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Guidelines for Perioperative Care for Pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations

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Abstract

Background 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 summarised 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 centres and across national borders. It facilitates multi-institutional prospective cohort registries and adequately powered randomised trials.

Introduction

Enhanced Recovery After Surgery (ERAS), Fast-Track or Clinical Pathway programmes are multimodal strategies that

This work was conducted on behalf of ERAS® Society, the European Society for Clinical Nutrition and Metabolism and the International Association for Surgical Metabolism and Nutrition.

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aim to attenuate the loss of, and improve the restoration of, functional capacity after surgery. Morbidity is reduced [1] and recovery enhanced by reducing surgical stress, by optimal control of pain, early oral diet and early mobilisation. 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 programmes after pancreaticoduodenectomy (PD, Whipple's procedure) have been published [4–9], but the reported series employed different protocols, or no prospective protocol at all [6]. 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 randomised 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) system [10–12]. 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 preferences [12]. 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 1.

Evidence and recommendations

Preoperative counselling

Preoperative counselling targeting expectations about surgical and anaesthetic procedures may diminish fear and anxiety and enhance postoperative recovery and discharge [13–15]. Personal counselling, leaflets or multimedia information containing explanations of the procedure along with tasks that the patient should be encouraged to fulfil may improve perioperative feeding, early postoperative mobilisation, pain control, and respiratory physiotherapy; and hence reduce the risk of complications [16–18]. Ideally, the patient should meet with the surgeon, anaesthetist and nurse.

Summary and recommendation	Patients should receive dedicated preoperative counselling routinely.
Evidence level	Low
Recommendation grade	Strong

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Table 1 Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations

Item	Summary and recommendations	Evidence level	Recommendation grade
Preoperative counselling	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 μmol/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 abstention: 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 5–7 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 anaesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anaesthesia. 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
Preanaesthetic 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. Mechanical measures should probably be added for patients at high risk	High	Strong
Antimicrobial prophylaxis and skin preparation	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 procedure	High	Strong
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 Overall morbidity: low	Weak
Intravenous analgesia	Some evidence supports the use of PCA or intravenous lidocaine analgesic methods. There is insufficient information on outcome after PD	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 TAP blocks: moderate	Weak

Table 1 continued

Item	Summary and recommendations	Evidence level	Recommendation grade
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 anaesthesia. Multimodal intervention during and after surgery is indicated	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 hyperglycaemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycaemia with intravenous insulin in the ICU setting improves outcomes but hypoglycaemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycaemic control without the risk of hypoglycaemia. Hyperglycaemia should be avoided as far as possible without introducing the risk of hypoglycaemia	Low	Strong
Nasogastric intubation	Pre-emptive use of nasogastric tubes postoperatively does not improve outcomes, and their use is not warranted routinely	Moderate	Strong
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes. Perioperative monitoring of stroke volume with transoesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9 % saline	Fluid balance: high oesophageal 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 <5,000 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 catheterisation is superior to transurethral catheterisation 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 POD 1–2: 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 3–4 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 mobilisation	Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet daily targets for mobilisation	Very low	Strong
Audit	Systematic improves compliance and clinical outcomes	Low	Strong

Preoperative biliary drainage

Five meta-analyses [19–23], and two articles from a randomised controlled trial (RCT) not included in the meta-analyses [24, 25], assessed the role of biliary drainage before PD. The first meta-analysis from 2002 [19], included randomised ($n = 5$) and non-randomised trials ($n = 18$). A Cochrane review [21] included 5 randomised 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. 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-analyses [24] (and which included patients with serum bilirubin concentrations <250 μmol/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 survival [25].

