

Consensus guidelines for enhanced recovery after gastrectomy

Enhanced Recovery After Surgery (ERAS®) Society recommendations

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Background: Application of evidence-based perioperative care protocols reduces complication rates, accelerates recovery and shortens hospital stay. Presently, there are no comprehensive guidelines for perioperative care for gastrectomy.

Methods: An international working group within the Enhanced Recovery After Surgery (ERAS®) Society assembled an evidence-based comprehensive framework for optimal perioperative care for patients undergoing gastrectomy. Data were retrieved from standard databases and personal archives. Evidence and recommendations were classified according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system and were discussed until consensus was reached within the group. The quality of evidence was rated 'high', 'moderate', 'low' or 'very low'. Recommendations were graded as 'strong' or 'weak'.

Results: The available evidence has been summarized and recommendations are given for 25 items, eight of which contain procedure-specific evidence. The quality of evidence varies substantially and further research is needed for many issues to improve the strength of evidence and grade of recommendations.

Conclusion: The present evidence-based framework provides comprehensive advice on optimal perioperative care for the patient undergoing gastrectomy and facilitates multi-institutional prospective cohort registries and adequately powered randomized trials for further research.

Paper accepted 8 May 2014

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.9582

Introduction

Enhanced recovery protocols for perioperative care have proven valuable in reducing complications after surgery, improving overall outcomes and shortening length of stay, thus also saving resources¹. Updated and evidence-based guidelines have been developed by the Enhanced Recovery After Surgery (ERAS®) study group and are now available for colonic and rectal resections and pancreaticoduodenectomies^{2–7}. Although several publications have highlighted sporadic efforts to evaluate enhanced recovery or fast-track pathways for patients undergoing elective gastrectomy for cancer^{8,9}, a comprehensive and evidence-based framework is lacking.

A large body of literature suggests that such protocols are pivotal in improving patient outcomes. An international working group with extensive experience in enhanced recovery following surgery aimed to construct a comprehensive and evidence-based framework for best perioperative care in elective gastric cancer surgery and to process this through an expanded international group to achieve consensus behind the recommendations.

Methods

The group was initiated from within the ERAS® Society and was reinforced with acknowledged specialists from

several countries to achieve a broad knowledge base and ensure international validity for the conclusions. A core group (K.M., K.L., M.N., K.S., M.S.) performed a comprehensive literature search between September 2012 and April 2013, and constructed a primary set of recommendations based on reports published between 1985 and 2013. The entire authorship group repeatedly added scientific content, and adjusted evaluation of evidence and strength of conclusions. As most of the authors had worked together on previous guidelines^{3,10} and meet repeatedly in person, communication for these guidelines consisted solely of e-mail contact. Lastly, the collaborators offered important input on the guidelines.

All authors screened web-based databases and personal archives for relevant papers. Emphasis was placed on recent publications and papers of good quality (moderate- and high-quality randomized clinical trials (RCTs) and large, high-quality cohort studies as well as systematic reviews and meta-analyses of these). Retrospective series were included if data of better quality were lacking.

The author group specifically included only literature on elective gastric cancer surgery. This was because of the large differences in the extent of dissection necessary in oncological surgery compared with surgery for benign disease such as bariatric surgery, the consequences of which are very different postoperative courses for these patients, and so varying needs for perioperative treatment guidelines. Emergency surgery of any kind was not included.

Quality assessment and grading

The level of evidence and final recommendations were evaluated and adjusted until consensus was achieved. Level of evidence and recommendations were set according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system^{11–13}. Level of evidence was based on trial design and risk of bias, but also negatively affected if there was inconsistency of results or indirectness of evidence, such as extrapolation from other areas of surgery^{11–13}. As for recommendations, the GRADE guidelines state: '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 were based not only on the quality of evidence (high, moderate, low, very low) but also on the balance between wanted and unwanted effects, and on values and preferences¹³. The latter implies that, in some instances, strong recommendations may be reached from low-quality data and *vice versa*.

Procedure-specific items *versus* general upper abdominal surgery items

Several enhanced recovery items are probably unrelated to the specific intra-abdominal procedure (for example glycaemic control, fluid management, antimicrobial prophylaxis) and these are referred to here as 'general' as opposed to 'procedure-specific' items. Recent publications have assessed a large number of general enhanced recovery care items, and reached a consensus on perioperative care recommendations for patients undergoing pancreaticoduodenectomy^{3,6}. In the absence of procedure-specific evidence, the author group has considered some of these updated recommendations to be valid also for patients undergoing elective gastrectomy. These items are presented in part 2 of the results.

RESULTS PART 1: PROCEDURE-SPECIFIC ITEMS

A summary of the procedure-specific guidelines is shown in *Table 1*.

Preoperative nutrition

A uniform definition of malnutrition that identifies those who will benefit from preoperative nutrition is suggested in the 2009 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines¹⁴. Malnutrition is associated with increased morbidity after surgery^{15–17}. It appears prudent to identify these patients¹⁸ and give enteral sip feeds, or nasogastric or nasojejunal tube feeding, although data to support intervention are weak. If the tumour precludes access to the duodenum, parenteral nutrition may be warranted¹⁹. For patients not suffering from significant malnutrition, preoperative artificial nutrition has not been shown to confer benefits¹⁴.

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 before surgery.

