biliodigestive anastomosis leakage	3 (6%)	1 (2%)	0.618
Sepsis/MOF	2 (4%)	6 (11%)	0.271
Post pancreaticoduodenectomy hemorrhage	5 (9%)	5 (9%)	1.000
Urinary tract infection	3 (6%)	5 (9%)	0.761
Gastrojejunostomy leak	1 (2%)	0 (0%)	0.850
Chylus leakage	0 (0%)	2 (4%)	0.495
Diabetes mellitus de novo	1 (1,8%)	3 (6%)	0.618
CVA	0 (0%)	1 (2%)	0.850
Cardiac	6 (11%)	9 (16%)	0.580

All statistics with fisher's exact test. *Chi-square

ERAS outcomes

NG tubes were either not placed or directly removed after surgery in all patients. As Table 10.5 indicates compliance with resumption of oral fluid intake on POD 1 was high in both groups (96% in the younger and 95% in the older group). Solid oral intake was started from POD 2 onwards in 56% of patients in the younger group and 51% of patients in the older group ($P=ns$).

Table 10.5 ERAS outcomes

	≤65 years of age (n=55)	≥70 years of age (n=55)	p-value
Resumption of fluid intake POD 1	53 (96%)	52 (95%)	0.647
Resumption of solid intake POD 2	31 (56%)	35 (63%)	0.436
Mobilization from POD 1	33 (60%)	35 (63%)	0.695
Drain removal on POD 4	26 (47%)	28 (51%)	0.703
Urinary catheter removal on POD 2	38 (69%)	33 (60%)	0.319
Removal epidural on POD 3	44 (80%)	43 (78%)	0.815

All statistics were performed with Chi-square

Reasons for not starting solid intake were nausea and malaise. Mobilization on POD 1 was 60% in the younger and 63% in the older group. A lower compliance with mobilization was mainly due to weakness, hypotension or pain. Prophylactic abdominal drains were removed in 47% of the patients on POD 4 in the younger group and 51% in the older group ($p=ns$). In half of the patients the drain was not removed on POD 4 because the drain removal criteria were not met. In the other half this was due to logistic problems (e.g. POD 4 fell on a weekend day and drain removal was overlooked or laboratory results came in later). The number of patients having their urinary catheter removed on POD 2 was lower than expected. This was mainly due to the fact that the epidural catheter was removed on POD 3 in a considerable number of patients. Consequently, urinary catheters were often removed only after epidural analgesia was stopped. Also, some patients needed longer catheterization because of bladder problems or in order to monitor urine output in critically ill patients.

For completeness, the results of the 25 patients in the age-group that was left out (66-69 years) are presented in Appendix 8 and 9. These are similar to the results of both other groups.

DISCUSSION

This study describes the results of the implementation of an ERAS program in PD in elderly patients. It compares results in patients ≤65 years of age with those in patients

≥70 years. Implementing an ERAS program for PD in the elderly appeared to be feasible since compliance with the different ERAS protocol elements was similar in younger and older patients. Its safety also seems confirmed since readmission, morbidity and mortality rates did not differ significantly between the two groups.

Several studies have evaluated risks and outcomes after PD in the elderly and have shown that it is possible to perform PD with acceptable morbidity and mortality rates^{2,5}. However, overall morbidity rates vary greatly between single-center studies (21-73%)²⁸. The variance may not only reflect differences in outcome between high- and low-volume HPB centers and registration flaws in retrospective studies, but also failure to use a standardized complication registration system and unanimous definitions for specific complications. In this study universal definitions for complications were used and complications were classified according to Dindo-Clavien²⁷. Overall morbidity in the present study was roughly compared to the morbidity reported in a recent case series involving 2698 patients undergoing PD (42% <80 years and 53% 80-89 years)²⁹. The slightly higher morbidity in the present study might be due to the meticulous prospective complication registration in the present study. Some studies report higher incidences of pancreatic fistula (PF) and DGE after PD in the elderly, but the current study did not confirm this^{2,4,30}. In line with previous reports, the mortality rate we recorded, though not significantly, tended to be higher in the older group than in the younger group (10.9% and 5.5% respectively, $P=0.489$)^{28,30-32}. The mortality rate for the elderly as shown in our study was at the high end of the range reported in studies with similar sample sizes (mortality 0-10.5%)^{3,4,30,32,33}. However, not all these studies defined mortality in an exact manner or restricted themselves to 30-day mortality rates, compared to a 90-day mortality defined in this study. Moreover, two population-based studies including 23518 and 3736 patients undergoing pancreatic resection showed even higher mortality rates in the elderly population (up to 15.5% and 11.4% respectively)^{34,35}. This was also confirmed in a Dutch study including 2155 PD's (10.4% in patients >70 compared to 4.4% in the younger group)³⁶.

Planned discharge in this study was on POD 8-10. This target appeared to be feasible only in patients without postoperative complications (median discharge at day 9). The overall median length of stay was 14 days. This was probably due to the fact that more than half of the patients had complications. Another explanation of the relatively high median LOS might be the fact that physicians are reluctant to discharge PD patients early after surgery, since major complications can even occur with some delay after surgery. In a recent study in patients undergoing colonic surgery, only half of the patients were discharged when all discharge criteria were met³⁷, and 43% of this group was kept in hospital because of surgeons' judgment.

The reported length of stay in the present study is in line with other studies on reporting a postoperative length of stay after PD of approximately 13 days in the ERAS

group^{15,16}. In other studies on PD in elderly with traditional care median length of stay varied from 13-25 days in the older population^{34,35,38}.

Overall compliance with the various ERAS elements was acceptable (73%). Ahmed et al. already showed that an ERAS protocol compliance of more than 77% does not further improve outcome in colorectal surgery³⁹. Removal of NG tubes and epidural analgesia and resumption of fluid intake were achieved for the majority of patients. However, compliance with other ERAS elements such as mobilization on POD 1, removal of urinary catheters on POD 2 and removal of prophylactic intra-abdominal drains was lower. There is still considerable debate on if and when drains should be placed and removed⁴⁰⁻⁴³. Early drain removal (<72h) may be advised for patients with a low risk of PF¹⁸.

There is no official definition for the term “elderly”, but most studies performed on pancreatic resections in the elderly population use a cut-off age above 70 years^{4,32,33,44-46}. A recent analysis on a large cohort showed an age of 68.5 years can be considered as ‘surgical oldness’⁴⁷. We decided to define an interval centered on this age and considered older than 70 years as “elderly” and below 65 years as younger patients.

Resection is the sole curative option for patients with malignant disease of the pancreas. Also in the elderly the survival benefit after resection is not diminished³⁴. It is nevertheless crucial to carefully select older patients using meticulous pre-operative assessment⁴⁸. Better selection of patients might also contribute to lowering mortality rates. Importantly, older patients should be well informed about the risks and the fact that hospital volume and surgeon experience play a significant role in the outcome^{35,49,50}.

To conclude, this study evaluated the results of implementation of an ERAS program in elderly patients (≥70 years) undergoing PD as compared to patients below 65 years of age. It shows that an ERAS program for the elderly is feasible and it can be safely implemented with comparable readmission, morbidity and mortality rates. Compliance to protocol was similar in both groups. However, efforts must be made to improve compliance with specific protocol elements to further reduce morbidity and mortality, especially in high-risk patients.

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CHAPTER 11

Attitudes of patients and care providers to enhanced recovery after surgery programs following major abdominal surgery

M Hughes, MME Coolson, EK Aahlin, EM Harrison, SJ McNally¹ CHC Dejong, K Lassen, SJ Wigmore

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ABSTRACT

Importance

Enhanced recovery after surgery (ERAS) is a well-established pathway of perioperative care in surgery in an increasing number of specialties. In order to implement protocols and maintain high levels of compliance, continued support from care providers and patients is vital.

Objective

To assess the perceptions of care providers and patients of the relevance and importance of the ERAS targets and strategies.

Design

Multicenter cross sectional survey.

Setting

Three northern European tertiary referral centers.

Participants

109 patients and 57 care providers were surveyed.

Exposure

Pre-operative and post-operative surveys were completed by patients who underwent major hepatic, colorectal or esophagogastric surgery in these institutions. Anonymous web-based and paper surveys were sent to surgeons, anesthetists and nurses experienced in delivering enhanced recovery protocols. Each questionnaire asked the responder to rate a selection of enhanced recovery targets and strategies in terms of perceived importance.

Main outcome measure

Patient and care provider evaluation of enhanced recovery components.

Results

109 patients and 57 care providers completed the pre-operative survey. Overall both patients and care providers rated found the majority of items as important and supported ERAS principles. Being free from nausea (median 10, IQR 8-10) and being free from pain at rest (median 10, IQR 8-10) were rated highest by the patients. Care providers also rated these two items the highest. Early return of bowel function (median 7, IQR 5-8) and avoiding pre-anesthetic sedation (median 6, IQR 3.75-8) were scored the lowest by care providers.

Conclusion and relevance

ERAS principles are supported by both patients and care providers. This is important when attempting to implement and maintain an ERAS program. Controversies still remain regarding the relative importance of individual ERAS components.

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols have become established practice in patients undergoing major surgery¹. The original success in colorectal surgery has been followed by its application in other fields including hepatobiliary², vascular³ and orthopedic surgery⁴.

The main measurements of success of enhanced recovery programs have been the reduced peri-operative morbidity and mortality and reduced post-operative length of hospital stay¹.

However, deviation from ERAS protocols is commonly reported and this is associated with prolonged length of stay⁵. As well as this, barriers to implementing fast track protocols are commonly encountered⁶, with reluctance by care providers to accept care strategies that differ from personally preferred practice being a major factor⁷.

Patient acceptance is vital when attempting to achieve successful results with enhanced recovery approaches. Moreover, care provider support for enhanced recovery care components is critical in order to successfully implement post-operative care pathways relying on multi-disciplinary team input⁷.

It is therefore necessary to explore the views of both patients and care providers regarding their personal priorities pertaining to recovery and the favored strategies used to achieve these aims. This information is crucial to determine whether enhanced recovery programs have the correct patient-centered approach to post-operative recovery and the appropriate support of care providers in order to optimize implementation.

This survey of patients and healthcare professionals was performed to investigate these views and provide clarification of patient and clinician care priorities.

METHODS

Following satisfying the requirements of the respective institutional review boards a survey was carried out by the investigators across three Northern-European centers – Edinburgh (UK), Tromsø (Norway) and Maastricht (The Netherlands). These institutions were selected as they represent the home institutions of the collaborating authors. They are high volume tertiary referral centers experienced in delivering ERAS protocols in hepatic, colorectal and esophagogastric surgery.

The authors developed a questionnaire for the purpose of this survey. The questionnaire aimed to quantify the responder's perception of the importance of individual enhanced recovery outcomes and strategies.

The questionnaire was divided into two sections. The first assessed individual targets to be achieved during recovery following abdominal surgery (questions 1-8). These incorporated the major domains of ERAS principles⁸ – pain control, gut restitution,

mobility, overall function and hospital discharge. These items were identical for questionnaires given to care providers and patients. The second section assessed strategies on how to achieve the recovery targets specified in section 1. The items chosen reflected common strategies utilized in enhanced recovery protocols as advocated by the best available evidence⁸. The patients were given four questions and the care providers were given 13 different questions relating to strategy (Appendices 10 and 11).

The questions were formulated in English and then translated into Dutch and Norwegian. A further separate translation of the questions back into English was performed to ensure accurate translation. The questionnaire was trialed locally to ensure satisfactory comprehension by responders.

Responders in each institution were given a standardized verbal explanation as to what the survey entailed and advice regarding how to complete the survey. They were asked to rate each component from 0-10 on an 11 point Likert scale, depending on how important they believed each component was. The scale used indicator statements of “not important” and “very important” at the relevant extremes of the scale to assist with scoring. An example was performed by the investigator with each responder to ensure comprehension and then the patient was left to complete the questionnaire unaided.

The survey was conducted between November 2012 and November 2013. Consecutive patients scheduled for hepatic, colorectal or esophagogastric surgery were approached and asked to complete a questionnaire on the morning of their operation or during out-patient work-up prior to surgery. This was repeated following surgery when the patient returned to the out-patient clinic two to four weeks later. Due to the exploratory nature of this survey a sample size calculation was not performed. However, it was determined that each center would recruit a minimum of 35 patients to complete the questionnaire before and after surgery. The exclusion criteria were an inability to comprehend the survey or unwillingness to participate.

A random sample of senior surgeons, anesthetists and nurses working in the centers involved in the care of these patient groups were also surveyed. This questionnaire was administered using an internet-based tool (Survey Monkey, Palo Alto, US; for Tromsø: Questback®) or an identical paper-based version depending on convenience.

Results were collated and analyzed with Excel 2010 (Microsoft Corp., Seattle, US) and presented as median and interquartile range (IQR). Statistical analysis was performed with R (R Foundation for Statistical Computing, version 2.9.0). Discrete variables were compared with Fischer’s exact or Chi-square tests where appropriate. Continuous data were assessed with Mann Whitney U test. Scores between care-provider specialties were compared with the Kruskal-Wallis test. Statistically significant differences between pre-operative and post-operative patient scores were assessed by the Wilcoxon signed-rank test. Significance tests were adjusted for multiple comparisons using the Bonferroni correction.