Summary and recommendation	Preoperative endoscopic biliary drainage should not be carried out routinely in patients with a serum bilirubin concentration <250 μmol/l
Evidence level	Moderate
Recommendation grade	Weak

Preoperative smoking and alcohol consumption

Overall postoperative morbidity is increased by two- to threefold in alcohol abusers [26]. 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 loss [31]. 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 surgery [32–34]. 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-analyses [35–41] conclude that there is a benefit from perioperative and postoperative IN in patients undergoing major gastrointestinal surgery, but results remain inconsistent [42–44]. 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 LOSH [45]. 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 sepsis [46]. 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 elderly [47]. 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 surgery [50]. 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 evidence [51]. Overnight fasting increases insulin resistance and discomfort after abdominal surgery [52, 53]. Guidelines recommend the intake of clear fluids up to 2 h before the induction of anaesthesia as well as a fasting period of 6 h for solids [54]. The latter recommendation has a weak scientific basis [55]. Intake of a complex clear carbohydrate-rich drink designed for preoperative use $\leq$2 h before the induction of anaesthesia has been shown to reduce hunger, thirst and anxiety, and to decrease postoperative insulin resistance [56–58]. Earlier resumption of gut function after colorectal surgery has also been suggested [59], and an RCT including some PD patients concluded that oral carbohydrate treatment may preserve skeletal muscle mass [60]. An RCT conducted in patients undergoing cholecystectomy did not show any benefit [61]. 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 anaesthesia does not increase gastric residual volume and is recommended before elective surgery. Intake of solids should be withheld 6 h before anaesthesia. 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-anaesthetic medication

Anxiety makes postoperative pain more difficult to control. Pre-emptive treatment of anxiety could lower pain scores and reduce the demand for opiates [64]. However, pre-induction anxiolytic medication increases postoperative sedation [65], and a meta-analysis did not demonstrate reduced postoperative pain with pre-emptive use of analgesics [66]. 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 impaired [67]. Additionally, oral fluids and a carbohydrate-rich beverage have been shown to reduce preoperative anxiety [57]. 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 VTE [69]. 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 discharge [71]. Concomitant use of LMWH and epidural catheters is controversial [72–75]. It has, therefore, been recommended that the catheter be inserted ≥12 h after a dose of LMWH, and removed ≥12 h after administration of LMWH [76]. The risk of an epidural or spinal haematoma is increased in patients who are also on anti-platelet drugs or oral anticoagulants [73]. Combined prophylactic modalities have been shown to be superior to pharmacological measures only in preventing VTE [77]. Mechanical intermittent pneumatic leg compression [77], and elastic stockings may be used as adjuncts in patients who are at moderate or high risk for VTE [78].

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 favouring 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 manner [80]. However, an extra dose should be provided every 3–4 h during the procedure if drugs with a short half-life are chosen [81]. 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 infections [83]. However, the difference is likely to be very small because excellent results are obtained with povidone-iodine [84]. Alcohol-based scrubs have been reported to be used in fire-based and burn injuries [85].

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 surgery [86]. 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 surgery [87]. A decreased prevalence of ileus was found for epidural administration of local anaesthetic after laparotomy compared with systemic or epidural opioids in one Cochrane review [88]. With respect to complications after abdominal or thoracic surgery, a meta-analysis [89] 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 resistance [90]. Despite the widespread use of epidural analgesia after pancreatic surgery [91], 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 complications [92]. It has been suggested that thoracic epidural analgesia after PD is associated with haemodynamic instability, which might compromise enteric anastomoses, intestinal perfusion and recovery of gastrointestinal function [92]. In experimental acute pancreatitis and in sepsis, however, thoracic epidurals improved perfusion in gastrointestinal mucosal capillaries [93]. 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 haemodynamic consequences are adequately controlled with vasopressors [94]. 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 anaesthetic epidurals and those receiving systemic or epidural opioids [95].

A potential drawback with epidurals is that as many as one-third of epidurals may not function satisfactorily in some centres [96, 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 anaesthetic 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 anaesthesia. 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 mobilisation 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 anaesthesia 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 recovery [98].