Evidence level: Very low

Recommendation grade: Strong

Preoperative oral pharmaconutrition

Pharmaconutrition (PN) or immunonutrition, denoting the administration of immune-stimulating nutrients (generally arginine, glutamine, ω -3 fatty acids and/or nucleotides), has been evaluated extensively in major surgery and more than 20 RCTs have included patients undergoing upper gastrointestinal surgery²⁰. Conclusions are difficult as PN is administered to different patient

Table 1 Procedure-specific guidelines for perioperative care for gastrectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations

	Summary and recommendations	Evidence level	Recommendation grade
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition before surgery	Very low	Strong
Preoperative oral pharmaconutrition	The benefit shown for major gastrointestinal cancer surgery in general has not been reproduced in dedicated trials on patients undergoing gastrectomy. Although a benefit cannot be excluded, there is presently insufficient evidence for this patient group	Moderate	Weak
Access	<i>Distal gastrectomy:</i> Evidence supports LADG in early gastric cancer as it results in fewer complications, faster recovery and may be performed to a standard that is oncologically equivalent to open access surgery.	High	Strong
	For advanced disease, T2–T4a gastric cancer, more data on long-term survival comparing LADG and ODG are needed	Moderate	Weak
	<i>Total gastrectomy:</i> There is some evidence supporting LATG owing to lower postoperative complications, shorter hospital stay and oncological safety. However, LATG is technically demanding	Moderate	Weak
Wound catheters and TAP block	Evidence is conflicting regarding wound catheters in abdominal surgery	Wound catheters: Low to moderate	Weak
	Evidence is strong in support of TAP block in abdominal surgery in general, although the effect is evident only during the first 48 h after surgery and none of the evidence is from gastrectomies	TAP blocks: Low	Weak
Nasogastric/nasojejunal decompression	Nasogastric tubes should not be used routinely in the setting of enhanced recovery protocols in gastric surgery	High	Strong
Perianastomotic drains	Avoiding the use of abdominal drains may reduce drain-related complications and shorten hospital stay after gastrectomy	High	Strong
Early postoperative diet and artificial nutrition	Patients undergoing total gastrectomy should be offered drink and food at will from POD 1. They should be advised to begin cautiously and increase intake according to tolerance	Moderate	Weak
	Patients clearly malnourished or those unable to meet 60% of daily requirements by POD 6 should be given individualized nutritional support	Moderate	Strong
Audit	Systematic audit improves compliance and clinical outcomes	Low	Strong

LADG, laparoscopically assisted distal gastrectomy; ODG, open distal gastrectomy; LATG, laparoscopically assisted total gastrectomy; TAP, transversus abdominis plane; POD, postoperative day.

groups, at different time periods relating to surgery, in different combinations and dosages, and compared with control preparations that are not always isonitrogenous. Many trials are more than 10 years old, few are blinded and few investigated only a single component. For major abdominal cancer surgery as a group, there appears to be a benefit from perioperative enteral PN with respect to the rate of infectious complications in malnourished patients, but results are inconsistent^{20–26}. In a recent double-blind RCT²⁷, preoperative PN did not show any benefit in patients, of whom two of three underwent major upper gastrointestinal or hepatopancreatobiliary (HPB) cancer surgery, and all were at nutritional risk. A reduction in mortality has never been demonstrated. A meta-analysis²⁰ in 2011 identified only one double-blinded trial with adequate blinding assessing PN for gastric cancer surgery. In this trial²⁸, postoperative PN reduced the rate of surgical wound healing complications. Two recent reviews^{19,29} have come to conflicting conclusions regarding PN after oesophageal resections, and no benefit was found in a double-blinded RCT³⁰ in predominantly oesophago-gastric surgery. In two recent large RCTs^{31,32}, PN, given for 5–7 days after operation to patients undergoing gastrectomy or oesophagogastric surgery, did not confer any benefit. Further trials are warranted and, as this is an issue that lends itself well to double-blinded RCTs, this should be the study design. Future trials should be conducted in modern perioperative care settings and with single immune-enhancing substances.

Summary and recommendation

The possible benefit of reduced infectious and wound healing complications after major gastrointestinal cancer surgery in general has not been reproduced in dedicated, high-quality trials on patients undergoing gastrectomy. Although a benefit cannot be excluded, there is presently insufficient evidence to support routine administration in this patient group and its use is not recommended

Evidence level: Moderate

Recommendation grade: Weak

Access: distal gastrectomy

Distal gastrectomy is defined here as resection of the lower two-thirds of the stomach with lymph node harvest (D1, D1+ and D2) performed according to recommendations from the latest Japanese Gastric Cancer Association treatment guidelines³³. Early gastric cancer is defined as T1 and any N category, and advanced gastric cancer as T2–4 and any N category.

Six meta-analyses^{34–39} (of 6 RCTs, 8 prospective studies and 32 retrospective series) compared laparoscopically

assisted distal gastrectomy (LADG) with open distal gastrectomy (ODG). Combining these meta-analyses, a total of 4574 patients with largely early gastric cancer treated with LADG and 4260 with ODG were compared. Although three analyses^{35–37} reported longer operating times (mean 71 min), all reported that laparoscopic access resulted in significantly less blood loss. Three analyses^{34,35,38} reported shorter time to oral intake (a mean gain of 1 day) and shorter hospital stay (mean 4.5 days less). Overall postoperative morbidity (in particular pulmonary complications) was also reduced after LADG. Two analyses^{36,39} reported less postoperative analgesic consumption. There were no differences in anastomotic complications between LADG and ODG. The number of harvested lymph nodes during LADG has been of concern in many publications. Three meta-analyses^{35–37} reported a mean of 4.2 fewer lymph nodes harvested, whereas the other three^{34,38,39} reported no difference between LADG and ODG. Three RCTs^{40–42} including early and advanced gastric cancer reported data on long-term survival (24–62 months), which was found to be similar.