As we had devised a novel questionnaire, we undertook validation of the instrument. High internal consistency would be expected if responders scored items within the two sections (outcomes and strategies) similarly. Internal consistency of questionnaire components was determined with Cronbach's alpha including 95% bootstrapped confidence intervals. Cronbach's alpha increases with greater inter-correlation of questionnaire components and can be interpreted as an overall measure of internal consistency.

Exploratory factor analysis was performed to assess the underlying structure of the questionnaire. The questionnaire had two sections, "attitudes to outcomes" and "attitudes to strategies". It might be expected that answers to questions assessing each of these domains would be correlated. The factor analysis examines whether questions might cluster into alternative groupings representing different underlying concepts. Principal component analysis was performed and eigenvalues generated (representing the proportion of the variance explained by each additional new factor). Eigenvalues were plotted on a scree plot and a cut-off determined. Maximum likelihood factor analysis was then performed with varimax rotation retaining the appropriate number of factors.

RESULTS

Demographics

One hundred and nine patients scheduled for major abdominal surgery were approached and participated in the pre-operative survey (100% response). Patients were included from all three centers – Edinburgh (n=38), Tromsø (n=36) and Maastricht (n=35). The demographic and clinical characteristics of the patients are shown in Table 11.1. Eighty-one per cent (88/109) of patients responded to the follow-up survey administered after surgery. The post-operative non-responders had higher ICU admission rates (29% vs. 8%, $P<0.05$) and a higher proportion of esophagogastric resections (24% vs. 7% $P<0.05$) performed when compared to the patients who completed the post-operative questionnaire. Sixteen anesthetists (median age 51, IQR 42-61), 23 nurses (median age 35, IQR 29-38) and 18 surgeons (median age 52, IQR 43-59) were surveyed from across all three sites.

Questionnaire validation

The inter-correlation of items within the two parts of the questionnaire was good suggesting internal consistency: care providers outcomes $\alpha=0.89$ (0.83-0.93), care providers strategies $\alpha=0.83$ (0.75-0.89); patients outcomes $\alpha=0.96$ (0.79-1.00.), patient strategies $\alpha=1.00$ (0.34-1.00).

An exploratory factor analysis was performed on the questionnaire components for care providers to assess underlying structure. Three factors were shown to provide an adequate fit. Items relating mainly to enhanced recovery outcomes loaded onto one factor and those relating to individual strategies to a second. Interestingly, four items (two outcomes and two strategies) – “to be completely free from pain at rest”, “to be completely free from pain on movement”, “using epidural analgesia for 48 hours” and “optimizing fluid balance” – loaded onto a third factor, suggesting additional structure not appreciated in the original questionnaire design (Figure 11.1).

Table 11.1 Patient demographics and clinical details

	Tromsø (n=36)	Edinburgh (n=38)	Maastricht (n=35)	Total (n=109)
Operation n(%)				
Hepatic resection	2 (6)	38 (100)	20 (57)	60 (55)
Colorectal/small bowel	19 (53)	-	15 (43)	34 (31)
Esophagogastric	8 (22)	-	-	8 (7)
Pancreatic	2 (6)	-	-	2 (2)
Other	5 (13)	-	-	5 (4)
Length of Stay				
Days, median (range)	5 (3-96)	7 (4-38)	7 (3-30)	7 (3-96)
Complications n(%)				
Yes	11 (31)	17 (45)	14 (40)	42(39)
No	25 (69)	21 (55)	21 (60)	67(61)
ICU admission n(%)				
Yes	6 (17)	2 (5)	2 (6)	10 (8)
No	30 (83)	36 (95)	33 (94)	99 (92)
Readmission n(%)				
Yes	7 (19)	4 (11)	6 (17)	17 (16)
No	29 (81)	34 (89)	29 (83)	92 (84)
Pathology n(%)				
CLM	2 (6)	25 (66)	19 (54)	46 (42)
Cholangiocarcinoma	-	2 (5)	-	2 (2)
HCC	-	5 (13)	-	5 (4)
Other	4 (11)	3 (8)	-	7 (6)
Primary adenocarcinoma	28 (77)	-	16 (46)	44 (40)
Benign	2 (6)	3 (8)	-	5 (5)
Previous hospital stay n(%)				
Yes	27 (75)	32 (84)	32 (91)	91 (83)
No	9 (25)	6 (16)	3 (9)	18 (17)
Age (years)				
Median (range)	66 (35-93)	63.5 (32-79)	65 (36-85)	64 (35-93)
Sex n(%)				
M	25 (69)	25 (66)	20 (57)	70 (64)
F	11 (31)	13 (34)	15 (43)	39 (36)
ASA n(%)				
I	2 (6)	4 (11)	5 (14)	11 (10)
II	25 (69)	28 (74)	17 (49)	70 (64)
III	8 (22)	6 (15)	13 (37)	27 (25)
IV	1 (3)	-	-	1 (1)
Employment status n(%)				
Employed	12 (33)	16 (42)	7 (20)	35 (32)
Retired	22 (61)	18 (47)	22 (63)	62 (57)
Unemployed	2 (6)	4 (11)	6 (17)	12 (11)

Figure 11.1 Factor analysis of questionnaire items. Each number represents the factor loading which can be thought of as a correlation coefficient between a questionnaire item and one of the three factors. Three distinct groups were identified as illustrated above. This signifies uniformity of scoring patterns occurring within these three groups.

Patient outcomes

The overall scores were high with the lowest median score being 8/10. The preoperative impressions of patients awaiting surgery were unchanged by the subsequent surgery, with no significant differences observed between pre- and post-operative scores (i.e. $P > 0.05$ for each comparison following adjustment for multiple comparisons), as determined by the Wilcoxon signed-rank tests (Figure 11.2).

Patients scored freedom from nausea (median 10 IQR 8-10) and freedom from pain at rest (median 10 IQR 8-10) as the two most important factors. Achieving independent mobility was also scored highly by patients (median 9, IQR 8-10). Early discharge (median 9, IQR 6.5-9) and early return of bowel movements (median 9, IQR 7.25-10) received the lowest scores when taking the IQR into account (Figure 11.2).

Patient strategy

Patients highlighted pre-operative counseling (median 10, IQR 8.75-10) and avoiding infection in hospital (median 10, IQR 9-10) as a priority in achieving recovery (Figure 11.2).

Figure 11.2 Patient ratings of ERAS outcomes and strategies. Pre-operative scores are compared with post-operative scores for each item. Wilcoxon signed-rank test was used to compare scores. No statistically significant differences were observed between scores.

Care provider outcomes

Outcomes were in general scored highly by the care providers with all items being scored with a median of 7/10 or higher. The outcomes scored as most important by

care providers were control of nausea (median 9, IQR 8-10) and being free from pain at rest (median 9, IQR 8-10) (Figure 11.3).

Being able to move the bowels as soon as possible was scored the lowest (median 7, IQR 5-8) by the care providers. Also being discharged from hospital as soon as possible received lower scores (median 8, IQR 6-9) as did returning to daily activities as soon as possible (median 8, IQR 5.5-10) (Figure 11.3).

Figure 11.3 Combined care providers ratings of ERAS outcomes.

Care provider strategy

The range of scores was more varied in this area of responses. The highest rated items of care strategy as scored by the care providers were: provision of pre-operative

counseling (median 10, IQR 9-10); promotion of early mobilization (median 9.5, IQR 9-10) and optimization of IV fluid administration (median 9, IQR 8-10) (Figure 11.4). Avoiding wound drains (median 7, IQR 4.5-8), avoiding bowel preparation (median 7, IQR 4-8) and avoiding anesthetic pre-medication (median 6.5, IQR 3.5-8) were scored the lowest (Figure 11.4). Sub-group analyses using the Kruskal Wallis test were performed to compare scores of each item by individual specialties of care providers and between the care provider nationalities. Following adjustment for multiple comparisons no significant differences between care provider specialty nor nationality scores were observed.

Figure 11.4 Combined care providers' ratings of ERAS strategies.

DISCUSSION

This study investigated the opinions and perceptions of both providers and receivers of enhanced recovery protocols following major abdominal surgery in three European countries. It is the first study of its kind.

The novel questionnaire was designed for the purposes of this study and validated successfully. Good internal consistency was observed and the factor analysis performed revealed a logical separation of items into ERAS outcomes and strategies. This suggests consistent and distinct scoring patterns within these groups of questionnaire items indicating satisfactory validity of the items selected. These results also reflect the consistently high scores throughout the survey and overall support for the outcomes and strategies used in the questionnaire.

The post-operative response rate of eighty-one per cent was satisfactory. The non-responders underwent a greater proportion of esophagogastric resections and fewer hepatic resections than those who completed the post-operative questionnaire. Although the ICU admission rate was higher in this sub-group, readmission and complication rates remained unchanged. This likely reflects a tendency for esophagogastric resections to be managed initially in ICU routinely, which was not the case for hepatic resections, and their absence was not thought to adversely influence the post-operative responses observed.

Patients attributed high importance to all of the ERAS aims and strategies asked of them. This represents concordance between patients' beliefs and current recommendations by ERAS experts⁸ and this finding should be used to encourage and develop ERAS implementation.

Previous studies have also shown that compliance with ERAS protocols can be compromised resulting in deviation from care plans⁵. However, our results show that patient support for the ERAS process is high and therefore we suggest it is unlikely that lack of patient acceptance is the main cause of deviation from protocols. Moreover, we did not show a difference in patient opinion pre- and post-operatively, suggesting that patient support for such care plans does not change even after having gained experience of the care principles.

A qualitative assessment of patient experience following ERAS surgery⁹ found that decreased satisfaction was reported in a subgroup of patients who suffered a complication following discharge. Our survey sample included patients who suffered complications at rates that would be expected from these types of surgery. This did not cause significantly different pre-operative and post-operative patient scoring and so we do not concur with the view that the development of a complication negatively impacts on patients' support for the ERAS principles.

The clinicians also scored highly for the majority of targets and strategies and good inter-specialty agreement was observed, representing streamlined support for ERAS principles. Opinions of different professional groups involved in delivering ERAS

programs has not been assessed before and represents a novel finding of the study and justification for continued implementation.

However, although our scores were high there were some areas of relatively lower scoring. There was a broad range of scores for the importance of epidurals, particularly from surgeons (range 1-10). This reflects the controversy that surrounds routine epidural use¹⁵. The use of alternative analgesic modalities, such as intrathecal analgesia and continuous wound infiltration, has become increasingly popular^{10,11}. The UK Department of Health's Enhanced Recovery Partnership Program (ERPP) consensus opinion¹² has subsequently advocated less routine epidural use and increased alternative analgesic methods.

Fluid balance optimization was scored highly by care providers. Both inappropriate fluid restriction and excessive fluid administration have been shown to be associated with prolonged hospital stays¹³ and increased post-operative morbidity¹⁴ reflecting the importance of accurate fluid balance. Epidural use is associated with vasodilation and hypotension and can be associated with excessive intravenous fluid administration¹⁵. It may be that these perceived drawbacks associated with epidural use are contributory to its lower rating. Indeed the factor analysis identified epidural use, fluid balance and minimization of pain as a distinct group separate from ERAS outcomes and strategies, reflecting an independent but uniform scoring pattern for these items by the care providers.

Strategies scored lowest overall by care providers were the avoidance of post-operative abdominal drains, oral bowel preparation and pre-anesthetic sedatives. There is high-level evidence in colorectal surgery advocating against drain insertion¹⁶. Similarly, there is good evidence suggesting no benefit of routine bowel preparation prior to abdominal surgery¹⁷.

The stimulation of gut motility was also scored in the lower half of results, particularly by anesthetists and, to a lesser degree, surgeons. Liberal laxative use to prevent constipation and achieve restoration of bowel function is often advocated as a preventative measure against post-operative ileus¹⁸ and is a component of many enhanced recovery protocols. However the care provider responses were at odds with this evidence.

These results may be partly due to of the presence of resections other than colorectal in the study population where there is less clear evidence for the benefits of drain avoidance and less relevance of bowel preparation and stimulation. However, the reluctance to abandon previously well-established practice despite evidence to the contrary is recognized in the literature^{6,19}. This is a potential obstacle to the implementation and continued establishment of ERAS principles and is a phenomenon that continues to be observed²⁰ and requires attention when addressing failing ERAS implementation.

Potential drawbacks to the study are the relatively small sample size and the post-operative response rate. It is also acknowledged that due to the small sample size and

the high concordance in the overall scoring it is not possible to determine which items are considered more important relative to each other. However it is possible to determine those items scored highest and lowest and an appropriate qualitative assessment of these items was performed. Additionally, the overall high internal consistency of the results suggests that the sample provides valid results and is an acceptable number for this descriptive analysis.

The survey was performed on patients, for the most part, undergoing major open abdominal surgery for malignant disease processes. This therefore represents a population representative of the majority of ERAS recipients however is not strictly relevant to non-abdominal surgery.

In conclusion, this novel study has shown good patient and multidisciplinary care provider approval for the principles of enhanced recovery care after surgery and supports on going development and implementation of such programs. It highlights potential areas of concern for care providers, namely epidural use and fluid administration. These issues remain controversial and could be a focus for future research. Lastly, we identified several items scored low priority by care providers where there is a strong evidence base to the contrary. This highlights a potential barrier to ERAS implementation and is an area that requires consideration and education if continued sustainability and development of ERAS programs is to be achieved.

