INVITED REVIEW

Complications after Supramajor Gastrointestinal Surgery: Role of Enhanced Recovery after Surgery

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Abstract

Background: Enhanced recovery after surgery (ERAS) is currently the standard of care in perioperative medicine, but it is widely underutilized in our healthcare setting because of the lack of awareness of benefits exerted by ERAS and its components. ERAS is a multidisciplinary collaboration, where intensivists play an important role in the implementation of the protocol during the perioperative period.

Aim: This review article aims to appraise the role of ERAS pathway on complications following supramajor gastrointestinal surgery.

Review: A summary and review of evidence was conducted on the role of ERAS and its elements on non-specific and surgery-specific complications. Enhanced recovery pathways (ERPs) and its elements were directly found to be associated with lower incidence of hospital-associated infections, postoperative ileus, and postoperative pulmonary complications. Although there are no specific elements of ERPs found to have beneficial effect in preventing major adverse cardiac and cerebrovascular events, and surgery-specific complications such as postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, post-hepatic liver failure, bile, and anastomotic leak, studies have demonstrated that implementation of an ERP bundle can decrease the incidence of these complications. Implementation of an ERP was associated with an increase in the incidence of acute kidney injury with minor elevations in creatinine that returned to baseline before discharge.

Conclusion: Although there is ample evidence that ERAS is beneficial in reducing complications and hospital stay following supramajor gastrointestinal surgery, there is scope for further research to unravel the role of ERAS on patient-reported outcomes.

Keywords: Acute kidney injury, Anastomotic leak, Catheter-associated urinary tract infection, Enhanced recovery after surgery, Epidural analgesia, Gastrointestinal surgery, Pancreatic fistula, Perioperative medicine, Postoperative complications, Surgical site infection.

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Introduction

Gastrointestinal surgery has evolved dramatically with improved perioperative outcomes over the past few decades. Increased volume of procedures coupled with more radical approach and complex techniques place gastrointestinal surgery as one of the most challenging offshoots of modern surgery. However, complication rates still remain high (33–44%).[1] Despite advances in surgical techniques, high morbidity can be attributed to an accelerated catabolic physiology secondary to surgical stress, extended surgical indications, and spectrum of patients such as elderly and those with multiple comorbidities. Enhanced recovery after surgery (ERAS) encompasses a multidisciplinary evidence-based perioperative component that attenuates surgical stress response to restore physiological homeostasis.[2] Enhanced recovery after surgery has been widely accepted as standard of care since its inception into clinical practice by Professor Henrik Kehlet in 1990s. The idea percolated from colorectal surgery through to various surgical disciplines. This evidence-based review briefly summarizes possible complications following supramajor surgery and the impact of enhanced recovery pathway (ERP) on postoperative outcomes.

Supramajor gastrointestinal surgery can be subdivided into pancreatic, hepatobiliary, colorectal, and upper gastrointestinal surgery. Indications for these procedures can be benign or malignant. The Clavien Dindo classification (Table 1) is most widely used and validated method to grade surgical complications. Grade I to IIIa are considered minor complications, and grades IIIb to V are major complications. Complications after gastrointestinal surgery can be classified as general surgical complications and surgery-specific complications.

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Enhanced Recovery after Surgery Components and Physiological Basis

ERPs incorporate a set of preoperative, intraoperative, and postoperative components that are implemented by a multidisciplinary team (MDT). This MDT comprises of surgeons, anesthetists, nurses, intensivists, physiotherapists, nutritionists, and other allied health specialties. The key components of ERAS are listed in Flowchart 1.

The primary aim of ERP is to minimize perioperative stress response to surgery. Surgical stress consists of anxiety, fasting, tissue injury, hemorrhage, hypothermia, fluid and electrolyte disturbances, pain, hypoxia, ileus, and cognitive dysfunction. The hormonal and metabolic stress response to surgery consists of hematological, immunological, and endocrine elements. There is an initial inflammatory systemic cytokine response followed by an anti-inflammatory response.