Summary and recommendation

Evidence supports LADG in early gastric cancer as it is associated with fewer complications, faster recovery and may be performed to a standard that is oncologically equivalent to open access surgery. For advanced disease, T2–T4 gastric cancer; more data on long-term survival comparing LADG and ODG are needed.

Evidence level: Early gastric cancer – High

Advanced gastric cancer – Moderate

Recommendation grade: Early gastric cancer – Strong

Advanced gastric cancer – Weak

Access: total gastrectomy

Three meta-analyses^{43–45} compared results of laparoscopically assisted total gastrectomy (LATG) in 1497 patients with those of open total gastrectomy (OTG) in 1486 patients treated for both early and advanced gastric cancer. All studies reported longer operating times (mean 54 min) for LATG and all three analyses reported that patients treated by a laparoscopic approach had lower blood loss (mean 120 ml less) and shorter hospital stay (mean stay almost 5 days shorter). One analysis⁴⁵ reported less postoperative pain, two^{43,45} reported earlier passage of flatus by a mean of 1.2 days, one⁴⁵ documented fewer postoperative complications (wound infections and ileus) and one⁴³ found no differences. No meta-analysis reported any difference in number of retrieved lymph nodes between LATG and OTG, and two meta-analyses^{44,45} found an equal 60-month recurrence-free survival. Concerns were

raised about higher anastomotic leak rates after LATG in another publication⁴⁶. Although the results after laparoscopic distal and total gastrectomies are promising, it must be borne in mind that the evidence level is only moderate owing to the shortage of RCTs, and the heterogeneity of data in the prospective and retrospective series on which these trends are based.

Summary and recommendation

Most publications suggest that LATG results in a lower rate of postoperative complications and shorter hospital stay. Data are inconclusive regarding oncological safety for advanced gastric cancer. LATG may be recommended for early gastric cancer wherever surgeons are proficient in the technique and the procedure is established.

Evidence level: Moderate

Recommendation grade: Weak

Wound catheters and transversus abdominis plane block

Wound catheters and transversus abdominis plane (TAP) block offer the potential of incisional analgesia without the need for more invasive methods such as epidural analgesia (EDA). The technique offers an attractive alternative to EDA as peripheral block of afferent stress-mediating impulses is achieved without troublesome and potentially hazardous hypotension. Furthermore, the risk of complications such as epidural haematomas and abscess formation is avoided. Although there are no specific data regarding gastrectomy, several meta-analyses^{47–49} have assessed the efficacy of wound infusion with local anaesthetic agents for postoperative analgesia after abdominal surgery in general. One meta-analysis⁴⁹, comprising a wide range of surgical procedures, including general surgical laparotomies, showed a significant reduction in postoperative pain, opioid consumption, as well as postoperative nausea and vomiting (PONV). Similarly, in patients undergoing colorectal surgery, there was a reduced use of opioids and reduction in length of hospital stay in patients randomized to preperitoneal wound catheter placement⁵⁰. A more recent meta-analysis⁴⁷ did not, however, show any effect of wound infusion with regard to postoperative pain intensity or in opioid consumption after laparotomy. The inconsistency in results may reflect the heterogeneity in techniques used, including catheter placement (subcutaneous, subfascial, preperitoneal), and type, concentration and dose of local anaesthetic. No differences in risk of infectious complications were found between patients in whom a wound catheter was used and those managed without one^{47,49–51}.

Several RCTs and meta-analyses^{52–55} have suggested a significant reduction in postoperative pain and opioid consumption during the first 24–48 h after surgery with the use of TAP blocks. There are no studies specifically addressing gastrectomy and most procedures included in these trials, such as cholecystectomies, appendicectomies and caesarean sections, are indeed less invasive, with regard to both abdominal wall incision and extent of internal dissection, than open gastrectomy for cancer^{52–55}. Another limitation of TAP blocks in postgastrectomy analgesia is that there is no evidence of an effect exceeding the first 48 h after operation^{52–55}. None of the studies available has suggested an increased risk of infection related to TAP blocks^{52–55}. One RCT⁵⁶ comparing wound infiltration and patient-controlled analgesia (PCA) using opiates with EDA after open liver resection found that the latter conferred superior analgesia but not faster mobilization or recovery.

Summary and recommendation

Evidence is strong in support of TAP blocks for abdominal surgery in general, although the effect is evident only during the first 48 h after surgery and none of the evidence is from gastrectomies.

Evidence level: Wound catheters – Low to moderate

TAP blocks – Low

Recommendation grade: Weak

Nasogastric/nasojunal decompression

Nine RCTs^{8,57–64} and two meta-analyses^{65,66} have specifically studied nasogastric/nasojunal tubes in gastrectomies. One RCT⁶¹ not included in the published meta-analyses showed results compatible with those from the RCTs and meta-analyses. A Cochrane review⁶⁷ evaluated nasogastric/nasojunal tubes after several types of operation with a subgroup analysis dedicated to 'gastroduodenal operations'.