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CHAPTER 12

General discussion and summary

GENERAL DISCUSSION AND SUMMARY

The principal aim of this thesis was to investigate the feasibility of ERAS programs for HPB surgery. There is abundant evidence demonstrating that ERAS programs are preferred over traditional care in colonic surgery. Also in other surgical fields ERAS programs have been proven to result in shorter hospital stay, lower morbidity rates and reduced hospital costs¹⁻⁴. However, until now it remained unclear whether it is also feasible to implement ERAS programs in major abdominal surgery such as HPB surgery. In summary, the aims of the present thesis were as follows:

- 1) To critically appraise the literature regarding ERAS programs for HPB surgery and endpoints in pancreatic surgery (Part I, chapter 2,3,4,5)
- 2) To develop perioperative ERAS guidelines for pancreaticoduodenectomy (Part II, chapter 6)
- 3) To initiate a trial evaluating the effect of prophylactic intra-abdominal drainage for patients undergoing pancreaticoduodenectomy in an ERAS program (Part II, chapter 7)
- 4) To evaluate the implementation of an ERAS program in HPB surgery (Part III, chapter 8,9,10,11)

Part I: Critical appraisal of literature: ERAS programs in HPB surgery and endpoints in pancreatic surgery

The first aim of this thesis was to assess what is already known about ERAS programs in HPB surgery and compare existing studies. We performed a systematic review of ERAS programs in pancreatic surgery (**chapter 2**). Also, a meta-analysis was performed but only on articles related to patients undergoing pancreaticoduodenectomy (PD) because this is the most common surgical pancreatic procedure and is considerably different from other forms of pancreatic surgery. From the eight studies described in this review we concluded that an ERAS protocol helps to shorten (hospital) length of stay (LOS) without compromising morbidity and mortality. Meta-analysis of four studies focusing on PD showed that there were no differences in readmission or mortality rates and that morbidity rates were significantly lower for patients managed according to ERAS principles. We also performed a systematic review of ERAS programs for liver surgery (**chapter 3**). Six studies were included in this review and analysis showed that an ERAS program can be successfully implemented in liver surgery without altering morbidity, mortality or readmission rates. For both reviews, some limitations are mentioned. First, there were no randomized controlled trials (RCTs) available for inclusion. Only a few randomized trials comparing ERAS with traditional care in colorectal surgery exist^{2,3} but no such trials have been conducted in the field of liver and pancreatic surgery. This is probably due to the fact that randomized controlled trials are difficult to organize for multimodal recovery programs under greatly varying conditions. Moreover, several protocol elements of an ERAS program have already become standard practice in many

hospitals during the last decade (e.g., thromboprophylaxis, prevention of hypothermia with Bair Huggers, early mobilization). This raises ethical concerns with respect to randomization because patients in the control group may not receive specific evidence-based interventions.

Second, the methodological quality of the studies was variable since they consisted mostly of retrospective or prospective case series and comparative studies based on historical controls. Furthermore, individual studies used slightly different study protocols. The items incorporated in the various protocols were not identical making it difficult to compare the studies. Also, the degree of compliance to the ERAS-protocol was not reported in the studies. Finally, definitions of complications were ill-defined in the studies and complications were not registered in a standardized classification system (e.g. the Dindo-Clavien classification). We concluded that there is need for a standardized and procedure-specific ERAS program for pancreatic and liver surgery to be implemented and used in future studies. Furthermore, standardized registration systems should be used to classify complications and uniform definitions for specific complications must be maintained. It is also important to describe adherence to protocol in studies reporting on ERAS programs.

The omission of prophylactic postoperative intra-abdominal drains is one of the components of an ERAS program in colonic surgery. For most abdominal surgical procedures there is little evidence indicating the benefits of drains. In certain cases they may even be considered harmful⁵⁻⁷. However, in pancreatic surgery surgeons are reluctant to omit prophylactic intra-abdominal drains because they can serve to indicate a bleeding or leakage of the pancreatic anastomosis. We performed a systematic review and cumulative meta-analysis of three studies comparing patients undergoing PD in a drain and no-drain group (**chapter 4**). In this study, a traditional meta-analysis of the available evidence pointed to a significantly lower complication rate in the group without routine drainage. However, when a *cumulative* meta-analysis was performed with adjustment for repeated testing and heterogeneity, this difference was no longer statistically significant. In conclusion, the routine use of abdominal drains after pancreatic resection may carry a higher risk of complications but the evidence remains inconclusive. A recently published review on the use of abdominal drains after pancreatic resections adopted a slightly different approach, using a standard Mantel–Haenszel random-effects model for meta-analysis and separate evaluations of overall and specific complications, respectively⁸. In line with our findings, this review concluded that more evidence is required before any firm conclusions on the use of prophylactic abdominal drains can be drawn. Evaluation of early (postoperative day 3) versus late (postoperative day 5 and beyond) drain removal has been examined in a RCT of Bassi et al.⁹. Early removal of the drain in patients at low risk of pancreatic fistula (amylase value in drains <5,000 U/l at postoperative day 3) was associated with a significantly decreased rate of pancreatic fistula, abdominal and pulmonary complications. Another prospective study comparing drain removal on day 4 versus day

8 showed that drain removal on postoperative day 4 was an independent factor in reducing the incidence of complications after PD including intra-abdominal infections¹⁰. So, until further data are available a conservative approach with systematic postoperative drainage and early removal in patients at low risk of pancreatic fistula (firm pancreas, wide pancreatic duct) is recommended. However, given the inconclusive evidence for drainage after PD, further exploration by RCTs is needed and differences in postoperative outcomes between early drain removal and a no-drain regimen after PD should be examined.

Few RCTs have been performed in pancreatic surgery^{10,11}. An important factor contributing to this is the relatively low incidence of pancreatic disease. Furthermore, in RCTs focusing on pancreatic surgery the usefulness of outcomes as surgery-related mortality or specific PD-related morbidity as a primary endpoint is limited because individually they have a relatively low incidence. Consequently, large sample sizes are needed to obtain adequate statistical power. Another problem in research into pancreatic surgery is that comparability of studies is low due to ill-defined definition of complications and a lack of standardized complication registration systems. Use of a PD-specific composite endpoint containing outcome parameters that are well-defined and of significant severity could overcome this problem. In **chapter 5** the development of a PD-specific composite endpoint (CEP) is described. In a CEP several outcome parameters are combined to form a single dichotomous endpoint¹². The individual parameters that are combined in a CEP should also be dichotomous, highly specific for the given surgical procedure and of clinical relevance. Scoring a CEP results in a higher incidence than the incidence of individual specific endpoints. Using CEP as a primary endpoint therefore increases statistical power and allows for smaller sample sizes when performing RCTs. Because CEPs are well-defined they enhance the performance of RCTs and subsequent meta-analysis as well as their quality and comparability. The PD-specific CEP components were selected after a systematic review of the literature and consensus between 25 international pancreatic surgeons by means of a web-based survey. Consensus on definitions for these components was also reached. From a total of eighteen single component endpoints, intra-abdominal abscess, sepsis, post- PD-hemorrhage, bile leakage, gastrojejunostomy leakage, leakage of the pancreatic anastomosis, delayed gastric emptying and operative mortality within 90 days were selected to be included in the PD-specific CEP. Since it is imperative for the components to have a similar clinical relevance or severity¹³, all individual components of the CEP have to be classified with a Dindo-Clavien grade of 3 or more¹⁴. The event rate and effect of the PD-specific CEP was consequently evaluated in two prospective cohorts of patients who underwent PD in two high-volume HPB centers (MUMC+, Maastricht and Royal Free Hospital, London). The incidence of the individual components with a Dindo-Clavien grade ≥ 3 varied between 0.5% and 15.7% in the MUMC+ and from 1.7-8.3% in the Royal Free Hospital. Subsequently, the incidence of the PD-specific CEP was calculated and was found to be 24.7% in the Maastricht cohort and 23.3% in the

London cohort. Compared to the use of single-component primary endpoints, the incidence rates obtained with a PD-specific CEP lead to a two-fold reduction of the theoretical, calculated sample size for an adequately powered RCT. A drawback of using CEPs is that its individual components may be ill-defined and show differences in severity or incidence. Furthermore, the components may not be affected in the same manner by the intervention¹⁵. In developing our CEP we tried to address these issues in a systematic way by reaching international consensus on definitions of the individual components and by classifying only complications with a Dindo-Clavien grade of 3 or more. Quality of life was not included in this CEP since experts did not consider this to be PD-specific enough. Even so, patient perception should not be disregarded since patients may consider the consequences of complications (e.g. pain, fatigue or confusion) as more critical than physicians do. This issue should be addressed in future research on CEPs.

It may be also necessary to develop CEPs for other forms of pancreatic surgery as well as for drug-related pancreatic research. Furthermore, weighing of specific components of a CEP, not only by clinicians but also by patients, might be considered in future work. The use of CEPs in RCTs for surgical research seems promising but prospective evaluation is needed.

Part II: Development of ERAS guidelines and a multicenter trial for pancreaticoduodenectomy

As pointed out in chapter 2, studies on the implementation of ERAS programs in pancreatic surgery and in particular in PD employ ERAS protocols with a varying set of elements¹⁶⁻¹⁸ or report no protocol at all¹⁹. These studies are therefore not fully comparable. **Chapter 6** describes the development of a consensus framework of ERAS guidelines for PD by the international ERAS group. This framework has come about after a systematic literature search and grading of the selected studies. The strength of evidence and conclusive recommendations for each protocol element (27 in total) were assessed and agreed by all authors in a meeting in May 2012 and taken together to form ERAS guidelines for PD.

ERAS programs have been strongly associated with reduced length of hospital stay (LOS) but this may not be the best indicator of the quality of functional recovery, which an ERAS program pursues²⁰. Emphasis must also be placed on reducing morbidity. Multimodal ERAS programs are complex interventions that pose significant challenges to evaluation by conventional RCTs²¹. The most obvious of these challenges are standardization of the intervention and ethical and practical concerns. This may, to some extent, explain the relative lack of RCTs evaluating ERAS programs and the somewhat limited effect that has been shown on endpoints other than LOS. It may be reasonable to propose that, if RCTs have proven the benefit, a protocol of items, which are supported by RCTs, should not need analysis in an RCT itself. Feasibility, however, must be ensured. Hence, multicenter and multinational prospective validation of this

perioperative care protocol for PD in consecutive cohorts of patients undergoing PD is warranted.

In the ERAS guidelines for PD no consensus was reached regarding omission or inclusion of prophylactic intra-abdominal drainage since the evidence from literature remained inconclusive, as also shown in chapter 4. For this reason, we decided to design a multicenter RCT comparing prophylactic abdominal drainage with a no-drain policy in patients undergoing pancreaticoduodenectomy (**chapter 7**). This trial will be carried out in 10 different hospitals across the Netherlands and Europe. All patients in this study are treated according to the developed ERAS guidelines as posed in **chapter 6**. Also, the recently developed composite endpoint for pancreaticoduodenectomy will be used as one of the outcomes as validation (**chapter 5**). A sample size of 360 patients was calculated on the primary endpoint (need for radiological or surgical interventions). The trial started enrolling patients from January 2013 in MUMC+. The other hospitals followed in the months thereafter after approval of the Ethical Committee. With this multicenter international RCT we hope to shed light on the risk and benefits of omitting a postoperative intra-abdominal drain after pancreaticoduodenectomy and gain conclusive evidence whether a no-drain policy is better than early removal of the perianastomotic drain.

Part III: Evaluation of implementing an ERAS program in liver and pancreatic surgery

In the Maastricht University Medical Center (MUMC), the ERAS program for colonic surgery was implemented from 2000 onwards²². In 2005, a pilot was started in Maastricht and Edinburgh resulting in the successful implementation of the ERAS program in liver surgery (**chapter 8**). This was a prospective study involving 61 patients. Outcomes were compared with those in a consecutive series of 100 patients who underwent liver resection before the start of the study. Fifty-six patients (92%) in the ERAS group tolerated fluids within 4 h of surgery and a normal diet on day 1 after surgery. Median hospital stay, including readmissions, was 6 days compared with 8 days in the control group ($P<0.001$). There were no significant differences in rates of readmission (13% and 10.0% respectively), morbidity (41% and 31%) and mortality (0% and 2.0%) between ERAS and control groups. Nasogastric tubes (NGT) were removed on the day of surgery in 92% of the patients in the ERAS group, whereas in the control group none of the NGTs was removed on the day of surgery ($P<0.001$). Also, prophylactic abdominal drains were used only in 2% in the ERAS group versus 66% in the control group ($P<0.001$). Fifty-two (85%) of 61 patients in the ERAS group were completely mobile on the third day after operation and 29 (48%) were discharged from the hospital within 5 days. We concluded that an ERAS program can be safely and effectively implemented in liver surgery. In this study, the ERAS program allowed for early oral intake, promoted postoperative recovery and a reduced hospital stay. The impact of the ERAS liver program became more evident at the end of the 2006 pilot.