Elevated level of stress hormones, such as cortisol, growth hormone, catecholamines and glucagon, along with the inflammatory response, leads to insulin resistance. Insulin resistance is characterized by a catabolic state with loss of structural and functional body protein, thus leading to delayed wound healing, immunosuppression, and muscle weakness. Muscle weakness delays mobilization, impairs respiratory function, and increasing morbidity. Hyperglycemia is associated with poor outcomes and increased morbidity.[3]

Table 1: Clavien Dindo classification of surgical complications

Grade I	Deviation from the normal post-operative course not requiring surgical, radiological, endoscopic or pharmacological intervention
	Allowed medications and treatment include antiemetics, analgesics, antipyretics, diuretics, electrolytes and physiotherapy
Grade II	Pharmacological therapy required with drugs other than the ones mentioned in grade I.
	This grade of complication also includes blood transfusion and TPN therapy
Grade III	Complication requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not requiring a general anesthetic procedure
IIIb	Intervention requiring a general anesthetic procedure
Grade IV	Life-threatening complication requiring intensive care therapy
IVa	Single organ dysfunction
IVb	Multiorgan dysfunction
Grade V	Death/mortality

Suffix "d" is added to the grade if the patient suffers from the complication at the time of discharge, "d" denoting disability

The ERAS interventions that potentially modulate insulin resistance include minimizing preoperative fasting, carbohydrate loading, epidural analgesia, early postoperative oral intake, and perioperative normoglycemia. Minimally invasive surgery is beneficial by reducing direct tissue trauma and thus attenuating the neurohumoral response. Normovolemia is achieved preoperatively by adequate hydration and avoiding bowel preparation intraoperatively, through goal-directed fluid therapy to prevent salt and water retention and its deleterious effects and postoperatively by early initiation of oral diet. Maintenance of normothermia reduces infectious complications.

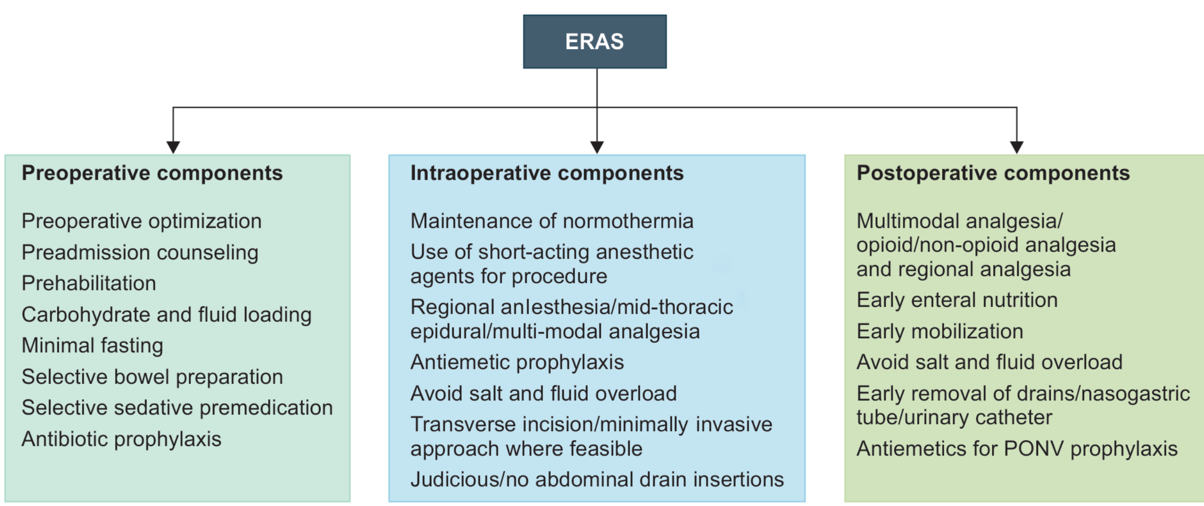
Pain activates the hypothalamic–pituitary–adrenal axis and stimulates the sympathetic nervous system causing release of inflammatory mediators that potentiate the stress response. ERAS advocate multimodal analgesia pain management targeting somatic, visceral, or neuropathic pain components. Prolonged immobilization leads to a linear decline in exercise capacity, muscle weakness, loss of bone, insulin resistance, and complications, such as pressure ulcers, thromboembolism, and atelectasis. ERP emphasizes the importance of early structured mobilization to prevent these deleterious effects. There may not be high-quality evidence regarding benefits of individual ERAS components, integration of the components of ERAS makes pathophysiological sense, and benefits are demonstrated akin to the concept of aggregation of marginal gains.