There is strong evidence against the routine use of nasogastric/nasojunal decompression following gastrectomy. Surgical morbidity was not significantly influenced by decompression^{65–67}. The most recent of the meta-analyses⁶⁵ and the Cochrane review⁶⁷ concluded that patients without routine decompression experienced significantly fewer pulmonary complications, earlier time to passage of flatus, earlier time to oral diet and shorter hospital stay. This was not confirmed in another meta-analysis⁶⁶.

Summary and recommendation

Nasogastric/nasojunal tubes should not be used routinely in the setting of enhanced recovery protocols in gastric surgery.

Evidence level: High

Recommendation grade: Strong

Perianastomotic drains

Two RCTs^{68,69} including a total of 278 patients treated by subtotal gastrectomy with D1 or D2 lymphadenectomy found no difference in postoperative course in terms of time to passage of flatus, intake of soft diet or length of hospital stay between patients in whom drains were or were not used. Postoperative complication rates at 30 days were also similar^{68,69}. Another RCT⁷⁰ with 60 patients undergoing D2 gastrectomy found that the group with drains experienced longer hospital stays, higher postoperative morbidity with more frequent reoperations, and longer time to oral intake.

A meta-analysis of four RCTs⁷¹ including 438 patients randomized to either perianastomotic drain or no drain found no differences between the groups with respect to wound infection, postoperative pulmonary infection, intra-abdominal abscess, mortality, time to flatus, and initiation of soft diet. Both incidence of postoperative complications and length of stay were lower in the no-drain group. A Cochrane analysis⁷² concluded that there was no convincing evidence to support routine use of postoperative drains after gastrectomy for gastric cancer.

Summary and recommendation

Avoiding the use of abdominal drains may reduce drain-related complications and shorten hospital stay after gastrectomy.

Evidence level: High

Recommendation grade: Strong

Early postoperative diet and artificial nutrition

Patients subjected to total gastrectomy are probably at greater risk of malnutrition and cachexia at the time of surgery than other groups of patients with abdominal cancer¹⁹. This may result both from the location of their tumours, but also following neoadjuvant chemotherapy in a large proportion of the patients. A nil-by-mouth regimen for several days after surgery has traditionally been used for these patients⁷³. The absence of a gastric remnant has its advantages, but oesophagojejunostomy is probably a more vulnerable reconstruction than that following a distal or subtotal gastric resection. Most trials challenging the ubiquitous nil-by-mouth routine have done so in the setting of distal gastrectomy^{74,75} or only partly, introducing light food on postoperative day (POD) 2^{9,76,77}. Data from Western centres are scant. A large Norwegian multi-centre trial⁷⁸ randomized patients undergoing major upper gastrointestinal and HPB surgery to food at will from POD 1. Of 447 patients included, 77 had undergone total gastrectomy and a significant reduction in the number of intra-abdominal abscesses was demonstrated for those

allowed food at will in this subgroup⁷⁸. Importantly, no trial has reported any adverse outcome from any attempt at introducing patient-controlled or early introduction of food for patients undergoing gastrectomy.

It may be assumed that total calorie intake is low for the first few days and that some patients will need additional sip feeds or artificial tube or catheter feeding. A recent educational review⁷⁹ on nutritional care for patients undergoing oesophageal and gastric surgery recommends nutritional support after operation in patients who have not reached 60 per cent of desired intake by the first week following surgery⁷⁹. Nutritional support should preferably be by high-energy oral sip feeds. Enteral tube feeding is indicated where oral intake is not possible, and parenteral nutrition only when the gut is not working or is inaccessible. Although robust data are lacking, it appears pragmatic and safe to provide more intensive nutritional support both before and after operation to severely malnourished patients.

Summary and recommendation

Patients undergoing total gastrectomy should be offered drink and food at will from POD 1. They should be advised to begin cautiously and increase intake according to tolerance.

Evidence level: Moderate

Recommendation grade: Weak

Patients clearly malnourished or those unable to meet 60 per cent of daily requirements by POD 6 should be given individualized nutritional support, as detailed above.

Evidence level: Moderate

Recommendation grade: Strong

Audit

Regular audit is crucial to determine clinical outcome, and ascertain the implementation and sustained use of a care protocol. There are indications that audit in itself improves clinical results through feedback⁸⁰ and several real-time graphical methods are now available to monitor surgical treatment outcomes of gastro-oesophageal surgery^{81,82}. 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. Multi-institutional agreement on a common evidence-based treatment platform and joint use of a prospective database is a powerful tool for audit and research.

Summary and recommendation

Systematic audit improves compliance and clinical outcomes.

Evidence level: Low

Recommendation grade: Strong

RESULTS PART 2: GENERAL (NOT PROCEDURE-SPECIFIC) ITEMS

The author group found that the data and recommendations published recently for patients undergoing pancreaticoduodenectomy seem valid for gastrectomy^{3,6}. In the following sections these recommendations are reiterated and the background for each recommendation is addressed briefly. For a fuller consideration of the available literature with expanded references, the reader is referred to the aforementioned publications^{3,6}. A summary of the general items is shown in *Table 2*.

Preoperative counselling

Personalized counselling, oral or written, and relaxation techniques may reduce anxiety and fear and improve recovery^{83–86}. Detailed explanations of procedure and specific daily targets for the postoperative period may facilitate eating, mobilization, pain control and respiratory function, thus reducing the risk of complications^{87–90}.