Several ERAS items were also implemented in pancreatic surgery but a standardized protocol was not yet available. In 2009 a concept protocol was established for PD and used ever since. The ERAS guidelines for PD (chapter 6) were implemented from 2013 onwards and will be evaluated in a multicenter international prospective project.

Chapter 9 describes an examination of patient characteristics, indications and outcome after PD in the period between January 1995 and January 2012 in MUMC and also evaluates the effects of implementing an ERAS program for PD. This time period is divided in three groups according to patients receiving no or (partial) ERAS perioperative care: Group 1 (1995-2005) “no ERAS”, group 2 (2006-2008) “ERAS-like” and group 3 (2009-2011) “ERAS”. Median length of stay (LOS) was significantly reduced from 20 days in group 1 to 13 days in group 2 and 14 days in group 3 ($P=0.001$). Patients discharged without complications had a median LOS of 15, 10 and 9 days, respectively, in group 1, 2 and 3 ($P<0.001$). Over time, resection volume increased significantly in the authors’ unit with more pylorus-preserving pancreaticoduodenectomies (PPPDs) being performed than classical Whipple’s procedures. Complication rates as well as mortality and readmission rates did not change. We concluded that an ERAS program for PD is feasible and that the implementation and increasing resection volume probably both contributed to a decrease of LOS without compromising other outcomes.

In addition, **Chapter 10** demonstrates that it is also feasible to subject patients of advanced age to an ERAS program. We prospectively evaluated a group of 110 patients undergoing PD and divided them in two groups (below 65 years and above 70 years of age). We found that compliance with the different aspects of the protocol, number of readmissions, morbidity and mortality rates were not significantly different between both groups, concluding an enhanced recovery program is also feasible for patients above 70 years of age undergoing a PD.

Since the ERAS colon protocol was already implemented in our clinic from 2000 onwards some major changes in different areas (anesthesiology, on the ward and physiotherapy department) had already been instituted, which made it easier to implement ERAS protocols for liver and pancreatic surgery as well. However, this does not hold true for all protocol elements. For instance, owing to tradition in the anesthesiology department NGTs were still used extensively in liver and pancreatic surgery and removing NGTs directly after surgery meant a major change in clinical practice for these kinds of operations. As shown in chapter 8 and 9 this change in routine did not result in more pulmonary complications. Also, especially in PD, postoperative enteral nutrition starting with fluid intake on the day of surgery and solid intake from day 1 was an evident change of practice, which was also tolerated well by most of the patients. For the ERAS PD protocol some elements of the protocol (e.g. the early removal of the urine catheter and abdominal drain) were not sufficiently complied with. The fact that implementing evidence-based care in practice can be challenging is shown by several studies. Lassen et al. performed a survey in 200 hospitals in five European countries distributed via departments of surgeons participating in the ERAS

group for colonic surgery. It appeared that perioperative routines in colonic cancer surgery differed widely between the countries and deviated considerably from the recommendations of the ERAS protocol (e.g. bowel preparation was still applied in the majority of the clinics as well as the use of NGTs)²³. Maessen et al. performed an international study to evaluate the implementation of an enhanced recovery program including 425 patients undergoing colonic resection²⁴. This study showed that protocol compliance was high before and during the surgical procedure but was low in the immediate postoperative phase (ranging from 36-85% for various protocol items). Furthermore, only 31% of the patients were discharged on the day of functional recovery. Most of the patients were discharged on median postoperative day (POD) 5 while functional recovery was already reached on POD 3. These results are in line with results for the ERAS program for PD as described in chapter 10 and suggest more effort should be put into improving compliance in the immediate postoperative phase, which could further accelerate recovery (e.g. continuous education of nurses and staff and the use of self-reporting diaries). Moreover, postoperative care should be planned better and re-organized to really discharge patients on days they meet the functional recovery criteria. Similarly, in a present study about fast track laparoscopic liver surgery in our unit functional recovery was reached two days before the actual discharge²⁵. This poses the question whether LOS is actually an appropriate readout to evaluate the impact of an ERAS program rather than the day functional recovery or discharge criteria are met. Questions are raised about some perioperative care elements of an ERAS protocol being more important than others. In a recent paper a multivariable analysis of care elements influencing LOS in 2,485 patients undergoing colonic surgery showed that cessation of IV fluids, mobilization on postoperative day 1, and postoperative administrations of laxatives (magnesium oxide) were associated with shortened LOS²⁶. Hence, ERAS programs may accelerate restoration of gut motility. In PD, this might help to lower the incidence of delayed gastric emptying (DGE). A lower incidence of DGE has been demonstrated before in patients undergoing PD in an enhanced recovery pathway, although this was not shown in our studies¹⁶. Another analysis of Vlug et al. using the data of the LAFA trial showed that enforced advancement of oral intake, early mobilization, laparoscopic surgery and female sex were independent determinants of early recovery²⁷. Another evaluation of implementation of an ERAS colon protocol and protocol compliance performed an univariable analysis which suggested that postoperative rather than preoperative and perioperative factors significantly influenced length of hospital stay²⁴. The previous data might suggest that there are indeed several care elements that contribute more to recovery than others. The influence of the degree of compliance to the ERAS protocol has also been examined. It is advocated that maximizing compliance to the various protocol is important to reach an optimal effect²⁴. However, one study examining two groups managed in an ERAS pathway after colonic surgery showed that an overall protocol compliance of 77% does not worsen outcome as compared to a compliance of 88%²⁸. In

another study evaluating an ERAS program in colorectal surgery, protocol compliance of less than 50% did show to deteriorate postoperative outcome (higher LOS, 30-day morbidity and readmission-rates) as compared to 70%, 80% or 90% compliance²⁹.

Compliance to an ERAS protocol in pancreatic surgery is a challenge. Pancreatic surgery still has high morbidity rates, and morbidity is an independent risk factor of a longer LOS as is shown in chapter 9. Furthermore, chapter 9 and 10 also showed that higher Dindo-Clavien grades correlated with longer LOS compared to complications with a lower Dindo-Clavien grade. In patients with a complicated postoperative course compliance to the postoperative items of the ERAS protocol is obviously less and sometimes even impossible. On the other hand, in uncomplicated patients this is easier and an LOS of 8-9 days as proposed in the ERAS protocol seems very well feasible. This is also shown by a recent retrospective study that reviewed 41 patients undergoing an uncomplicated PD. Twenty-one patients were managed in a fast track protocol and 20 patients received traditional care³⁰. The LOS (including readmissions) was 9 days in the fast track group versus 14 in the traditional care group. Based on multivariable analysis, management in a fast track protocol was the only independent factor of a shorter LOS. This is in line with results shown in chapter 9. Unfortunately, compliance to protocol in this study with uncomplicated PD patients is not reported. A study of Robertson et al. managing 50 patients undergoing PD in a fast track protocol did report on protocol compliance and found it varying for different items between 36 and 82% with the most challenging items being early mobilization, the removal of drains and urine catheters. Similar compliance with the aforementioned items is also reported in chapter 10. LOS in this study was 9 days for uncomplicated patients. Importantly, a delay of discharge was reported for 32% of the patients, owing to social or transport-related reasons. So here also, functional recovery would have been a better readout.

The majority of studies reporting on ERAS programs for PD do not describe definitions for complications and do not use a standardized complication classification system. However, this is important for comparability between studies, especially when a meta-analysis on non-randomized studies is performed since such a meta-analysis is often limited by heterogeneity. We therefore used definitions for complications in our studies that were universally agreed on by the International Study Group of Pancreatic Fistula (ISGPF) and the International Study Group of Pancreatic Surgery (ISGPS)³¹⁻³³. In addition, the well-validated Dindo-Clavien classification system for surgical complications was used in our studies¹⁴. The Dindo-Clavien classification aims to objectively group different complications with respect to the severity of therapeutic interventions and its use enhances comparability between studies.

In chapter 9, we described the outcome of patients undergoing PD in a 16-year time period in which the last 5 years patients were managed in an ERAS protocol. We noticed a reduction of 7 days in postoperative LOS in the ERAS group compared to the traditional care group. However, this decrease in LOS might not solely be attributable to the introduction of the ERAS program, since the increase in volume and

accompanying experience with perioperative care probably also has had its influence. Several studies have reported improved outcome (lower morbidity and mortality rates and lower LOS) after PD proportional with volume and centralization³⁴⁻³⁷.

In chapter 10 we evaluated elderly patients undergoing PD in an ERAS program. There is no official definition for the term “elderly”, but most studies performed on pancreatic resections in the elderly population use a cut-off age above 70 years³⁸⁻⁴³. A recent analysis on a large cohort showed an age of 68.5 years can be considered as ‘surgical oldness’⁴⁴. We decided to define an interval centered on this age and consider older than 70 years as “elderly” and below 65 years as younger patients. Inevitably, a selection bias is introduced in this study by presenting only the fittest elderly with less severe co-morbidity for PD. Resection is the sole curative option for patients with malignant disease of the pancreas and even in the elderly the survival benefit after resection is not diminished with age⁴⁵. However, the presence of risk factors and significant co-morbidities in the elderly result in lower overall survival rates and increased morbidity and mortality. Therefore it is very important to carefully select older patients and perform a meticulous pre-operative assessment. Older patients should be well informed about the risks and the fact that hospital volume and the experience of the surgeon play a significant role in the outcome³⁵⁻³⁷.

The main outcomes measured in studies about ERAS programs are LOS, morbidity and mortality rates. Patient perception and support are often overlooked but also essential for a successful implementation of an ERAS program. It has been proposed that patient-reported quality of life has been adversely affected by fast track surgery with higher levels of emotional distress reported when compared with conventional surgery⁴⁶. Also, difficulties with implementing ERAS programs are commonly encountered^{23,24,47}. In order to gain more insight in patient and caregiver perceptions on the relative importance of the main components of an ERAS program we performed a multicenter international study (**chapter 11**). Anonymous web-based and paper surveys were sent to surgeons, anesthetists and nurses in centers in Scotland, Norway and the Netherlands. Additionally, pre-operative and post-operative surveys were completed by patients scheduled for major abdominal surgery in these institutions. Each questionnaire asked the responder to rate a selection of enhanced recovery principles and strategies in terms of perceived importance. 105 patients and 57 care providers were surveyed. Overall, patients and care providers found the majority of items important and supported ERAS principles. The highest rated items were: being free from nausea and free from pain at rest. The lowest ranked items were: being discharged from hospital as soon as possible and early restoration of gut function. The results of the survey also highlighted an area of concern for care providers, namely epidural use and fluid administration. These remain controversial issues amongst care providers and therefore have implications for future research. Furthermore, we identified several items scored low priority by care providers (e.g. avoidance of post-operative abdominal drains, oral bowel preparation and pre-anesthetic sedatives), for

which there is a strong evidence base to the contrary. This underlines a potential barrier to ERAS implementation and is an area that requires consideration and education if continued sustainability and development of ERAS programs is to be achieved.

ERAS protocols are often seen as financially beneficial to institutions, particularly when analyzing the economic implications of reduced lengths of stay⁴⁸⁻⁵⁰. However, our survey did not show patient or care provider support for reduced length of stay to be achieved as a priority over recovery. It highlighted that the priorities of patients and care providers are to avoid surgical complications and to achieve functional recovery rather than minimise their admission time in hospital. This poses a potential conflict between cost-analyzers and patients. Also, previous work has reported that enhanced recovery can increase anxiety following discharge⁴⁶ and that patients who suffer a post-operative complication report more distress following early discharge than those with an uncomplicated recovery⁵¹. The results of our survey might therefore suggest that premature discharge is a potential source for anxiety in both patients and care providers.

Taking into account that there have been reports showing increased readmissions rates after an ERAS program⁵², post-discharge community surgical support is mandatory to lessen patient distress when attempting early discharge.

FUTURE PERSPECTIVES

Implementation

Despite a large amount of evidence to support the benefits of ERAS programs implementation of these programs into surgical practice is going slow. Several international surveys in Europe and the United States show that many institutions still do not perform evidence-based perioperative care in gastro-intestinal or HPB surgery^{23,47,53-55}. Problems with adopting guidelines in medicine has been described before in a large review⁵⁶. Potential barriers to physician guideline adherence were lack of awareness and familiarity, lack of agreement, lack of self-efficacy and lack of the ability to overcome inertia of traditional practice. In addition, time limits and insufficient staff expertise may also play a role in slowing down the implementation of guidelines and fast-track programs. Better provision of information and multi-disciplinary education about ERAS programs, especially in smaller institutions, can overcome these barriers. For this reason, the ERAS society has designed special implementation programs, which train perioperative teams to implement, reach and maintain high levels of compliance to the protocol elements (www.erassociety.org). Especially in the perioperative phase of the ERAS protocol many disciplines are involved. Consequently, a good organization and education for these disciplines is

imperative to the success of the program. Moreover, junior nurses and registrars change units frequently, so continuous re-education is important²⁴.

Validation

In chapter 6 we described the development of ERAS guidelines for PD. A framework of evidence-based recommendations for perioperative care for PD is presented. It forms the basis for future protocols. To assure the feasibility of this perioperative care protocol multinational and multicenter prospective validation in a large patient cohort is warranted. This also holds for the CEP for PD presented in chapter 5. An international RCT is now being initiated to evaluate the use of prophylactic intra-abdominal drains after PD and combines the aforementioned topics (chapter 7).

