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Enhanced Recovery After Surgery Pathway: How its Implementation Influenced Digestive Surgery Outcomes?

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Abstract

Introduction: In recent years, enhanced recovery after surgery protocols have increasingly been integrated into perioperative care of patients undergoing digestive surgery.

Aims: To conduct a non-systematic literature review related to the integration of enhanced recovery after surgery protocols in elective gastrectomy, colonic and rectal surgery, and the impact this had on outcomes.

Methods: The PubMed database was searched to identify studies that focused on the integration of enhanced recovery after surgery protocols in clinical practice, as well as their outcomes. 37 studies fulfilled the inclusion criteria and were reviewed accordingly between the years of 2007 and 2017.

Results: The enhanced recovery after surgery pathway has shown to reduce time to return of bowel function and to minimize length of hospital stay by at least one day, when compared to conventional care, in colorectal surgery and gastrectomy for gastric cancer. Optimal results are achieved with maximum compliance rates.

Conclusions: The enhanced recovery after surgery protocols may be safely implemented in colorectal surgery and gastrectomy for gastric cancer, producing improved patient outcomes. An adequate integration of the enhanced recovery after surgery protocols in these areas, with a high compliance rate, is a step towards a faster return of patients to their baseline activity.

Keywords: Enhanced recovery after surgery; Digestive; Gastrectomy; Colorectal; Colonic; Rectal; Gastrointestinal

Abbreviations: ERAS: Enhanced Recovery After Surgery; CHO: Complex Carbohydrates; ASA: American Society of Anesthesiologists; MBP: Mechanical Bowel Preparation; DVT: Deep Venous Thrombosis; LMWH: Low Molecular Weight Heparin; VTE: Venous Thromboembolism; LOSH: Length of Stay in Hospital; PONV: Postoperative Nausea and Vomiting; EDA: Epidural Analgesia; RCT: Randomized Controlled Trial; PCA: Patient Controlled Analgesia; BIS: Bispectral Index; TAP: Transversus Abdominis Plane; ED: Esophageal Doppler; NG: Nasogastric; BD: Bladder Drainage; UTI: Urinary Tract Infection; NSAIDs: Non-steroidal Anti-inflammatory Drugs; ICU: Intensive Care Unit; POD: Postoperative Day; IL: Interleukin; QR: Quality of Recovery.

Introduction

Despite steady advances in surgical and anesthetic techniques over the years, postoperative complications remain one of the major concerns regarding surgical procedures, not only because of the impact on the patient, but also on the health care system in general.

The ERAS programs, originally based on the "fast track" surgery concept introduced by Henrik Kehlet [1], were developed as multimodal perioperative pathways that include multiple interventions that individually produce small insignificant effects, but collectively have a strong synergistic impact on the patients' homeostasis [2]. These protocols strike to attenuate the metabolic stress through perioperative measures, and simultaneously to support the patient's rapid return to baseline function, producing therefore a decrease in complication rates and lessening the recovery time after surgery.

The present literature review aims to gather current scientific knowledge regarding outcomes of ERAS programs in digestive surgery. It was considered important to first briefly review the ERAS items, as it allows for a better comprehension of results. This review focuses on elective digestive surgery, more specifically on gastrectomy and colorectal surgery, for which the ERAS Society published guidelines for perioperative care.

Materials and Methods

This literature review is based on a PubMed search with the following instructions: Title/abstract: ("enhanced recovery after surgery" OR "eras") AND ("gastrectomy" OR "gastric" OR "colon" OR "colonic" OR " colorectal" OR "rectal"). The following filters were applied to the search: species: human; date: 2007-2017.

From the 131 articles found, 37 were selected for review. The excluded papers regarded non-elective surgery (e.g. emergency context), surgery of fields other than colorectal and gastric (bariatric surgery not included), studies that focused on the elderly or on the pediatric population, studies that used modified ERAS protocols, publications related to cost-effectiveness of ERAS protocol implementations, or because they did not adjust to the topics reviewed in this article. No procedure specific ERAS items have been revised.

Additional articles were referenced as they were found relevant for the debate of the state of the art of the subject.

Results

Surgical stress

The stress response to surgery is activated through the nervous system, which mainly results in hematological, immunological and endocrinological responses. The extent of this response correlates with the degree of tissue injury, which may be posteriorly amplified by postoperative complications [2,3].