Nonsurgery-specific Complications after Supramajor Gastrointestinal Surgery

Surgical Site Infections

Surgical site skin and subcutaneous tissue infections are a major cause of postoperative morbidity. Surgical site infections (SSI) are known to increase length of stay (LOS), duration of rehabilitation, and cost. A retrospective analysis demonstrated that SSI bundle,

Flowchart 1: ERAS perioperative components



which incorporated ERAS elements was associated with a significant reduction in SSI from 19.3 to 5.7%, LOS (72%), and cost (35%).[4] Similarly, a meta-analysis of 36 studies found ERP significantly reduced the incidence of hospital-associated infections (RR 0.75, 95% CI 0.58–0.98, p value = 0.04).[5] ERAS components demonstrated to decrease the incidence of SSIs include enhanced perioperative nutritional support, antibiotic prophylaxis, skin preparation with chlorhexidine, and maintenance of normothermia.

Catheter-associated Urinary Tract Infection and Postoperative Urinary Retention

Persistent postoperative use of an indwelling catheter causes discomfort, pain, decreases mobility, and increases the incidence of catheter-associated urinary tract infection (CAUTI). National Surgical Infection Prevention Project in 2,965 hospitals found perioperative surgical patients with indwelling catheters for more than 2 days were 50% more likely to develop CAUTI.[6] Early catheter removal or noninsertion of urinary catheters when feasible is an integral component of the ERP and is associated with lower incidence of CAUTI, improved mobility, and enhanced patient comfort and recovery.

Postoperative urinary retention (POUR) is a major concern with epidural analgesia and also a barrier for compliance with this component. Schreiber et al. demonstrated that early removal of urinary catheters in patients undergoing colorectal surgery with epidural analgesia reduced CAUTI in the ERAS group by 16%.[7] However, there was an insignificant increased incidence of POUR with epidural analgesia. POUR was associated with male gender, rectal surgery, and abdominal perineal resection. Appropriate indication and selection of patients for catheter insertion coupled with “Bladder bundles” and reminder/stop order interventions help in minimizing CAUTI and POUR.

Postoperative Ileus

Postoperative ileus (POI) is uncomplicated ileus that resolves within 2–3 days after surgery, and paralytic or adynamic ileus lasts beyond 3 days. Incidence of POI ranges from 4 to 19% and depends on the surgical procedure and other perioperative factors. Major predisposing factors are intraoperative bowel handling, perioperative opioids, immobility, and overzealous fluid management. In addition, inflammatory mediators secondary to stress response increase vascular permeability in the gastrointestinal mucosa further worsening gut dysfunction.

The implementation of ERPs suppresses the inflammatory cascade and maintains gut mucosal integrity. Barbieux et al. observed improved compliance with ERAS protocol was associated with decrease in median time to passage of flatus (MTPF) and global resumption of intestinal transit (GROT) time.[8] Ileus is associated with prolonged LOS and increased cost. ERP along with novel pharmacological agents like Alvimopan and a multifactorial approach help clinicians to minimize ileus and promote recovery.