Patients undergoing PD who are included in this trial will be managed in the ERAS protocol as proposed by the ERAS group. Furthermore, this trial will contribute to the validation of the CEP for PD, as this CEP is used as an outcome measure. Additionally, to further validate the ERAS guidelines, multinational implementation of this consensus protocol has taken place from 2013 onwards in the departments of the members belonging to the ERAS group and will be evaluated in a prospective project separately.

Patient perceptions

The composite endpoint, which was developed for PD in chapter 5, did not include patient perceptions or quality of life measures as the respondents of the survey did not find these outcomes to be sufficiently PD-specific. Nevertheless, including patient perceptions in a CEP may be valuable since patients probably assign more weight to the consequences of certain complications. The OMERACT initiative (Outcome Measures in Rheumatoid Arthritis Clinical Trial) introduced the development of a Core Outcome Set (COS), this COS comprises a minimum of outcomes that should be reported in trials and it also includes patient perceptions⁵⁷. More recently, the COMET initiative (Core Outcome Measures in Effectiveness Trials) extended this approach in order to develop COSs that are applicable to other disciplines as well, such as pediatrics and bariatric surgery^{58,59}. In addition to the CEP we are now developing a COS for pancreatic, liver and biliary surgery in collaboration with the COMET initiative.

Specific interventions

ERAS programs show promising results in improvements in outcome and reduction in LOS in many fields of surgery now. To achieve further improvement of outcomes research should be aimed at mediators that modify the stress response. As of yet there is still little information about which reactions in this stress response should be attenuated or stimulated.

In hepatobiliary surgery, minimally invasive techniques are gaining popularity since these are known to reduce morbidity by diminishing catabolism and immunosuppression. Laparoscopic liver resections and even robotic liver resections are increasingly performed⁶⁰⁻⁶³. Recently, the first reports of laparoscopic PD have been published⁶⁴⁻⁶⁶.

Pharmacological interventions have been proposed to attenuate the stress response. Perioperative β -blockage could have positive effects on postoperative mortality in high-risk patients⁶⁷ and when morphine analgesia is provided during surgery, a selective morphine antagonist in the postoperative phase could reverse the negative effects of morphine on bowel function and attenuate postoperative ileus⁶⁸. Glucocorticoids have been described to have an anti-inflammatory effect beneficial to outcome after major abdominal surgery. A meta-analysis of 11 RCTs found a decrease in complications and LOS when glucocorticoids were administered preoperatively⁶⁹. Biological modifiers, such as neuropeptides, mast cell inhibitors and cytokine antagonists are promising pharmacological agents which improve postoperative immune function and diminish tissue inflammation⁷⁰.

Additionally, advancement in analgesic and anesthetic techniques may also contribute to further improve fast-track surgery towards the ultimate goal: "creation of a stress and pain free operation with an enhanced recovery".

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Short summary

SHORT SUMMARY

Liver and pancreatic resections are complex major abdominal surgical procedures that are still associated with considerable morbidity (up to 50%) and mortality rates (2-4%). Traditional perioperative care for liver and pancreatic surgery has been conservative and dogmatic. Furthermore, evidence-based techniques and care elements have not yet been implemented extensively in this field. In this thesis we aimed to develop and implement an evidence-based “Enhanced Recovery After Surgery” (ERAS) care protocol in liver and pancreatic surgery in order to diminish the stress response to these major abdominal resections and accelerate recovery without compromising outcome.

In the past, ERAS programs have been implemented in colonic surgery. Multiple trials showed that these programs accelerate recovery and decrease morbidity in patients undergoing colonic resections. Additionally, hospital costs were shown to be reduced. However, despite the successes in colonic surgery, it is unclear whether an ERAS protocol can also be successfully implemented in major abdominal surgery, such as liver and pancreatic resections. It was the main purpose of this thesis to investigate whether this is indeed possible.

We started our research by conducting a systematic review and meta-analysis to evaluate the feasibility of ERAS programs in liver and pancreatic surgery. We concluded that there is some evidence for the effectiveness of an ERAS program in liver and pancreatic surgery. However, the number of high quality studies is low and protocols differ considerably amongst trials. Also, there is great variability in the endpoints and definitions used. For this reason, there is a need for uniform definitions and a core set of outcomes that should be reported in each study. We performed a systematic review and a web-survey amongst experts in hepato-pancreatico-biliary units. In this study we proposed definitions and a core outcome set as a composite endpoint. All experts reached consensus about using these definitions and the composite endpoint in future trials.

Subsequently, a uniform evidence-based ERAS protocol for pancreaticoduodenectomy was developed in collaboration with the ERAS group (www.erassociety.org) and proposed for further use. In this protocol consensus was reached on several items, but no consensus was reached on the use of prophylactic abdominal drainage. We therefore conducted a meta-analysis into this matter, which provided no conclusive evidence either. Subsequently we designed a multicenter, international randomized controlled trial, which examines the necessity of routine placement of a prophylactic abdominal drain after pancreaticoduodenectomy. This study is still ongoing.

Then we evaluated the implementation of an ERAS program in liver surgery and pancreatic surgery. We concluded that implementing an ERAS program in both forms of surgery is feasible with a decrease of postoperative length of stay without increasing morbidity, mortality or readmission rates. In addition, implementation of such an ERAS protocol in elderly patients undergoing pancreaticoduodenectomy seems feasible and

safe as well. However, adherence to the ERAS program becomes more difficult in case of complications. Finally, we assessed care providers' and patients' perceptions of the relevance and importance of the ERAS principles and concluded that ERAS principles are supported by patients and care providers. Patients and care providers rank functional recovery higher than reduced length of stay.

To conclude, we developed, implemented and evaluated an ERAS program in liver and pancreatic surgery and found that an ERAS program in these forms of surgery is feasible and does not compromise outcomes. However, morbidity remains high and efforts should be made to examine ways to further reduce complications rates and to increase protocol adherence.

Summary in Dutch

SUMMARY IN DUTCH

Lever en pancreas resecties zijn complexe en grote abdominale chirurgische procedures met een hoge morbiditeit (tot 50%) en tegenwoordig een acceptabele mortaliteit (2-4%). Traditionele perioperatieve zorg voor lever en pancreas chirurgie is conservatief en dogmatisch. Evidence-based technieken en zorgelementen zijn niet geïmplementeerd in deze vormen van chirurgie. Met dit proefschrift beogen we een versneld herstel programma na lever en pancreas chirurgie (ERAS) te ontwikkelen, implementeren en evalueren met als doel de stress respons na deze grote abdominale procedures te verminderen en het herstel te versnellen zonder dat andere uitkomstmaten gecompromitteerd worden.

ERAS programma's zijn al eerder ontwikkeld en geïmplementeerd in colonchirurgie. Meerdere trials laten zien dat een ERAS programma voor patiënten die een colonresectie ondergaan het herstel versnelt en morbiditeit doet afnemen. Tevens zijn de ziekenhuiskosten verminderd wanneer een ERAS programma gevolgd wordt. Ondanks het succes van deze programma's in de colonchirurgie, is het echter nog onduidelijk of een ERAS protocol ook kan worden geïmplementeerd in grotere abdominale ingrepen, zoals lever en pancreas chirurgie. Het voornaamste doel van dit proefschrift is om te onderzoeken of het implementeren van een ERAS programma in lever en pancreas chirurgie inderdaad mogelijk is.

We hebben ons onderzoek gestart met het verrichten van een systematisch review en meta-analyse om te haalbaarheid van ERAS programma's in lever en pancreas chirurgie te evalueren. We concludeerden dat er wel enig bewijs is voor de effectiviteit van ERAS programma's in lever en pancreas chirurgie. Echter, het aantal studies van hoge kwaliteit is laag en de aard van de geïmplementeerde ERAS protocollen verschilt behoorlijk tussen de studies. Er is ook een grote variabiliteit in de eindpunten en definities die voor complicaties gebruikt worden. Het is voor de vergelijkbaarheid van studies noodzakelijk om uniforme definities te gebruiken en een vaste set van uitkomsten zou beschreven moeten worden in elke studie. We verrichtten een systematisch review en online onderzoek onder experts die werkzaam zijn op hepato-pancreatico-biliare afdelingen. In deze studie stelden we definities voor specifieke complicaties voor en een vaste set van uitkomsten als één samengesteld eindpunt. Er werd door de experts consensus bereikt over deze definities en het samengesteld eindpunt, dat nu gebruikt kan worden in toekomstige trials.

Vervolgens ontwikkelden wij in samenwerking met de ERAS groep (www.erassociety.org) een evidence-based ERAS protocol voor pancreatico-duodenectomie. In dit protocol werd over een aantal zaken consensus bereikt, er werd echter geen consensus bereikt over het al dan niet achterlaten van een profylactische abdominale drain. Om nogmaals alle bewijs hiervoor kritisch te bekijken, verrichtten wij een meta-analyse. Dit gaf ons echter geen uitsluitsel. Daarom ontworpen we een nieuwe internationale multicenter gerandomiseerde trial, die de noodzaak van

routinematig profylactisch abdominaal draineren na een pancreaticoduodenectomie gaat onderzoeken. Deze studie is gestart en loopt op dit moment nog.

Hierna evalueerden we de implementatie van een ERAS programma in lever en pancreas chirurgie. We concludeerden dat het implementeren van een ERAS programma in beide vormen van chirurgie haalbaar is met een afname van de postoperatieve opname duur zonder dat de morbiditeit, mortaliteit en heropnames zijn toegenomen. Tevens blijkt de implementatie van een ERAS programma voor ouderen die een pancreaticoduodenectomie ondergaan haalbaar. Echter, het volgen van het ERAS protocol is moeilijker wanneer er complicaties optreden. Ten slotte beoordeelden we de percepties van patiënten en zorgverstrekkers over de relevantie en het belang van specifieke ERAS principes. We concludeerden dat de ERAS principes worden gesteund door zowel patiënten als zorgverstrekkers. Het blijkt dat patiënten en zorgverstrekkers het bereiken van functioneel herstel belangrijker vinden dan een snel ontslag uit het ziekenhuis.

Concluderend hebben we een ERAS programma ontwikkeld, geïmplementeerd en geëvalueerd in lever en pancreas chirurgie en vonden we dat een ERAS programma haalbaar is voor beide vormen van chirurgie zonder dat de andere uitkomstmaten gecompromitteerd worden. Echter, de morbiditeitscijfers blijven nog steeds hoog. We zouden daarom verder moeten onderzoeken hoe we de complicaties kunnen verminderen en de mate van precies volgen van het ERAS protocol kunnen vergroten.

Valorization

VALORIZATION

INTRODUCTION

In this thesis we aimed to implement Enhanced Recovery After Surgery (ERAS) programs in liver and pancreatic surgery. In short, an ERAS program addresses a variety of evidence-based perioperative interventions and demands a multidisciplinary approach in which surgeons, anesthesiologists, intensive care staff, and nurses work together as a team. The purpose of an ERAS program is to accelerate postoperative recovery and shorten postoperative length of stay (LOS) without an increased in or even with a lower morbidity and readmission rate. Perioperative management in an ERAS program has a major impact on the patient and his social environment.

Until recently patients undergoing liver or pancreatic surgery were not allowed to eat postoperatively, since surgeons thought this might compromise recent anastomoses and induce delayed gastric emptying. Patients were summoned to stay in bed to rest and drains in the abdomen were routinely placed after liver and pancreatic surgery. The ERAS program cares to provide better pre-operative information to the patient and allows patients to restart intake and mobilize directly after surgery. It has been shown that this does not harm the patient. On the contrary, the incidence of complications decreased (as shown in colonic surgery) and LOS was reduced after implementing an ERAS program in many surgical fields.

DUTCH REGISTRIES

Dutch registries for liver and pancreatic surgical treatment (Dutch Hepato Biliary Audit (DHBA) and Dutch Pancreatic Cancer Audit (DPCA))^{1,2} aim to register results of benign and malignant pancreatic and liver surgery throughout the Netherlands and give insight in quality of care in different institutes. Comparing results within the Netherlands and with other countries allows for developing the best treatment strategies and improve perioperative care. It is therefore important for Dutch hospitals and HPB departments to perform well. Consequently, ERAS programs are becoming more interesting for HPB groups since it has been shown (in this thesis) that implementation of an ERAS program improves care and decreases LOS^{3,4}. This leads to better results in the registries and encourages other departments to implement ERAS programs as well.

COST-EFFECTIVENESS

Health care costs in the Netherlands are rising each year with an expected increase of 5.3% in 2014 leading to a total of 1.97 billion euros⁵. It is therefore of utmost importance to control and cut down these costs whenever possible. Use of an ERAS program contributes significantly to reducing such health care costs.

Originally, ERAS programs were designed to reduce postoperative stress and accelerate recovery. However, many studies have shown that an ERAS program for HPB surgery also significantly reduces in-hospital expenses (Chapter 2 of this thesis)³. As an example, a study of Kennedy et al. on patients undergoing pancreaticoduodenectomy demonstrated that hospital costs after implementing an ERAS program were almost halved (from \$240,242 to \$126,566 per patient, $p < 0.001$)⁶. This dramatic decrease in costs is mainly due to the streamlining of care and decrease in postoperative hospital stay displayed in most studies. Thus, ERAS programs are very valuable when it comes to cost-effective use of health care. This is obviously favorable to health insurance companies as well. As Kennedy stated: "ERAS programs are one way to meeting the challenges of the oncoming 'pay to performance' era"⁶.