Stress response is proportional to the extension of the surgical wound, the degree of internal organ manipulation and tissue dissection and reflects increased demands on organ function [2].

The hormonal changes produced result, as an overall, in a hypermetabolic status where most biochemical reactions are accelerated. In evolutionary terms, it seems likely that this stress response was developed as a protective mechanism that aims to provide maximum chances of survival, through the increase of cardiovascular functions, volume preservation and mobilization of substrates [3-5]. In current surgical and anesthetic practice, it is questionable if this stress response is necessary as it turns out that a prolonged hypermetabolic state may result in the body's exhaustion, causing loss of weight, decreased resistance, delayed ambulation and increased morbidity and mortality [3,5]. This considered, in modern surgical practice, efforts are made to minimize the stress response [6].

Minimizing surgical injury through the eras pathway

The ERAS pathway strike to attenuate the physiological stress response to surgery and maintain preoperative organ function. The ERAS protocols include measures integrated before, during and after the surgical procedure.

Preoperative Items:- 1. Information, education and counseling: Preoperative anxiety, emotional distress and depression have been associated with higher complication rates, greater postoperative pain, cognitive disturbances and delayed convalescence [2].

Giving the patient, as well as of the caregivers, information about the surgical and anesthetic procedures is essential to reduce anxiety and to facilitate active participation in the recovery process [2,7-9]. Indicating specific daily targets for the postoperative period may facilitate eating, mobilization, pain control and respiratory function, therefore reducing complication risk [8].

In the case of patients undergoing rectal surgery, it is important to add specific information regarding the marking and management of stomas [9].

2. Preoperative medical optimization: The impact of preoperative physical conditioning on surgical outcomes is controversial, and increasing exercise preoperatively may benefit the patient's recovery [7-9].

Preoperative optimization also involves alcohol and smoking cessation and abstinence for at least 4 weeks before the surgery, to reduce the incidence of complications related to these habits [7-10]. Alcohol abusers have a two-to-threefold increase in postoperative morbidity, the most frequent complications being bleeding, wound and cardiopulmonary complications. Smokers have an increased risk for postoperative pulmonary and wound complications [7].

3. Fasting and carbohydrate loading: Standard care follows fasting guidelines supported by multiple anesthesia societies, that recommend that clear fluids and solid food should not be ingested 2 h and 6 h, respectively, before the induction of anesthesia. Although this is the recommendation, it is not uncommon for patients scheduled for elective surgery to fast since midnight [7,10]. There is no scientific evidence that fasting from midnight reduces the risk of pulmonary aspiration in elective surgery [7], and this practice has been shown to increase insulin resistance, produce patient discomfort [8] and potentially decrease intravascular volume [7,10].

Preoperative treatment with complex carbohydrate (CHO) drinks attenuates the catabolic state induced by overnight fasting and surgery, allowing patients to undergo surgery in a metabolically fed state [9]. The increase of preoperative insulin levels, reduces postoperative insulin resistance [9], maintains glycogen reserves, decreases protein breakdown and reduces the loss of muscle strength [2,7,9,10]. In addition to this, treatment with CHOs also has been shown to reduce preoperative thirst, hunger and anxiety [7,9]. Faster surgical recovery, as a consequence of this practice, still remains controversial [10].

Preoperative treatment with CHO drinks, following the "preoperative fasting status" ASA recommendations, is advised for all non-diabetic patients [9], and may be safely administered except in emergency surgeries [10,11], and in patients with documented delayed gastric emptying or gastrointestinal motility disorders [10,11]. Obese patients have been shown to have the same gastric-emptying characteristics as slim individuals. Diabetic patients with neuropathic affectation may have delayed gastric emptying for solids, which may increase the risk of regurgitation and aspiration. There isn't any conclusive data relating to delayed fluid emptying. In diabetic patients without neuropathy, gastric emptying has been reported as normal, and CHO drinks may be given along with diabetic medication [7].

4. Bowel preparations: Lately, the use of mechanical bowel preparation (MBP) has been strongly questioned. This practice, not only is distressing to the patient, but also causes dehydration and is associated with prolonged ileus after colonic surgery. In addition to this, the use of MBPs, on colorectal surgery, has been shown to increase the incidence of spillage of bowel contents, increasing the risk of postoperative complications [7]. However, when a diverting ileostomy is planned, MBP may be necessary [9]. If, for any reason, intraoperative colonoscopy might be carried out, MBP is also advised.