Postoperative Pulmonary Complications

The European Society of Anaesthesiology and European Society of Intensive Care Medicine formed a joint taskforce in 2015 to establish the European Perioperative Clinical Outcome definitions for post-operative pulmonary complications (PPC). PPCs are associated with increased morbidity, LOS, mortality, and healthcare expenditure. The incidence of PPC varies from 2–19% and it is estimated that one in five patients with PPC will succumb to death within 30 days of major surgery.[9]

Risk factors for developing PPCs include perioperative modifiable and non-modifiable variables. Induction of anesthesia causes basal atelectasis and reduction in functional residual capacity, high concentration of oxygen during preoxygenation, and neuromuscular blockade initiate the pathophysiological process for PPCs. The primary insult is worsened in postoperative period with residual sedation, inadequate analgesia, and ineffective cough reflex, leading to the development of PPCs. The incidence increases in patients with preexisting pulmonary pathology, smoking, compromised nutritional status, immunosuppression, and upper abdominal surgery. They can also occur secondary to intra-abdominal surgical complication. Preoperative risk assessment using scoring systems like the ARISCAT score, management of modifiable perioperative factors along with protective lung ventilation, and implementation of pulmonary care bundles prevent development of PPCs.

ERAS principles play a crucial role in prevention of PPCs, this has been demonstrated in a quality initiative study by Moore et al., and they observed reduction in PPCs (10.5 vs 19.3%) and a shorter LOS (9 vs 12 days) after implementation of ERP.[10] Preoperative optimization including smoking cessation, incentive spirometry, and nutritional support, and patient counseling has shown to influence outcomes. The strategy extends into the intraoperative and postoperative period where minimal use of opioids, use of long-acting anesthetics coupled with regional/epidural anesthesia, and minimally invasive surgery help in preventing basal atelectasis and promote early mobilization, coughing, and inspiratory exercises.

Major Adverse Cardiac and Cerebrovascular Events

The incidence of major adverse cardiac and cerebrovascular events (MACCE) is between 1 and 7%, with the incidence of perioperative myocardial infarction (PMI) being around 0.9%. However, there is a large subset of patients who develop myocardial injury after non-cardiac surgery, i.e., perioperative increased troponin levels without fulfilling the acute coronary syndrome criteria. Risk stratification scores for MACCE enable clinicians to predict these outcomes in patients undergoing noncardiac surgery. Although no specific component of ERAS is found to be beneficial in preventing MACCE, attenuation of surgical stress, maintenance of normovolemia and prevention of fluid shifts and electrolyte aberrations have shown that ERP can decrease the incidence of cardiovascular complications.[11]

Acute Kidney Injury

Acute kidney injury (AKI) after supramajor gastrointestinal surgery is a relatively common complication. Incidence rates range between 3 and 35% for abdominal surgery. Preoperative optimization of comorbidities, maintenance of normovolemia, avoidance of nephrotoxins, hemodynamic stabilization, and management of postoperative complications such as sepsis, respiratory failure, and renal supportive measures are the basis for management of AKI in the perioperative period. ERAS society initially recommended restrictive fluid strategy, which now has been demonstrated to be associated with increased incidence of postoperative AKI.[12] However, postoperative AKI diagnosed by RIFLE/KIDGO criteria are seen as minor elevations in creatinine, which return to baseline before discharge. Nevertheless, AKI increases severity of postoperative morbidity and mortality and also the likelihood of progression toward chronic kidney disease. It is also associated with increased LOS and cost.[13] The incidence of AKI was significantly higher (11.4% vs 2.3%) despite a favorable association between

ERP and LOS.[13] This study stresses on the impact of normovolemia during the perioperative period, where both hypervolemia and hypovolemia can lead to detrimental outcomes as shown also in the multicenter RELIEF (restrictive vs liberal fluid therapy for major abdominal surgery) trial.[12]

Surgery-specific Complications Following Supramajor Gastrointestinal Surgery

There is enough evidence in almost all areas of major abdominal surgeries to suggest that ERPs improve outcomes by reducing morbidity and LOS. In this section, we discuss procedure-specific complications and the impact of ERAS on these complications.