PATIENTS AND EVIDENCE-BASED CARE

Patients are more demanding nowadays and expect the best possible care. In addition, surgical care is increasingly demanded to be evidence-based. For this reason it currently seems unethical to subject patients to traditional non-evidence-based care. The ERAS program combines perioperative interventions that are all evidence-based and its implementation should consequently lead to better surgical care. Patients benefit from better perioperative care and accelerated recovery.

IMPLEMENTATION

Despite a large amount of evidence to support the benefits of ERAS programs, implementation of these programs into surgical practice is going slow. Several international surveys in Europe and the United States show that many institutions still do not adhere to evidence-based perioperative care in gastro-intestinal or HPB surgery⁷⁻¹⁰. Problems with adopting guidelines in medicine have been described earlier in a large review¹¹. Potential barriers to (physician) guideline adherence were lack of awareness and familiarity, lack of agreement, lack of self-efficacy and lack of the ability to overcome inertia of traditional practice. In addition, time limits and insufficient staff expertise may also play a role in slowing down the implementation of guidelines and fast-track programs. Better provision of information and multidisciplinary education about ERAS programs, especially in smaller institutions, can overcome these barriers. For this reason, the ERAS society has designed special implementation programs, which train perioperative teams to implement, reach and maintain high levels of compliance to the protocol elements (www.erassociety.org). Especially in the perioperative phase of the ERAS protocol many disciplines are involved. Consequently, a good organization and education for these disciplines is imperative to the success of the program. Moreover, junior nurses and registrars change units frequently, so continuous re-education is important¹².

INNOVATION

Kehlet and Wilmore were the first to describe and implement an ERAS protocol successfully in colonic surgery¹³. Subsequently, numerous studies have been published on this topic, not only in colonic surgery but also in many other fields of surgery (e.g., musculoskeletal¹⁴, breast¹⁵, aortic^{16,17}, bariatric^{18,19}, and prostate surgery²⁰). All of these studies showed a decrease in LOS, without increasing postoperative morbidity or mortality. Despite this, there is relatively little experience with ERAS programs for liver and pancreatic surgery. Wong-Lun-Hing et al. conducted a worldwide survey amongst 673 hepatobiliary centers (the response rate was 75%) and collected information the centers' experience with ERAS programs in different fields of surgery¹⁰. Only 17.4% of the centers had experience with an ERAS program for pancreatic surgery and 28% of the centers had experience with an ERAS program for liver surgery. As a comparison, for colonic surgery nearly 40% of the centers had experience with an ERAS program (Table 1). In conclusion, the adoption of ERAS programs for liver and pancreatic surgery worldwide is still limited. By developing the ERAS consensus-based guidelines for pancreaticoduodenectomy (PD) the ERAS group (which we are member of) leads the field.

Table 1 Centers with experience in fast-track perioperative care programs.

Region	Experience with ERAS programs in a specific type of surgery, n/total n (%)			
	No experience	In colon surgery	In liver surgery	In pancreatic surgery
Europe	31/72 (43.1%)	36/72 (50.0%)	22/72 (30.6%)	14/72 (19.4%)
North America	25/42 (59.5%)	6/42 (14.3%)	9/42 (21.4%)	8/42 (19.0%)
Central and South America	5/10 (50.0%)	4/10 (40.0%)	3/10 (30.0%)	1/10 (10.0%)
Asia	15/24 (62.5%)	8/24 (33.3%)	4/24 (16.7%)	3/24 (12.5%)
Oceania	2/8 (25.0%)	5/8 (62.5%)	6/8 (75.0%)	2/8 (25.0%)
Africa	4/5 (80.0%)	1/5 (20.0%)	1/5 (20.0%)	0/5 (0%)
Worldwide	82/161 (50.9%)	50/161 (37.3%)	45/161 (28.0%)	28/161 (17.4%)

ERAS, enhanced recovery after surgery.

PLANNING AND REALISATION

In chapter 6 we described the development of ERAS guidelines for pancreaticoduodenectomy (PD)^{21,22}. A framework of evidence-based recommendations for perioperative care for PD is presented. It forms the basis for future protocols. To assure the feasibility of this perioperative care protocol multinational and multicenter prospective validation in a large patient cohort is warranted. This also holds for the composite endpoint (CEP) for PD presented in chapter 5²³. An international randomized controlled trial (RCT) is now being initiated to evaluate the use of prophylactic intra-abdominal drains after PD and combines the aforementioned topics (chapter 7, NTR3224). Patients undergoing PD who are included in this trial will be managed in the ERAS protocol as proposed by the ERAS group. Furthermore, this trial will contribute to the validation of the CEP for PD, as this CEP is used as an outcome measure.

Additionally, to further validate the ERAS guidelines, multinational implementation of this consensus protocol has taken place from 2013 onwards in the departments of the members belonging to the ERAS group and will be evaluated in a prospective project separately.

Following the ERAS guidelines for PD, the ERAS group is now also working on guidelines for liver surgery. With the development of such guidelines we hope to achieve uniform and optimal perioperative care worldwide with favorable outcome for all of our patients.

In chapter 8, 9 and 10 we present outcomes after implementing an ERAS program for liver and pancreatic surgery. Length of stay (LOS) after liver surgery decreased with two days (from 8 to 6 days, $p<0.001$) and LOS after pancreatic surgery decreased significantly from 20 days (1995-2005) to 14 days (2009-2011), $p<0.05$ (versus 16 to 9 days for patients being discharged without complications, $p<0.05$). However, several publications have shown that LOS is influenced by several confounding factors and might therefore not be the best outcome parameter. Time to functional recovery or readiness for discharge is probably a better readout. Maessen et al. showed that 87% of the patients undergoing colonic surgery in an ERAS program were not discharged on the day that discharge criteria were fulfilled²⁴. Fiore et al. published similar results²⁵. Reasons for not being discharged were 'surgeons judgment', absence of sufficient support or planning, and patients required (more) training for stoma management. The authors encourage the use of time to readiness for discharge as a measure of short-term recovery. Our group already published a cohort of patients undergoing laparoscopic liver surgery in an ERAS program and found that time to functional recovery was reached 2 days before the actual discharge²⁶. In our cohort of patients undergoing liver and pancreatic surgery we did not specifically look at time to functional recovery, but the estimated difference between time to functional recovery and actual discharge should be similar in the patients undergoing liver surgery. For patients undergoing pancreatic surgery it might be even more, since surgeons are more cautious to discharge patients early after a PD, even when discharge criteria are met, because of the possible occurrence of late complications such as hemorrhage or pancreatic fistula.

Maessen et al. and Gillissen et al. presented the results of a 'Dutch breakthrough' project in which 33 Dutch hospitals signed up to implement an ERAS program for colonic surgery^{27,28}. This was a successful project in all hospitals resulting in ERAS patients eating 3 days earlier than patients treated in traditional care. Overall LOS was decreased from 9 to 6 days and functional recovery was achieved after 3 days. Now that we have gathered sufficient evidence for the implementation of ERAS programs in liver and pancreatic surgery, a national breakthrough project (such as the recent project for ERAS in colonic surgery) might be the way forward.

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Appendices

APPENDIX 1: WEB SURVEY PART I AND II

<p>1. Introduction</p> <p>This survey consists of four parts:</p> <p>PART I A systematic search was performed using PubMed, Embase and the Cochrane Library in order to identify clinical outcomes that have been used as primary or secondary endpoint in randomized controlled trials specific for pancreaticoduodenectomy (PD) published in the last 6 years.</p> <p>17 specific complications for pancreaticoduodenectomy were selected.</p> <p>You are asked to select which of the listed complications should be included as component of a PD specific composite endpoint (CEP).</p> <p>PART II You are asked to tell us which other complications you would include in the PD specific CEP.</p> <p>PART III Which problems do you foresee and should be anticipated on, using this CEP in PD trials?</p> <p>PART IV Are you interested in using the Accordion severity grading system for surgical complications by Strasberg et al. (derived from the Dindo-Clavien classification) in future PD trials?</p>
<p>2. Background composite endpoint components selection.</p> <p>We ask you to select complications that in your opinion should be included as components of the PD specific composite endpoint (CEP).</p> <p>For your information, we provide some general characteristics of CEPs (*).</p> <ol style="list-style-type: none"> 1. A CEP is a combined parameter that captures the number of patients experiencing one or more specified complications within the CEP 2. The components of a CEP should be ascertainable without bias and well defined 3. The components of the CEP must be associated with the primary objective of a clinical trial (e.g. the effect of an intervention on surgery related mortality and morbidity) 4. The validity of a CEP depends on similarity in <ul style="list-style-type: none"> - clinical importance of the components from the patient's perspective (preferably: equal or nearly equal severity grade) - effect of the intervention on the incidence of the component (preferably: equal or nearly equal effect size) - incidence rate of each component (preferably: equal or nearly equal incidence rate) <p>(*) Montori VM <i>et al.</i> Validity of composite end points in clinical trials. <i>BMJ</i> 2005;330(7491):594–596</p>

3. Part I. Which complications should be included in the PD specific composite

Proposed components are listed in the first column.

Incidence range and amount of times that endpoint was reported as outcome in a total of 33 RCT's.

Select which complications should be included in the PD specific composite endpoint according to you.

	YES	NO
Pleural effusion. median incidence:0%-52.6%. Reported as outcome:21.2%.	☐	☐
Ascites. median incidence:0.9%-16%. Reported as outcome:15.1%.	☐	☐
Wound infection. median incidence:0%-46%. Reported as outcome:60.6%	☐	☐
Intra-abdominal abscess. median incidence:0%-35.2%. Reported as outcome:57.5%.	☐	☐
Bile leakage/hepatojejunostomy leakage. median incidence:0%-8%. Reported as outcome:57.5%.	☐	☐
Gastrojejunostomy leakage. median incidence: 0-2%. Reported as outcome: 33.3%.	☐	☐
Sepsis. median incidence:0%-21%. Reported as outcome:21.2%.	☐	☐
Pneumonia. median incidence:0.9%-52.6%. Reported as outcome:36.3%.	☐	☐
Intra-abdominal hemorrhage/ post-pancreaticoduodenectomy hemorrhage. median incidence:0%-11.1%. Reported as outcome:57.5%.	☐	☐
Pancreatic fistula. median incidence:0%-42%. Reported as outcome:75.7%.	☐	☐
Pancreaticojejunostomy leakage. median incidence:0%-21%. Reported as outcome:84.8%.	☐	☐
Delayed Gastric Emptying. median incidence:0%-58%. Reported as outcome:75.5%.	☐	☐
Diabetis Mellitus de novo. median incidence:-. Reported as outcome:21.1%.	☐	☐

Acute renal failure. median incidence:0%-3.7%. Reported as outcome:0.9%.	☐	☐
Requirement of blood transfusion. median incidence:1.5%-17%. Reported as outcome:21.2%.	☐	☐
Operative mortality. median incidence:0%-8.3%. Reported as outcome:69.6%.	☐	☐
Costs. median incidence:2700-6400 euro. Reported as outcome:3%.	☐	☐
Quality of life. median incidence:-. Reported as outcome:12.1%.	☐	☐

4. PART II. Comment on the components of the CEP.

We would like to ask you if there is a potential component that isn't named in PART I and should be included in a PD specific composite endpoint according to you.

Would you be willing to share your data from a previously conducted randomized controlled trial in pancreatic surgery for determination of the current incidence rate and validation of the PD specific composite endpoint?

☐ Yes, contact me for further details

☐ No, I'm not interested in sharing my data

5. Part III. Problems that may occur.

Do you foresee problems that should be anticipated on, using this CEP in PD trails?

6. Part IV. The Accordion severity grading system for surgical complications

Accordion Classification(*)

The Accordion classification was developed as a simplified version of the Dindo-Clavien Classification. It appears the Grades I-V of the Dindo-Clavien classification leave some discussion. Furthermore, researchers tend to contract the different grades (e.g. grade 1/2 and 3a to grade I, and grade 3, 4a/b to grade II) and in many trials grades are labeled with quantitative measures (mild, moderate, severe). This means results from different trials are still not well comparable. The Accordion classification is more transparent and above all, Dindo-Clavien grades can be easily calculated from this classification when needed, while the other way around this is not possible. Below, you will find the Accordion Classification.(Dindo-Clavien grades between breaks.)

Grade Mild

1.(1.) Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy are permitted.

Grade Moderate

2.(2.) Requires pharmacologic treatment with drugs other than such allowed for minor complications, eg, antibiotics. Blood transfusions and total parenteral nutrition are also included.

Grade Severe

3.(3.) No general anesthesia: requires management by an endoscopic, interventional procedure or reoperation without general anesthesia.

4.(3b) General anesthesia or single-organ failure.

5.(4a-4b) General anesthesia and single organ failure or multisystem organ failure (2 organ systems).

Grade Death

6.(5) Postoperative death.