Most of the randomized control trials conducted on this matter, are focused on open colorectal surgery, therefore, extrapolating these results to laparoscopic surgery may be questionable [7].

According to ERAS Society recommendations, in gastrectomy, MBP should not be used [8].

5. Antibiotic prophylaxis and skin preparation: The use of prophylactic antibiotics with aerobic and anaerobic coverage, in colorectal surgery, has shown to reduce postoperative infectious complications. In gastrectomy and colorectal surgery, intravenous antibiotics should ideally be administrated 30-60 min before the first surgical incision [7,8]. A multidose regimen may be preferred in prolonged surgeries (>3 h), whenever it is appropriate considering the antibiotic's pharmacokinetics [7-9]. The optimal combination of antibiotics is still not defined, however the combination of

metronidazole and an aerobic antibiotic is often recommended. New generation drugs should be reserved for infectious complications [9].

A study comparing the use of povidone-iodine and chlorhexidine-alcohol in skin cleansing concluded that the latter is superior in preventing infectious complications [8,9], being associated with a 40% lower prevention of surgical site infections. The use of chlorhexidine-alcohol, however, may be a risk factor for burn injuries whenever diathermy is used [7].

6. Thromboprophylaxis: All patients undergoing abdominal or pelvic surgery should receive mechanical thromboprophylaxis with well-fitted stockings, as they have been shown to significantly reduce the incidence of deep venous thrombosis (DVT) in hospitalized patients. Intermittent pneumatic compression should be considered, above all, in patients with risk factors for thromboembolic events [7-9]. Risk factors include previous pelvic surgery, preoperative treatment with corticosteroids, malignant disease [7,9], major surgery, long periods of recumbence, chemotherapy [8] and other hypercoagulable states.

The benefits of pharmacological prophylaxis with low-molecular-weight heparin (LMWH) or unfractionated heparin in the prevention of venous thromboembolism are well established [7,8], they reduce the prevalence of symptomatic venous thromboembolism (VTE) without increasing side effects such as bleeding [9]. However, the benefit of extended (28 days) prophylaxis after discharge, is less consensual. Extended prophylaxis has been shown to significantly reduce the prevalence of symptomatic DVT, but, due to a very low prevalence of this complication in patients who did not receive prophylactic treatment, it is questionable whether a large number of patients should receive thromboprophylaxis to prevent a few symptomatic events [7]. Current ERAS Society guidelines advocate that this treatment should be reserved for patients who had major cancer surgery in the abdomen or pelvis or who have other important risk factors for VTE [7].

It is unknown if the implementation of ERAS protocols and/or the use of laparoscopic surgery, through the promotion of an early recovery, reduce the risk of VTE and, therefore, the need for pharmacological prophylaxis [9].

Incidence of asymptomatic DVT in colorectal surgical patients without thromboprophylaxis is approximately 30%, with fatal pulmonary embolus occurring in 1% of individuals [7].

8. Preanesthesia medication: Data from studies on abdominal surgery, show no evidence of clinical benefit from preoperative use of long-acting sedatives [8]. Their administration is associated with impaired postoperative mobilization and direct participation, resulting in prolonged length of stay in hospital (LOSH) [7,10]. Short-acting anesthetic drugs (e.g. fentanyl combined with small incremental doses of midazolam or propofol) may be safely administered, under monitorization, to facilitate anesthetic procedures (e.g. epidural or spinal anesthesia) previously to the induction of anesthesia, with minimal residual effect at the end of surgery [7].

Preoperative education and counseling may help reduce the need for anxiolytic medication, as well as other ERAS elements, such as the avoidance of MBP and prolonged fasting, and preoperative treatment with CHOs [7].

Intraoperative Items: 1. Laparoscopy: Laparoscopy is a minimally invasive surgical technique that has been shown to decrease inflammatory response to surgery when compared to open approaches. The ERAS Society guidelines recommend that proctectomy and proctocolectomy for benign disease, colonic resection and early gastric cancer gastrectomy be done laparoscopically, if an experienced surgeon is available. In this setting, laparoscopic surgery has shown to be safe and may lower hospital stay and decrease complication rates. However, ERAS Society guidelines do not recommend laparoscopic resection of rectal cancer outside a trial setting, due to lack of equivalent data on oncological outcomes, nor laparoscopically assisted total gastrectomy for advanced cancer, as there is inconclusive data as to the safety of this procedure [7-9].