Pancreas

Postoperative Pancreatic Fistula

After a major pancreatic resection (Whipple's procedure or distal pancreatectomy), pancreatic fistula can occur causing leakage of pancreatic fluid into the abdominal cavity. Postoperative pancreatic fistula (POPF) can lead to intra-abdominal abscess and occasionally hemorrhage. POPF is defined by drain output of any measurable volume after postoperative day (POD) 3 with the amylase level more than 3 times the upper limit of the institutional normal serum amylase level. This definition has been further modified by ISGPS to include only those fistulas that are clinically significant. There are three grades of POPF (Table 2).[14] The incidence of POPF ranges from 5 to 29% with risk factors such as soft texture of pancreas, small pancreatic duct, high BMI, diabetes, prolonged operative duration, and previous laparotomy. The incidence of POPF is higher in distal pancreatectomy compared to pancreaticoduodenectomy.

There is no clear benefit of minimally invasive surgery over open approaches in the prevention of POPF. However, due to less abdominal exposure and smaller wounds in minimally invasive surgery, risk of infection and septic POPF may be lower. Use of prophylactic octreotide does not reduce POPF; however, an RCT has demonstrated the efficacy of pasireotide, which has a broader affinity to somatostatin receptor subtypes, in the prevention of POPFs in pancreatic resections. Higher compliance (>80%) to the ERP was associated with significant reduction in the rate of clinically significant pancreatic fistula.[15]

Post-pancreatectomy Hemorrhage

Post-pancreatectomy hemorrhage (PPH) can be classified into three grades based on onset, location, and severity (Table 2).[16] Early bleeding is usually related to slippage of ligature, whereas late bleeding is generally associated with POPF and/or intra-abdominal sepsis. By decreasing the incidence of POPF and sepsis, ERP may indirectly have a positive effect on reducing PPH. However, currently, there is no data-suggesting role of ERP in reducing PPH.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) is the inability to tolerate oral diet by the end of POD7 and/or requirement of prolonged nasogastric intubation. There are three grades of DGE as described in Table 2. The incidence of DGE varies from 19 to 57%. In most cases, DGE coexists with intra-abdominal pathology such as POPF, hemorrhage, or sepsis. It is associated with prolonged hospital stay and increased costs. Although DGE is affected by surgical technique and type of digestive tract anastomosis, some studies have shown that adherence to the ERP is associated with reduced incidence of DGE.[17] Artificial nutrition in the form of nasojejunal feeding and/or parenteral nutrition should be used selectively in patients with DGE.

Table 2: Pancreas-specific complications as defined by International Study Group of Pancreatic Surgery (ISGPS)

Postoperative pancreatic fistula		
Grade	*Biochemical*	*Clinical*
Grade A	Drain amylase level >3 times upper limit of normal	No clinical significance
Grade B	Drain amylase level >3 times upper limit of normal	Drain left *in situ* for more than 3 weeks
		Drain repositioned through interventional procedures
Grade C	Drain amylase level >3 times upper limit of normal	Requires re-exploration
		Systemic complications/multiorgan failure
Post-pancreatectomy hemorrhage		
Grade	*Characteristics (onset, location)*	*Severity*
Grade A	Early intra/extraluminal	Mild
Grade B	Early, intra/extraluminal	Severe
	Late, intra/extraluminal	Mild
Grade C	Late, intra/extraluminal	Severe
Delayed gastric emptying		
Grade	*Nasogastric tube required*	*Oral diet not tolerated by postoperative day*
Grade A	From 4th–7th day or reinsertion > POD 3	7
Grade B	From 8th–14th day or NG reinsertion > POD 7	14
Grade C	>14 days or NG reinsertion > POD 14	21

Hepatobiliary

ERAS has been shown to be safe and effective in patients undergoing liver resection with reduced overall complications, shorter stay, and significantly better short-term quality of life with no effect on mortality and liver specific complications.