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 effects [99]. A recent RCT in patients undergoing laparoscopic colorectal resection using the ERAS programme showed no difference in return of gastrointestinal function and LOSH between continuous infusion of lidocaine and thoracic epidural anaesthesia [100].

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 anaesthetic agents as a postoperative analgesic method has been proven in a meta-analysis of different surgical procedures [101]. 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 laparotomy [102]. 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 anaesthetic, type of catheter, mode of delivery, or catheter location (subcutaneous or subfascial) [103]. In patients undergoing colorectal surgery, a significant opioid-sparing effect and reduction of LOSH were demonstrated when local anaesthetic was infused through a catheter positioned between the fascia and the peritoneum [104]. No significant increase in wound infections was found with the insertion of a catheter and infusion of local anaesthetics. No comparison has been made with other modalities (e.g., epidural analgesia) or in enhanced recovery programmes.

TAP blocks anaesthetise 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 postoperative period [105]. A meta-analysis of 5 RCTs (176 patients) confirmed previous results showing improved pain relief and reduced opioid-associated side effects [106]. However, no studies have compared TAP block with other analgesic methods such as epidural analgesia or infiltration of local anaesthetic into the abdominal wound. Furthermore, no studies have used an enhanced recovery programme [107] 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-randomised) study [7] showed that an ERAS protocol with early mobilisation, 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 surgery [3] 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 surgery [110]. High-risk individuals (three factors) should receive general anaesthesia with propofol and remifentanil and no volatile anaesthetics; and dexamethasone 4–8 mg at the beginning of surgery, supplemented with serotonin receptor antagonists or droperidol [110], or 25–50 mg metoclopramide 30–60 min before the end of surgery [111]. 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 unclear [112–115].

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 anaesthesia. 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 complications [118–120], bleeding and transfusion requirements [118–121], as well as the duration of post-anaesthetic recovery [122]. Furthermore, extending systemic warming in the perioperative period (2 h before and after surgery) has additional benefits [123]. Hence, the use of active cutaneous warming is highly recommended to reduce postoperative morbidity and enhance recovery. There is even evidence to suggest that circulating-water garments offer better temperature control than forced-air warming systems [124–126].

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 glycaemic 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 resistance [127] and plasma glucose [128]. 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 haemoglobin (HBA1c) and higher postoperative levels of glucose also predict postoperative morbidity [130].

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 anaesthesia.

Reducing the rate of hyperglycaemia 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 controversial [137], but it seems fair to advocate that hyperglycaemia should be avoided and that this will improve outcome irrespective of the baseline level. Achieving tight glycaemic control with intravenous insulin is challenging in the ward setting because of the risk of hypoglycaemia. Glucosuria with the risk of hypovolaemia will ensue when the renal threshold is passed at >12 mmol/l [137]. This level has 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 hyperglycaemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycaemia with intravenous insulin in the intensive-care setting improves outcomes but hypoglycaemia remains a risk. Several ERAS protocol items attenuate insulin resistance and facilitate glycaemic control without the risk of hypoglycaemia. Hyperglycaemia should be avoided as far as possible without introducing the risk of hypoglycaemia
Evidence level	Low
Recommendation grade	Strong

Nasogastric intubation

There is strong evidence that routine nasogastric decompression after elective laparotomy should be avoided [139]. 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 avoided [139]. Gastro-oesophageal reflux is increased during laparotomy if nasogastric tubes are inserted [141]. 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 surgery [139], 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 feasible [144]. This has also been corroborated by other non-randomised, 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 anaesthesia. Delayed gastric emptying is a specific problem in $\approx$10–25 % 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 kg [145, 146]. Excessive overload of salt and water in the perioperative period increases postoperative complication rates and delays the return of gastrointestinal function [146–149]. 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 hypovolaemia with hypotension, which is often interpreted and treated as fluid depletion. The result is copious volumes of fluid administration when a vasopressor would be preferable [150]. In a meta-analysis of elective colorectal patients, intraoperative flow-guided fluid therapy with trans-oesophageal Doppler (TOD) ultrasonography to accurately assess and monitor fluid status in relation to cardiac output reduced complications and LOSH [151]. Other methods, such as lithium dilution (LiDCO) are evolving and may prove to be equivalent to TOD.