Are you interested in using the Accordion severity grading system for surgical complications by Strasberg et al. instead of Dindo-Clavien severity grading scale in future PD trials?

(*)Literat

- Strasberg SM et al. The Accordion severity grading system of surgical complications. Ann Surg. 2009;250:177-86.
- Strasberg SM et al. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the American College of Surgeons national surgical quality improvement program. J Am Coll Surg. 2010;210:286-98.

7. End of this survey.

On behalf of the CEP Pancreas Team we would like to thank you for your time and your appreciated opinion.

1. Composite endpoint components and definitions

After the first part of the worldwide survey under pancreatic surgeons for developing a Composite Endpoint for

Pancreatic Surgery, the following components were identified to be included in the endpoint.

- Intra-abdominal abscess
- Bile leakage
- Gastrojejunostomy leakage
- Leakage of the pancreatic anastomosis/pancreatic fistula
- Sepsis
- Post pancreaticoduodenectomy hemorrhage
- Delayed gastric emptying
- Mortality

The individual components of the CEP are defined as follows:

Intra-abdominal abscess¹

Any quantity of purulent fluid leaking via the abdominal drain; walled-off collection of pus in the abdominal cavity at the time of radiological imaging, reoperation or percutaneous drainage; fluid in drain or intra-abdominal collection should be culture-positive.

Bile leakage/hepaticojejunostomy leakage¹

Any quantity of bile leaking via the abdominal wound or drains at least 48 h after surgery; intra-abdominal collection of bile at the time of radiological imaging, reoperation or percutaneous drainage; cholangiographic evidence of contrast leakage. Fluid in drain or intra-abdominal collection should have a bilirubin content at least three times higher than the upper normal serum level in patients with normal serum bilirubin levels after surgery, or a 50 per cent higher serum bilirubin level than that in patients with raised serum bilirubin levels after surgery.

Sepsis

Definition from the 2001 International Sepsis Definitions Conference²

Sepsis is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response.

Infection

Pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. Systemic inflammatory response syndrome Body temperature higher than 38°C or lower than 36°C; heart rate higher than 90 beats/min; hyperventilation evidenced by respiratory rate higher than 20 per min or arterial partial pressure of carbon dioxide lower than 32 mmHg; white blood cell count higher than 12 000 cells/μl or lower than 4000 cells/μl.

Post pancreaticoduodenectomy hemorrhage

According to the ISGPS classification of post pancreaticoduodenectomy hemorrhage³:

The three different grades of PPH (grades A, B, and C) are defined according to the time of onset, site of bleeding, severity, and clinical impact.(thus all these items should be reported)

A. Mild, early postoperative bleeding without major clinical impact.

B. Severe, early postoperative bleeding with a consecutive change in a given clinical pathway.

C. Severe, late postoperative bleeding with immediate diagnostic and therapeutic consequences
Operative mortality. Death of a patient during or after the initial surgical procedure that is related to the surgical procedure.

Operative mortality

Death of a patient, during or within 90 days after the initial surgical procedure, that is related to the surgical procedure.

2. Definition of the components II

Pancreatic fistula/leakage of the pancreatic anastomosis

Defined according to the International Study Group of Pancreatic Fistula ⁴

A pancreatic fistula is an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreasderived, enzyme-rich fluid. However, a Post Operative Pancreatic Fistula represents failure of healing/sealing of a pancreatic- enteric anastomosis, or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (eg, left or central

pancreatectomy, enucleation, and/or trauma). In this case, there is a leak from the pancreatic ductal system into and around the pancreas and not necessarily to another epithelialized surface (eg, via a surgical drain).

Grading

Grade A:

This grade has no clinical impact, requires little change in management or deviation from the normal clinical pathway. The patient is fed orally and remains clinically well, the use of total parenteral nutrition, antibiotics, or somatostatin analogues are not indicated. A computed tomographic (CT) scan typically shows no peripancreatic fluid collections. Grade A POPF is not associated with a delay in hospital discharge and is managed frequently by slow removal of the operatively placed drains.

Grade B:

This grade requires a change in management or adjustment in the clinical pathway. Often the patient is kept with nothing by mouth (NPO) and is supported with partial or total parenteral or enteral nutrition. The peripancreatic drains are usually maintained in place, but if the drains are not functioning to fully drain the fistula, a CT scan may show peripancreatic collection(s) requiring repositioning of the drains. When associated with abdominal pain, fever, and/or leukocytosis, antibiotics are usually required; somatostatin analogues may also be used. Grade B pancreatic fistula usually leads to a delay in discharge, or readmission. If an invasive procedure is needed, the POPF shifts into grade C.

Grade C:

In a grade C, a major change in clinical management or deviation from the normal clinical pathway occurs. Clinical stability may be borderline. Clinical intervention is aggressive with the patient kept NPO and Total parenteral nutrition or enteral nutrition, intravenous antibiotics, and somatostatin analogues instituted, often in an intensive care unit setting. A CT scan usually shows worrisome, peripancreatic fluid collection(s) that require percutaneous drainage. The patient typically requires an extended hospital stay with a major delay in hospital discharge.

Delayed Gastric Emptying (DGE)

Defined according to the International Study Group of Pancreatic Surgery ⁵

Consensus definition of DGE after pancreatic surgery.

DGE grade A:

These patients require a nasogastric tube (NGT) for about 4-7 days after surgery or reinsertion of the tube on or after postoperative day (POD) 3. The patients are unable to tolerate solid oral intake by POD 7. Vomiting/gastric distension doesn't necessarily occur, the use of prokinetics is usually not necessary.

DGE grade B:

Patients with DGE grade B require NGT for about 8-14 days after surgery or reinsertion of the tube on POD 7. Vomiting/gastric distension always occurs in a grade B DGE patient. The use of prokinetics is a necessity in grade B DGE.

DGE grade C:

Patients with DGE grade c require NGT for more than 14 days after surgery or reinsertion of the tube on POD 14. Vomiting/gastric distension always occurs in a grade C DGE patient. The use of prokinetics is a necessity in grade C DGE.

3. Definition of the components III

Gastrojejunostomy leakage⁶

Anastomotic incompetence documented either by confirmatory upper gastrointestinal contrast x-rays, CT scans, or reoperation.

References

1. van den Broek MA. et al. Development of a composite endpoint for randomized controlled trials in liver surgery. Br J Surg. 2011;98:1138-45.
2. Levy M et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29:530-8
3. Welsch T, Eisele H, Zschäbitz S, Hinz U, Büchler MW, Wente MN. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreatoduodenectomy. Langenbecks Arch Surg.2011;396:783-91. Epub 2011 May 25
4. Claudio Bassi et al. Postoperative pancreatic fistula:An international study group (ISGPF) definition. 2005 J Surgery volume 138, Number 1
5. Wente M et al. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS) J Surgery . 2007;142:761-8.
6. James W. Maher et al. Drain Amylase Levels Are an Adjunct in Detection of Gastrojejunostomy Leaks after Roux-en-Y Gastric Bypass J Am Coll Surg 2009, 208:881–886.

Do you agree with including the aforementioned items in the pancreas surgery specific CEP?

☐ YES

☐ NO

If no what should be added?

APPENDIX 2 DEFINITIONS OF COMPLICATIONS AFTER PANCREATICODUODENECTOMY

Intra-abdominal abscess

Any quantity of purulent fluid leaking via the abdominal drain; walled-off collection of pus in the abdominal cavity at the time of radiological imaging, reoperation or percutaneous drainage; fluid in drain or intra-abdominal collection should be culture-positive.

Sepsis

Definition from the 2001 International Sepsis Definitions Conference¹

Sepsis is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response.

Infection

Pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms.

Systemic inflammatory response syndrome

Body temperature higher than 38°C or lower than 36°C; heart rate higher than 90 beats/min; hyperventilation evidenced by respiratory rate higher than 20 per min or arterial partial pressure of carbon dioxide lower than 32 mmHg; white blood cell count higher than 12 000 cells/ μ l or lower than 4000 cells/ μ l.

Gastrojejunostomy leakage

Anastomotic incompetence documented either by confirmatory upper gastrointestinal contrast, x-rays, CT-scans or reoperation.

Post pancreatic surgery hemorrhage

Any quantity of blood leaking via the abdominal drain either with or without a drop in hemoglobin; intra-abdominal active bleeding during radiological imaging or reoperation. Other sources of hemorrhage should be excluded.

According to the ISGPS classification of post pancreaticoduodenectomy hemorrhage:

- a) Mild, early postoperative bleeding without major clinical impact
- b) Severe, early postoperative bleeding with a consecutive change in a given clinical pathway
- c) Severe, late postoperative bleeding with immediate diagnostic and therapeutic consequences

Delayed Gastric Emptying (DGE)

Defined according to the International Study Group of Pancreatic Surgery²

- a) These patients require a nasogastric tube (NGT) for about 4-7 days after surgery or reinsertion of the tube on or after postoperative day (POD) 3. The patients are unable to tolerate solid oral intake by POD 7. Vomiting/gastric distension doesn't necessarily occur, the use of prokinetics is usually not necessary.
- b) Patients with DGE grade B require NGT for about 8-14 days after surgery or reinsertion of the tube on POD 7. Vomiting/gastric distension always occurs in a grade B DGE patient. The use of prokinetics is a necessity in grade B DGE.
- c) Patients with DGE grade c require NGT for more than 14 days after surgery or reinsertion of the tube on POD 14. Vomiting/gastric distension always occurs in a grade C DGE patient. The use of prokinetics is a necessity in grade C DGE.

Bile leakage/hepaticojejunostomy leakage

Any quantity of bile leaking via the abdominal wound or drains at least 48 h after surgery; intra-abdominal collection of bile at the time of radiological imaging, reoperation or percutaneous drainage; cholangiographic evidence of contrast leakage. Fluid in drain or intra-abdominal collection should have a bilirubin content at least three times higher than the upper normal serum level in patients with normal serum bilirubin levels after surgery, or a 50 per cent higher serum bilirubin level than that in patients with raised serum bilirubin levels after surgery.

Pancreatic fistula/Pancreaticojejunostomy leakage

Defined according to the International Study Group of Pancreatic Fistula³

A pancreatic fistula is an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid. However, a Post Operative Pancreatic Fistula represents failure of healing/sealing of a pancreatic-enteric anastomosis, or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (eg, left or central pancreatectomy, enucleation, and/or trauma). In this case, there is a leak from the pancreatic ductal system into and around the pancreas and not necessarily to another epithelialized surface (eg, via a surgical drain).

Grading

- a) This grade has no clinical impact, requires little change in management or deviation from the normal clinical pathway. The patient is fed orally and remains clinically well, the use of total parenteral nutrition, antibiotics, or somatostatin analogues are not indicated. A computed tomographic (CT) scan typically shows no peripancreatic fluid collections. Grade A POPF is not associated with a delay in hospital discharge and is managed frequently by slow removal of the operatively placed drains.
- b) This grade requires a change in management or adjustment in the clinical pathway. Often the patient is kept with nothing by mouth and is supported with partial or total parenteral or enteral nutrition. The peripancreatic drains are usually maintained in place, but if the drains are not functioning to fully drain the fistula, a CT scan may show peripancreatic collection(s) requiring repositioning of the drains. When associated with abdominal pain, fever, and/or leukocytosis, antibiotics are usually required; somatostatin analogues may also be used. Grade B pancreatic fistula usually leads to a delay in discharge, or readmission. If an invasive procedure is needed, the POPF shifts into grade C.
- c) In a grade C, a major change in clinical management or deviation from the normal clinical pathway occurs. Clinical stability may be borderline. Clinical intervention is aggressive with the patient kept nil by mouth and (total) parenteral nutrition or enteral nutrition, intravenous antibiotics, and somatostatin analogues are instituted, often in an intensive care unit setting. A CT scan usually shows worrisome, peripancreatic fluid collection(s) that require percutaneous drainage. The patient typically requires an extended hospital stay with a major delay in hospital discharge.

Operative mortality

Death of a patient during or within 90 days after the initial surgical procedure that is related to the surgical procedure.

References

1. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med.* 2003;29:530-538.
2. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *J Surgery*. 2007;142:761-768.
3. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: An international study group (ISGPF) definition. *J Surgery* 2005;138:8-13.