Summary and recommendation

Patients should receive dedicated preoperative counselling routinely.

Evidence level: Low

Recommendation grade: Strong

Preoperative smoking and alcohol consumption

Overall postoperative morbidity is increased markedly in alcohol abusers⁹¹, and 4 weeks of abstinence before surgery was shown to improve outcome in patients who drank 'five or more drinks (60 g of ethanol) a day without clinical or historical evidence of alcohol related illness'⁹². Daily smokers have an increased risk of complications^{93,94}. RCTs^{94–96} have shown reduced postoperative morbidity after 1 month of smoking cessation. Preoperative physiotherapy reduces postoperative pulmonary complications and length of hospital stay after elective cardiac surgery⁹⁷, and preoperative pulmonary rehabilitation before lung cancer surgery decreases postoperative respiratory morbidity and complications^{98,99}.

Summary and recommendation

For alcohol abusers, 1 month of abstinence before surgery is beneficial. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted. Preoperative pulmonary rehabilitation is advised.

Evidence level: Alcohol abstinence – Low

Smoking cessation – Moderate

Recommendation grade: Strong

Oral bowel preparation

Mechanical bowel preparation (MBP) may cause dehydration, and fluid and electrolyte imbalance, especially in the elderly¹⁰⁰. Meta-analyses^{101,102} of trials on patients undergoing colonic surgery have not shown MBP to be beneficial. There are no data comparing MBP *versus* a routine without MBP and unrestricted diet up to midnight before operation.

Summary and recommendation

Extrapolation of data from colonic surgery suggests 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 is not supported by evidence¹⁰³, and increases insulin resistance and discomfort following abdominal surgery^{104,105}. Guidelines¹⁰⁶ recommend intake of clear fluids up to 2 h before induction of anaesthesia and solids up to 6 h. A complex clear carbohydrate-rich drink designed for use within 2 h before anaesthesia reduced hunger, thirst, anxiety and length of stay, as well as postoperative insulin resistance^{107–109}. The most recent meta-analysis¹¹⁰ showed no reduction in in-hospital complication rates. Data on patients having gastrectomy are inadequate¹¹⁰, and data for diabetic patients are wanting^{111,112}.

Summary and recommendation

Preoperative fasting should be limited to 2 h for clear fluids and 6 h for solids. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given to patients without diabetes.

Evidence level: Fluid intake – High

Solid intake – Low

Carbohydrate loading – Low

Recommendation grade: Fasting – Strong

Carbohydrate loading – Strong

Preanaesthetic medication

Reduced postoperative pain has not been demonstrated following pre-emptive use of analgesics¹¹³, but medications for chronic pain should be continued around the time of operation. Preinduction anxiolytic medication might increase sedation on POD 1^{114,115}, and benefits are uncertain. Short-acting drugs to alleviate anxiety may be

Table 2 General (not procedure-specific) enhanced recovery care items as suggested recently for pancreaticoduodenectomy

	Summary and recommendations	Evidence level	Recommendation grade
Preoperative counselling	Patients should receive dedicated preoperative counselling routinely	Low	Strong
Preoperative smoking and alcohol consumption	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted	Alcohol abstinence: Low	Strong
	For daily smokers, 1 month of abstinence before surgery is beneficial	Smoking cessation: Moderate	
	For appropriate groups, both should be attempted		
Oral bowel preparation	Extrapolation of data from studies on colonic surgery shows that MBP has no proven benefit; MBP should not be used	Moderate	Strong
Preoperative fasting and preoperative treatment with carbohydrates	Intake of clear fluids ≤ 2 h before anaesthesia does not increase gastric residual volume and is recommended before elective surgery	Fluid intake: High	
	Intake of solids should be withheld 6 h before anaesthesia	Solid intake: Low	Fasting: Strong
	Data extrapolation from studies on major surgery suggests that preoperative oral carbohydrate treatment should be given to patients without diabetes	Carbohydrate loading: Low	Carbohydrate loading: Strong
Preanaesthetic medication	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	No long-acting sedatives: Moderate	Weak
	Short-acting anxiolytics may be used for procedures such as insertion of epidural catheters		
Antithrombotic prophylaxis	LMWH reduces the risk of thromboembolic complications. 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 within 1 h 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 use of 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	PCA: Moderate Intravenous lidocaine: Moderate	Weak
Anaesthetic management	Short-acting anaesthetic drugs and short-acting muscle relaxants are suggested. Titration of anaesthetic agents can be achieved using the BIS	BIS: High	Strong
	Low-tidal volume ventilation is suggested	Low-tidal volume ventilation: High	

Table 2 Continued

	Summary and recommendations	Evidence level	Recommendation grade
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
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 improves outcomes but hypoglycaemia remains a risk. Several enhanced recovery 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
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes	Fluid balance: High	Strong
	Perioperative monitoring of stroke volume with transoesophageal Doppler to optimize cardiac output with fluid boluses may improve outcomes	Oesophageal Doppler: Moderate	
	Balanced crystalloids should be preferred to 0.9% saline	Balanced crystalloids <i>versus</i> 0.9% saline: Moderate	
Urinary drainage	Suprapubic catheterization is superior to transurethral catheterization if used for > 4 days. Transurethral catheters can be removed safely on POD 1–2 unless indicated otherwise	High	Suprapubic catheter use: Weak Removal of transurethral catheter on POD 1–2: Strong
Stimulation of bowel movement	A multimodal approach with epidural and near-zero fluid balance is recommended	Chewing gum: Low	Weak
	Oral laxatives given after surgery may accelerate gastrointestinal transit	Laxatives: Very low	
Early and scheduled mobilization	Patients should be mobilized actively from the morning of POD 1 and encouraged to meet daily targets for mobilization	Very low	Strong