Post-hepatectomy Liver Failure

International Study Group of Liver Surgery (ISGLS) defines post-hepatectomy liver failure (PHLF) as elevated INR and bilirubin on or after POD5. Preoperative nutritional supplementation, carbohydrate loading, and steroid administration may play a role in prevention of liver failure; however, the evidence to support this is weak.[18]

Bile Leak

ISGLS defines bile leak as biochemically, a drain fluid bilirubin concentration at least three times or peritonitis requiring intervention.[19] Preoperative chemotherapy, major liver resection, and biliodigestive anastomosis have been identified as independent predictors for bile leak. Patients with low risk of postoperative bile leak such as those undergoing left lateral resections and benign lesions resections would benefit from avoiding routine drains in minimizing retrograde infections and promoting postoperative mobility.[20] Both, PHLF and bile leak are classified into three grades as described in Table 3.

Colorectal

Elective colorectal surgery is most suited and likely to gain maximum benefit from ERAS in comparison to other major gastrointestinal surgeries such as hepato-pancreatico-biliary surgery. Some of the ERAS elements such as, perioperative opioid-sparing analgesia, avoidance of nasogastric tubes and peritoneal drains, early oral feedings, and ambulation; minimally invasive surgical approach are utilized far more in colorectal surgeries. Preoperative education and colostomy site selection help patients adhere to an ERAS program. Data from various prospective studies and randomized trials show that ERAS protocols are associated with reduced hospital stay and morbidity, faster recovery, and reduced costs, compared to traditional care in both young and elderly patients.

Anastomotic Leak

Anastomotic leak is the most feared complication after colorectal surgery and associated with high morbidity and mortality. It is multifactorial related to patient, disease, treatment, and surgical procedure. Several RCTs and meta-analysis have shown that there is no advantage of mechanical bowel preparation and routine peritoneal cavity and pelvic drains in preventing/detecting anastomotic leaks. Early enteral feeding does not affect anastomotic leak rates.

Table 3: Hepatobiliary-specific complications as defined by the International Study Group of Liver Surgery (ISGLS)

Post-hepatectomy liver failure	
Grade	*Intervention*
A	Abnormal laboratory parameters but requiring no change in the clinical management of the patient
B	A deviation from the regular clinical management but manageable without invasive treatment
C	A deviation from the regular clinical management and requiring invasive treatment
Bile leak	
Grade	*Intervention*
A	No change in clinical management
B	Active therapeutic intervention, without relaparotomy
C	Requires relaparotomy

Upper Gastrointestinal Surgery

Upper gastrointestinal surgery includes some of the highest risk elective surgical procedures performed and has a potential to gain a large benefit from ERAS. These benefits have been shown in patients undergoing major gastric resections in several meta-analyzes by reducing hospital stay and cost.[21] Major life-threatening surgical complications after gastrectomy include duodenal stump blowout and anastomotic leak, and those with esophageal surgeries include respiratory failure and anastomotic breakdown. A systematic review and meta-analysis evaluating ERAS in esophageal surgery found a significant reduction in nonsurgical and pulmonary complication postoperative LOS.[22] In bariatric surgery, a substantial body of evidence indicates that implementation of ERAS results in shorter hospital stay;[23] however, there remains sparse evidence suggesting increase in rates of complications or readmissions in ERAS patients.

Conclusion

ERAS has revolutionized surgical patient care pathway. Transition from age-old concepts and practices that prevented a return to physiological baseline to an evidence-based dynamic perioperative approach is time consuming, requires reinforcement of core concepts, and willingness to change. There exists conclusive and substantial evidence with concordance among clinicians that ERAS leads to better outcomes by improvement in local systems/processes with lower morbidity and mortality in supramajor gastrointestinal surgery; however, some of the surgery-specific complications may remain unaltered with ERAS. A better understanding of what surgery does to the human physiology and tailoring enhanced recovery pathways to restore equilibrium/homeostasis will enable clinicians to reap the full benefits of this evolving field of surgery.

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