APPENDIX 3 FLOWCHART PANDA TRIAL

APPENDIX 4: ELEMENTS OF AN ERAS PROGRAMME FOR PANCREATODUODENECTOMY

<p>Preoperative outpatient visit</p> <p>Pre-admission counselling</p> <ul style="list-style-type: none"> • Give consent form and patient information <p>Day before surgery / Admission</p> <ul style="list-style-type: none"> • Normal oral nutrition until midnight • No pre-anesthetic medication • Obtain signed informed consent form <p>Day of surgery</p> <ul style="list-style-type: none"> • Carbohydrate drinks up to 2 hours prior to surgery • Start anti-thrombotic prophylaxis • Preoperative anti-microbial prophylaxis • Mid-thoracic epidural anesthesia • Short-acting I.V. anesthetic agent • Preferably no nasogastric drainage or remove after surgery • Warm I.V. fluids and upper and lower body bear hugger • Jugular catheter (till resumption of oral intake) • Avoidance of excessive I.V. fluids <p> No prophylactic abdominal drainage / 1 or 2 Abdominal drains</p> <ul style="list-style-type: none"> • Patient sent to recovery ward (ICU setting) • Restart oral intake of water or iced-chips ($\leq 30\text{ml/hr}$) with or without syrup added <p>POD 1</p> <ul style="list-style-type: none"> • Patient sent to surgical ward • Patient mobilizes a minimum of four times a day • Patient is capable of drinking at least 1.5 Litres of water • Continue portable epidural analgesia • Antiemetics if based on nausea score • 1000mg Paracetamol every 6 hours • 1000mg Magnesiumoxide twice daily <p>POD 2</p> <ul style="list-style-type: none"> • If patient is capable resumption of regular diet • Continue mobilization • Remove urinary catheter • Continuation epidural analgesia • Stop low dose opioids • Check functional recovery criteria 	<p>POD 3</p> <ul style="list-style-type: none"> • Stop epidural analgesia • Discontinue I.V. fluids • Start NSAIDs based on pain score • Continue mobilization • Regular diet • Check functional recovery criteria <p>POD 4</p> <p> Prophylactic drain removal (if appropriate)</p> <ul style="list-style-type: none"> • Continue analgesics based on pain score • Continue mobilization • Regular diet • Check functional recovery criteria <p>POD 5</p> <ul style="list-style-type: none"> • Continue analgesics based on pain score • Continue mobilization • Regular diet • Check functional recovery criteria <p>POD 6</p> <ul style="list-style-type: none"> • Continue analgesics based on pain score • Continue mobilization • Regular diet • Check functional recovery <p>POD 7</p> <ul style="list-style-type: none"> • Continue mobilization • Regular diet • Check functional recovery criteria • Make outpatient appointment for after discharge <p>POD 8</p> <ul style="list-style-type: none"> • Continue analgesics based on pain score • Continue mobilization • Regular diet • Check functional recovery criteria • Discharge from hospital
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APPENDIX 5 DEFINITIONS OF COMPLICATIONS

Mortality

Death of a patient, during or within 90 days after the initial surgical procedure that is related to the surgical procedure.

Readmission

Every re-hospitalization due to a complication of the index hospitalization within the first 6 months.

Intra-abdominal abscess

Any quantity of purulent fluid leaking via the abdominal drain; walled-off collection of pus in the abdominal cavity at the time of radiological imaging, reoperation or percutaneous drainage; fluid in drain or intra-abdominal collection should be culture positive.

Wound infection defined according to the Centers for Disease Control and Prevention

Superficial incisional surgical-site infection and deep incisional surgical site infection, which occurs within 30 days after surgery. This includes both the superficial surgical-site infections and the deep incisional surgical site infections. Most of these wound infections were opened at bedside by the physician or surgeon.

Pancreatic fistula/pancreaticojejunostomy leakage

Defined according to the International Study Group of Pancreatic Fistula (Grade A, B and C)

Delayed gastric emptying

Defined according to the International Study Group of Pancreatic Surgery (Grade A,B and C)

Biliodigestive anastomosis leakage

Any quantity of bile leaking via the abdominal wound or drains at least 48 h after surgery, intra-abdominal collection of bile (confirmed radiologically) or cholangiographic evidence of contrast leakage. Laboratory: three times higher bilirubin in the drain or intra-abdominal collection compared with normal serum bilirubin levels.

Sepsis/multi organ failure

Definition from the 2001 International Sepsis Definitions Conference

Post pancreaticoduodenectomy hemorrhage

Definition according to the ISGPS classification of post pancreaticoduodenectomy hemorrhage

Gastrojejunostomy leakage

Leakage of the gastrojejunostomy anastomosis documented either by confirmatory upper gastrointestinal contrast x-rays. CT scans, or reoperation.

CT-drainage

Drainage of intra-abdominal fluid collections during CT by inserting a percutaneous drain during the hospitalization or readmission period.

Relaparotomy

Any complication after the initial PPPD or Whipple operation leading to a laparotomy as an intervention, during the index hospitalization or the readmission period.

APPENDIX 6 COMPLICATIONS BY TYPE OF RESECTION

	Whipple (n=53)	PPPD (n=177)
Intra abdominal abscess	7 (13.2)	28 (15.8)
DGE	3 (5.7)	19 (10.7)
Pancreatic fistula	10 (18.9)	18 (10.2)
Gastrojejunostomy leakage	1 (1.9)	3 (1.7)
Bile/hepaticojejunostomy leakage	2 (3.8)	11 (6.2)
Post-pancreatectomy hemorrhage	4 (7.5)	7 (4.0)
Sepsis	2 (3.8)	9 (5.1)
Mortality	4 (7.5)	7 (4.0)
Urinary tract infection	3 (5.7)	6 (3.4)
Ileus	2 (3.8)	7 (4.0)
Abdominal wound dehiscence	2 (3.8)	4 (2.3)
Pneumonia	4 (7.5)	12 (6.8)
Wound infection	7 (13.2)	23 (13.0)
Diabetes Mellitus de novo	0	3 (1.7)
Cerebrovascular accident	0	2 (1.1)
Gastro-intestinal ulcer	0	1 (0.6)
Cholangitis	2 (3.8)	1 (0.6)
Dumping	0	1 (0.6)
Patients without complications	35 (66)	102 (58)

Values in parentheses are percentages.

† $p < 0.05$

DGE: delayed gastric emptying

APPENDIX 7: PATIENT DEMOGRAPHICS, PATHOLOGY AND OPERATIVE DATA FOR THE 66-69 AGE GROUP

	≤65 years of age (n=55)	66-69 years of age (n=25)	≥70 years of age (n=55)
Age median (range)	57 (45-65)	68 (65-69)	77 (70-86)
Sex			
Male/female	35/20	12/13	22/33
ASA class			
I	28 (51%)	8 (32%)	1 (2%)
II	21 (38%)	13 (52%)	34 (62%)
III	5 (9%)	4 (16%)	20 (36%)
IV	1 (2%)	0	0 (0%)
Comorbidity			
Cardiovascular	13 (24%)	7 (28%)	25 (45%)
Pulmonary	2 (4%)	3 (12%)	10 (18%)
Diabetes	6 (11%)	6 (24%)	12 (21.8%)
Renal disease	1 (2%)	2 (8%)	6 (10.9%)
BMI (range)	24.9 (18.0-36.1)	24.6 (18-47)	24.4 (18.6-36.8)
Pathology			
Pancreatic head carcinoma	34 (62%)	12 (48%)	33 (60%)
Duodenal cancer	2 (4%)	4 (16%)	3 (5%)
Ampullary carcinoma	8 (15%)	5 (20%)	12 (22%)
Distal cholangiocarcinoma	5 (9%)	3 (12%)	5 (9%)
Metastasis in pancreas head	1 (1.8%)	1 (4%)	0 (0%)
Chronic pancreatitis	2 (4%)	1 (4%)	2 (4%)
IPMN	1 (2%)	0	0 (0%)
Neuro-endocrine tumor	2 (4%)	0	0 (0%)
Operation type			
Whipple	9 (16%)	3 (12%)	8 (15%)
PPPD	46 (84%)	22 (88%)	47 (85%)
Duration of OR time (min)	345 (180-810)	310 (190-610)	340 (217-715)

ASA=American Society of Anesthesiologists, BMI=Body Mass Index. PPPD=pylorus preserving pancreaticoduodenectomy

APPENDIX 8: POSTOPERATIVE OUTCOMES FOR THE 66-69 AGE GROUP

	≤65 years of age (n=55)	66-69 years of age (n=25)	≥70 years of age (n=55)
Dindo-Clavien classification			
<i>Minor (I/II)</i>	15 (27.2%)	8 (32%)	20 (36.3%)
<i>Moderate (IIIa/b)</i>	15 (27.2%)	4 (16%)	8 (14.5%)
<i>Severe (Iva en IVb)</i>	0 (0%)	1 (4%)	2 (3.6%)
Mortality <90days	3(5,5%)	1 (4%)	6 (10.9%)
Readmissions <6 months	11 (20%)	1 (4%)	7 (12.7%)
Median length of hospital stay (range)	14 (6-100)	14 (6-64)	14 (6-65)
Length of stay uncomplicated (median)	9 (6-15)	9 (6-14)	9 (6-22)
Median LOS Dindo-Clavien grade <III (range)	10 (6-100)	14 (6-60)	14 (7-59)
Median LOS Dindo-Clavien grade >III (range)	32 (11-83)	51 (26-64)	33 (14-65)
Interventions			
<i>CT/US-drainage</i>	10 (18.1%)	3 (12%)	8 (14.5%)
<i>Re-operation</i>	6 (10.9%)	1 (4%)	4 (7.2%)

APPENDIX 9: ERAS OUTCOMES FOR THE 66-69 AGE GROUP

	≤65 years of age (n=55)	66-69 years of age (n=25)	≥70 years of age (n=55)
Resumption of fluid intake POD 1	53 (96%)	25 (100%)	52 (95%)
Resumption of solid intake POD 2	31 (56%)	17 (68%)	35 (63%)
Mobilization from POD 1	33 (60%)	17 (68%)	35 (63%)
Drain removal on POD 4	26 (47%)	16 (64%)	28 (51%)
Urinary catheter removal on POD 2	38 (69%)	13 (52%)	33 (60%)
Removal epidural on POD 3	44 (80%)	20 (80%)	43 (78%)

APPENDIX 10

Questionnaire for patients, part II: Targets for recovery

Please indicate how important you feel that each of the following targets is for recovery after an abdominal operation.

	NOT IMPORTANT											VERY IMPORTANT
1. To be completely free of pain at rest	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. To be completely free of pain upon movement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. To be completely free of nausea – not feeling or being sick	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. To be able to eat and drink as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. To be able to move the bowels as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. To be independently mobile in hospital as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. To be discharged from hospital as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. To be able to return to all daily activities as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Questionnaire for patients part III: Achieving recovery

Think about yourself recovering successfully after an abdominal operation. How important do you view the following care items to be in achieving this recovery?

	NOT IMPORTANT											VERY IMPORTANT
1. To be completely free of pain at rest	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. To be completely free of pain upon movement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. To be completely free of nausea – not feeling or being sick	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. To be able to eat and drink as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. To be able to move the bowels as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. To be independently mobile in hospital as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. To be discharged from hospital as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. To be able to return to all daily activities as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

APPENDIX 11

1. Please indicate how important you feel that each of the following targets is for recovery after an abdominal operation.

	NOT IMPORTANT										VERY IMPORTANT
1. To be counselled preoperatively by nurse, anesthetist and surgeon	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. To be without any intra venous line as soon as possible	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. To avoid any infection while in hospital	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. To be allowed normal diet at will after the operation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

2. Think about successful recovery after an abdominal operation as you perceive it. How important do you view the following care items to be in achieving this recovery?

	NOT IMPORTANT										VERY IMPORTANT
1. Preoperative counselling by nurse, anesthetist and surgeon	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Avoiding oral bowel preparation preoperatively	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Preoperative fasting kept at absolute minimum	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. Avoiding preanesthetic sedative medication	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. Oral carbohydrate loading preoperatively	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Antimicrobial prophylaxis and skin preparation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. Using epidural analgesia for approximately 48 hrs. postop.	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Avoiding nasogastric tube after the operation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Optimising fluid balance	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. Avoiding a wound drain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. Allowing normal diet at will after the operation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. Stimulation of gut motility	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. Promoting early and scheduled mobilisation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

List of publications

LIST OF PUBLICATIONS

- M.M.E. Coolsen, M. Bakens, R.M. van Dam, S.W.M. Olde Damink C.H.C. Dejong. Implementing an enhanced recovery program after pancreaticoduodenectomy in elderly patients - is it feasible? *World J Surg*. 2014 Sep 12. Epub ahead of print
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Dankwoord

DANKWOORD

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Curriculum vitae

CURRICULUM VITAE

Mariëlle Coolsen was born on the 24th of January 1984 in Eindhoven, The Netherlands. After graduating from Rythovius College secondary school in 2002 (cum laude) she started studying medicine at Maastricht University graduating cum laude in 2008. During her study she worked as a student researcher with dr. Ronald M. van Dam. Here she laid the foundation for her later PhD research on Enhanced Recovery After Surgery (ERAS). In 2008 she was awarded a Kootstra fellowship for fundamental research in orthopedic surgery. It was in the orthopedic field where she started her surgical residency in July 2009. However, soon after she started her residence Mariëlle decided to switch to general surgery and worked for the remainder of her first two years under dr. R.J. Welten in Heerlen. In July 2011 Mariëlle continued her surgical residency under prof. L.P.S. Stassen in Maastricht. Recently, she returned to Heerlen for the last two years of her residency, now under the guidance of dr. M.N. Sosef, for the differentiation of surgical oncology. She plans to finish her residency in January 2016. In 2011 Mariëlle also started a PhD with prof. C.H.C. Dejong. This PhD continued where Mariëlle left off in her days as a student researcher and involved the application of ERAS protocols to liver and pancreatic surgery. In her spare time Mariëlle is an active board member of the SEOHS committee and its national counterpart SWOAHs. Music and Latin dancing remain her most important hobbies. She is happily married, lives in Maastricht and is mother of a daughter.