In the absence of procedure-specific evidence for these items, the author group considers extrapolation of these recommendations to patients undergoing total gastrectomy to be safe and feasible. For discussion and references please see original papers^{3,6}. MBP, mechanical bowel preparation; LMWH, low molecular weight heparin; PCA, patient-controlled analgesia; BIS, bispectral index; PONV, postoperative nausea and vomiting; ICU, intensive care unit; POD, postoperative day.

helpful during insertion of an epidural catheter in some patients. A carbohydrate-rich drink has also been shown to attenuate anxiety¹⁰⁸.

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

Antithrombotic prophylaxis

A large tumour burden, major surgery, chemotherapy and prolonged periods of recumbency are risk factors for venous thromboembolism (VTE). Heparins are effective at preventing VTE¹¹⁶ and fractionated low molecular weight heparin (LMWH) has better compliance (once-daily administration)¹¹⁷. Injections are usually started 2–12 h before surgery and continued until the patient is mobilized. Data even support postdischarge treatment for several weeks¹¹⁸. Use of LMWH and epidural catheters is

controversial^{119–122} and a 12-h interval should probably separate LMWH and catheter insertion and removal¹²³. Mechanical measures (intermittent pneumatic leg compression and elastic stockings) may provide additional benefits in patients at increased risk of VTE^{124,125}.

Summary and recommendation

LMWH reduces the risk of thromboembolic complications. Administration should probably be continued for 4 weeks after hospital discharge. Concomitant use of EDA 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 sufficient evidence to support the prescription of antimicrobial prophylaxis for major abdominal procedures^{126,127}. Recent studies recommend prescription in a single-dose manner¹²⁷, usually advocated within 1 h before incision; however, recent data suggest that the timing may not be crucial¹²⁸. An extra dose should be given every 3–4 h during the procedure if drugs with a short half-life are used¹²⁹. The choice of antibiotic varies according to local guidelines, but should be different from the drug used for management of established infections. Skin preparation with a scrub of chlorhexidine–alcohol has been claimed to be superior to povidone–iodine in preventing surgical-site infections¹³⁰.

Summary and recommendation

Antimicrobial prophylaxis prevents surgical-site infections and should be used in a single-dose manner initiated 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

Continuous EDA with or without opioids leads to significantly less postoperative pain than parenteral opioids after open abdominal surgery¹³¹. A Cochrane review¹³² demonstrated that EDA is better than patient-controlled intravenous opioid analgesia in relieving pain 72 h after open abdominal surgery, and epidural administration of local anaesthetic led to a lower rate of ileus after laparotomy than systemic or epidural opioids¹³³. EDA was also associated with fewer complications, as well as an

improvement in pulmonary function, decreased risk of postoperative pneumonia, better arterial oxygenation after abdominal or thoracic surgery¹³⁴, and reduced insulin resistance¹³⁵. Data from a recent RCT¹³⁶ indicate that, for patients undergoing gastrectomy for cancer specifically, patient-controlled EDA appears to result in superior pain relief and lower stress response than patient-controlled intravenous analgesia.

Adverse perfusion effects of EDA may be caused by prolonged and extended sympathetic block. This suggests that the beneficial effects of EDA can be preserved provided that the haemodynamic consequences are adequately controlled with vasopressors¹³⁷. Concerns about negative effects on anastomotic healing have been raised after colorectal surgery, but one meta-analysis¹³⁸ did not identify differences in rates of anastomotic leakage between patients treated with postoperative local anaesthetic epidurals and those receiving systemic or epidural opioids. A potential drawback with EDA is that up to one-third of epidurals may not function adequately^{139,140}, possibly owing to catheter misplacement, inadequate dose or pump failure. For upper abdominal incisions, epidural catheters should be inserted between T5 and T8 root levels. Sensory block should be tested before induction of general anaesthesia. EDA should continue for 48 h and, after a successful stop test, replaced by oral multimodal analgesia. If needed, functioning epidural catheters may be used for a longer duration.

Summary and recommendation

Mid-thoracic epidurals are recommended based on data from studies of 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

In situations where EDA cannot be employed, PCA with opioids is the most common alternative. In a clinical trial¹⁴¹ of the use of PCA in patients undergoing distal pancreatectomy this was the only analgesia employed. No comments were made, however, on the impact of systemic analgesia on accelerating recovery. Intravenous infusion of lidocaine has analgesic, anti-inflammatory and antihyperalgesic properties, and has been assessed as an analgesic modality for abdominal surgery. A systematic review of eight trials¹⁴²

showed a decrease in the duration of ileus, length of hospital stay, postoperative pain and adverse effects, compared with placebo. A recent RCT¹⁴³ in patients undergoing laparoscopic colorectal resection using the ERAS® programme showed no difference in return of gastrointestinal function and length of hospital stay between continuous infusion of lidocaine and thoracic EDA, whereas a recent RCT¹⁴⁴ in patients undergoing laparoscopic gastrectomy showed a reduction in postoperative fentanyl consumption and pain with preoperative and intraoperative injection of lidocaine by PCA.