Hyperchloraemic acidosis results from infusion of 0.9 % saline. Recent studies have shown that excessive use of 0.9 % saline leads to renal oedema, reduced flow velocity in the renal artery, renal cortical tissue perfusion [152], and an overall increase in postoperative complications when compared with balanced crystalloids [153]. A recent meta-analysis [154] 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 crystalloids [155], there is no evidence from clinical trials and meta-analyses that colloids result in better clinical outcome than crystalloids [156]. 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-oesophageal Doppler to optimize cardiac output with fluid boluses improves outcomes. Balanced crystalloids should be preferred to 0.9 % saline
Evidence level	Fluid balance: High; Oesophageal 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 rate [157]. Moreover, patients who used these drains had a significantly greater incidence of intra-abdominal collections or fistulas (pancreatic and enterocutaneous) [157]. A series with historic controls failed to identify any increased risk after a no-drain regimen, but this design is prone to selection bias [158]. Evaluation of early (postoperative day 3) versus late (postoperative day 5 and beyond) drain removal has been examined in an RCT [159]. 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. 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 [159–161]) 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 72 h may be advisable in patients at low risk (i.e., amylase content in drain <5,000 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 secretion [162]. 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 surgery [163–166]. The most recent meta-analysis involved 17 trials with 1,457 patients undergoing PD and 686 undergoing distal or other resections [166]. 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 unchanged [166]. Subgroup analyses of the PD patients showed no significant effect of somatostatin/octreotide on any of the reported outcomes [166]. 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 catheterisation was superior to transurethral catheterisation [167]. Patients found suprapubic catheters more acceptable, and morbidity was reduced [167]. Most trials in the meta-analysis evaluated urinary drainage for 4–7 days. The only trial in the meta-analysis focusing specifically on hepatopancreaticobiliary surgery [168] 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 catheterisation 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-catheterisation when compared with removal on day 3–5 [169].

Summary and recommendation	Suprapubic catheterisation is superior to transurethral catheterisation 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 procedure [171]. In this context, DGE was less common in a fast-track group compared with a traditional care group in one study [7]. 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 DGE [172]. Occasionally, DGE persists and may necessitate enteral feeding delivered beyond the gastrojejunostomy (or even parenteral nutrition). The available definition of DGE [170] 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 postoperatively [175]. 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 advocated [6]. 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 rates [6]. However, no randomised 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 surgery [176–178]

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 multicentre RCT in patients undergoing only major upper gastrointestinal and hepatopancreaticobiliary 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 benefit [144]. This is in keeping with other reports, [179] including enteral tube feeding after other major abdominal surgery [180]. 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 nutrition [181]. 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 unacceptable [31]. 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 lacking [184].

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 mobilisation

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 mobilisation.

Summary and recommendation	Patients should be mobilized actively from the morning of the first postoperative day and encouraged to meet the daily targets for mobilisation
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 feedback [187]. 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 centres 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® programmes 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 standardised and appropriate enhanced recovery programmes based on best available scientific evidence.

Multimodal ERAS programmes are complex interventions that pose significant challenges to evaluation by conventional RCTs [175, 188]. The most obvious of these challenges are standardisation of the intervention and a rapidly closing window of opportunity from ethical and practical concerns [189]. This may, to some extent, explain the relative paucity of RCTs evaluating ERAS programmes 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 effects [190, 191]. This implies that the collateral effect on the infrastructure and management culture to implement such a comprehensive programme 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 group [175], this is nevertheless a benefit related to the use of these programmes. For these reasons it may be argued that a randomised 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, multicentre 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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