Summary and recommendation

Some evidence supports the use of PCA or intravenous lidocaine analgesic methods.

Evidence level: PCA – Moderate

Intravenous lidocaine – Moderate

Recommendation grade: Weak

Anaesthetic management

Although no trials exist, short-acting induction anaesthesia agents such as propofol and dexmedetomidine, and opioids such as sufentanil and remifentanyl, are widely used. Likewise, short-acting muscle relaxants are suggested. Deep neuromuscular block is usually necessary to ensure optimal access, particularly in laparoscopic surgery. Titration of anaesthetic agents can be achieved using the bispectral index (BIS), thereby avoiding sedation that is too deep, which can be harmful in elderly patients¹⁴⁵. Recent data suggest that a significant benefit for postoperative morbidity can be achieved by intraoperative low-tidal-volume ventilation¹⁴⁶.

Summary and recommendation

Short-acting induction agents, opioids and muscle relaxants are recommended. Maintenance should be guided by the BIS. Low-tidal-volume ventilation is suggested.

Evidence level: BIS – High

Low-tidal-volume ventilation – High

Recommendation grade: Strong

Postoperative nausea and vomiting

A comparative non-randomized study¹⁴⁷ indicated that an enhanced recovery protocol with early mobilization, metoclopramide and removal of the nasogastric tube on POD 1 or 2 reduced the rate of PONV after pancreaticoduodenectomy. Until further evidence becomes available for gastric cancer surgery, the suggestions for patients undergoing colorectal surgery¹⁰ should be applicable.

Patients with two risk factors (non-smoker, female, a history of motion sickness (or PONV), postoperative administration of opioids)^{148,149} should be given prophylaxis with dexamethasone upon induction or a serotonin receptor antagonist at the end of surgery¹⁵⁰. High-risk individuals (3 risk factors) should receive general anaesthesia with propofol and remifentanyl and no volatile anaesthetics, with dexamethasone 4–8 mg at the start of surgery, with the addition of a serotonin receptor antagonist or droperidol¹⁵⁰, or 25–50 mg metoclopramide 30–60 min before the end of surgery¹⁵¹. A possible risk of impaired anastomotic healing caused by single-dose dexamethasone or other perioperative steroids is of concern, but remains unclear^{152–155}.

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 history of PONV, type of surgery and type of anaesthesia. Multimodal intervention, during and after surgery, is indicated.

Evidence level: Low

Recommendation grade: Strong

Avoiding hypothermia

Numerous meta-analyses and RCTs have shown that preventing hypothermia during major abdominal surgery reduces the occurrence of wound infections^{156,157}, cardiac complications^{157–159}, bleeding and transfusion requirements^{157–160}, as well as the duration of postanaesthetic recovery¹⁶¹. Prolonging systemic warming in the perioperative period (2 h before and after surgery) confers further benefits¹⁶². There is even evidence to conclude that circulating-water garments offer superior temperature control to forced-air warming systems^{163–165}.

Summary and recommendation

Intraoperative hypothermia should be avoided by using cutaneous warming in the form of forced-air or circulating-water garment systems.

Evidence level: High

Recommendation grade: Strong

Postoperative glycaemic control

Morbidity and mortality after major gastrointestinal surgery are associated with insulin resistance¹⁶⁶ and plasma glucose levels¹⁶⁷. Treatment of hyperglycaemia

with intravenous insulin in the intensive care setting improves outcomes, although hypoglycaemia remains a risk. Core elements of enhanced recovery protocols alleviate postoperative insulin resistance and, therefore, also lower glucose concentrations^{168,169}. The most evident protocol items are: avoidance of preoperative fasting and oral bowel preparation; use of oral carbohydrate treatment and stimulation of gut function by optimal fluid balance and avoidance of systemic opioids; and reduction of the stress response by use of EDA. Target thresholds for glucose are disputed, but glucosuria with the risk of hypovolaemia will ensue when the renal threshold is exceeded at 12 mmol/l¹⁷⁰. This level has been used as the control regimen in seminal studies^{171,172} and should probably be regarded as a limit, irrespective of settings.

Summary and recommendation

Insulin resistance and hyperglycaemia are strongly associated with postoperative morbidity and mortality. Hyperglycaemia should be avoided as far as possible without introducing the risk of hypoglycaemia.

Evidence level: Low

Recommendation grade: Strong

Fluid balance

Overload of salt and water, and hypovolaemia in the perioperative period all increase postoperative complication rates^{173–177}, suggesting that near-zero fluid balance should be achieved around the time of surgery. Determining the correct amount required is complicated by the use of EDA as it causes vasodilatation and hypovolaemia with hypotension, often diagnosed and treated as fluid depletion. This may result in the administration of unnecessary and large volumes of fluid¹⁷⁸. To avoid unnecessary fluid overload, vasopressors should be considered for intraoperative and postoperative management of epidural-induced hypotension, bearing in mind the risk of drug-induced splanchnic vasoconstriction¹⁷⁹. Several cardiac output monitoring devices provide dynamic indicators of fluid responsiveness and haemodynamic assessment. These vary from invasive pulmonary artery catheters to non-invasive pulse pressure analysis, bioimpedance, applied Fick principle and Doppler imaging¹⁸⁰. Intraoperative flow-guided fluid therapy with transoesophageal Doppler ultrasonography to assess and monitor fluid status accurately has been shown to reduce complications and length of hospital stay after major abdominal surgery^{181,182}. All devices providing haemodynamic surveillance show only whether an increase in fluids infused actually leads to improved cardiac output, and not whether the patient actually has hypoperfusion in need of

treatment. Data for high-risk patients (American Society of Anesthesiologists grade III) are lacking. Excessive use of 0.9 per cent saline leads to an increase in postoperative complications compared with balanced crystalloids^{183–185}. Although use of colloids results in improved blood volume expansion and less interstitial space overload than administration of crystalloids¹⁸⁶, there is no evidence from clinical trials or meta-analyses that they contribute to better clinical outcome¹⁸⁷.

Summary and recommendation

Near-zero fluid balance as well as avoiding overload of sodium results in improved outcomes. High-risk patients need dedicated, individualized, goal-directed fluid therapy handled by an experienced team to secure optimal tissue perfusion. A Doppler-guided technique may improve outcome. Balanced crystalloids should be preferred to 0.9 per cent saline.

Evidence level: Fluid balance – High

Oesophageal Doppler – Moderate

Balanced crystalloids versus 0.9 per cent saline – Moderate

Recommendation grade: Strong

Urinary drainage

A meta-analysis¹⁸⁸ of RCTs on urinary drainage after surgery showed that suprapubic catheterization was better than transurethral catheterization, and more satisfactory to patients. However, the majority of patients were catheterized for 4 days or longer. A recent RCT¹⁸⁹ of patients undergoing major surgery with thoracic epidurals found that removal of the transurethral catheter on POD 1 led to lower infection rates and did not lead to an increased rate of recatheterization compared with removal on POD 3–5.

Summary and recommendation

Suprapubic catheterization is probably superior to transurethral catheterization if used for more than 4 days. Transurethral catheters can be removed safely on POD 1 or 2 unless indicated otherwise.

Evidence level: High

*Recommendation grade: Suprapubic catheter use – Weak
Removal of transurethral catheter
on POD 1–2 – Strong*

Stimulation of bowel movement

There is no high-level evidence to support a precise motility-enhancing drug. The use of oral laxatives such

as magnesium sulphate or bisacodyl may stimulate early gastrointestinal transit after colonic resections^{190,191}. Use of epidurals and maintaining a near-zero fluid balance are associated with an enhanced return of peristalsis after abdominal surgery^{133,175}. Chewing gum has been shown to be safe and helpful in restoring gut activity after colorectal surgery in one meta-analysis¹⁹². This was, however, not confirmed in recent RCTs^{193,194}.

Summary and recommendation

A multimodal approach with epidural and near-zero fluid balance is recommended. Oral laxatives given after surgery may accelerate gastrointestinal transit.

Evidence level: Laxatives – Very low

Chewing gum – Low

Recommendation grade: Weak

Early and scheduled mobilization

Delayed resumption of gut function combined with surgical trauma leads to a lengthened recovery period in patients undergoing major gastrointestinal surgery. Extended bed rest is associated with several unwanted effects^{195,196}. With little evidence, the present authors support the use of written day-to-day instructions for patients with detailed postoperative targets. This improves autonomy and cooperation with patients. Day-to-day progress can be documented with simple monitoring devices. Analgesia must be adequate.

Summary and recommendation

Patients should be mobilized actively from the morning of POD 1 and encouraged to meet daily targets for mobilization.

Evidence level: Very low

Recommendation grade: Strong

Comments

A comprehensive set of guidelines for enhanced recovery after gastrectomy for cancer is presented. Although the magnitude of effect following the successful implementation of these guidelines is yet to be established, they represent an opportunity to apply the best available, updated perioperative practice to a group of patients at high risk of complications and morbidity.

For many of the items included, evidence is scarce and of low quality, and the use of a consensus-based process by an international author group is an attempt to minimize these shortcomings.

Consensus was unproblematic for most of the procedure-specific items covered in these guidelines, with the exception of PN and access. Literature on the former subject is incongruent and further high-quality RCTs with single-component administration in enhanced recovery settings are needed to reach more definite conclusions and recommendations. The subject of access is complex. Although there is an abundance of literature confirming perioperative benefits of laparoscopic treatment and safety for distal gastrectomy, there is a significant learning curve and studies describing outcomes after total gastrectomy are still wanting. Furthermore, the oncological aspect of minimally invasive surgery for proximal gastric cancer remains largely undocumented in RCTs as literature reporting long-term survival after total gastrectomy is limited and further studies are needed. Comparing laparoscopic and open resections in RCTs is challenging owing to the skill-dependent nature of these interventions and consequently a predictably low validity of the results¹⁹⁷. Implementation of minimally invasive surgery for the treatment of gastric cancer, nevertheless, offers a potential evolution in the postoperative clinical course of these patients.

A recent review¹⁹⁸ on enhanced recovery in upper gastrointestinal surgery calls for international guidelines with standardization of clinical pathways, allowing comparison of results between institutions and across nations. The present consensus-based guidelines for enhanced recovery after gastrectomy offer such a framework, allowing the establishment of multi-institutional prospective cohort registries.

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Acknowledgements

O.L. serves as advisor for Nutricia.

Disclosure: The authors declare no other conflict of interest.

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