2. Anesthetic management: Although there are no trials comparing general anesthetic techniques for gastrointestinal surgery [7,8,10], ERAS protocols aim for a minimal impact of anesthetic agents and techniques on organ function, and for a rapid awakening, allowing an early return to baseline activity [10]. To do so, it is sensible to assume that short-acting agents should be preferred.

Short-acting induction agents, such as propofol, combined with short-acting opioids, such as fentanyl or remifentanil, are widely used, as well as short-acting muscle relaxants [7,8,10]. Recently, a review on the use of continuous intravenous lidocaine infusion in the perioperative of abdominal surgery concluded that it provides significant pain relief, reduces postoperative opioid consumption, decreases opioid-induced nausea and vomiting, and promotes a faster return of bowel function, allowing for reduced LOSH. There is a continuous effort to reduce opioid administration because they are associated with several complications, such as respiratory depression, sedation, postoperative nausea and vomiting (PONV), ileus and urinary retention [11,12]. A recent RCT in patients undergoing colorectal surgery with the ERAS program, showed no difference between continuous lidocaine infusion and thoracic epidural analgesia (EDA), in return of bowel movements and LOSH, whilst another RCT focused on patients undergoing laparoscopic gastrectomy showed a reduction in postoperative fentanyl consumption and pain with lidocaine infusion by patient-controlled analgesia (PCA) [8].

Muscle relaxants can be titrated using neuromuscular monitoring, allowing for administration of the minimal dose necessary to produce the intended effect. The maintenance of a deep neuro-muscular blockage is essential to allow adequate vision and surgical access [7], particularly in laparoscopic surgery [8]. Despite this, reversal of profound muscle relaxation, can occasionally be incomplete. In these cases, the use of sugammadex to counter act the action of large doses of muscle relaxants, has proven to facilitate recovery [9].

The maintenance of anesthesia can be made using inhalation anesthetics or intravenous anesthesia, in which case, target controlled pumps may be used. These are especially useful in patients with susceptibility to PONV [7]. Short-acting agents should also be used in maintaining anesthesia, always adjusted the estimated duration of surgery.

Depth of induction and maintenance anesthesia can be monitored using the bispectral index (BIS) monitor, which enables titration of the minimum amount of anesthetic necessary to avoid complications [7-10]. Anesthetic depth guided by BIS is a key aspect in preventing awareness and in allowing for a faster immediate recovery, although time to discharge home seems unaffected [10]. To this effect, BIS index should be between 40 and 60. Studies have highlighted that too deep anesthesia should be avoided, as this reflects increased suppression of brain activity and can lead to postoperative confusion, mainly in the elderly [10].

Regional anesthetic blockage, used in addition to general anesthesia, can minimize the need for postoperative intravenous opiates and reduce the stress response. This includes a reduction in insulin resistance, an important causing mechanism of postoperative hyperglycemia [7].

Another important component of the anesthetic management is the regulation of ventilation and airway. Attention to intubation techniques is important to reduce risk of micro-aspiration and subsequent postoperative lung infection. To this end, adequate sized endotracheal tubes with cuff-pressure control should be used [7]. Lung ventilation with low tidal volumes, limiting peak air pressure, is suggested to reduce the risk of barotraumas [9].

Surgical stress demands for an increased fraction of inspired oxygen, to overcome hypoxia under anesthesia. It has been suggested that, in patients undergoing general anesthesia, high inspired oxygen concentrations (>80% [9]) reduces the prevalence of surgical site infections. Other than this, it is also said to reduce the incidence of late (>24 h postoperatively) nausea and vomiting, in patients receiving volatile anesthesia without antiemetic prophylaxis [10]. It has been suggested that excessive use of high concentrations of inspired oxygen on cancer patients undergoing abdominal surgery can have deleterious long-term effects and that using 100% inspired oxygen may be associated with an increased risk of atelectasis. Therefore, inspired oxygen concentration should be titrated to produce normal oxygen saturations, avoiding both hypoxia and hyperoxia [10].

3. Regional anesthetic techniques: Insertion of a thoracic epidural catheter is useful in open and laparoscopic procedures to provide improved pain management. Local anesthetics can be administered throughout the procedure, either in bolus or in a continuous infusion [9]. An optimal postoperative analgesia provides an adequate pain relief, early mobilization, early return of gut function and feeding, without associated side effects [7]. Interestingly, a RCT [13] in context of colectomy, showed that, although EDA produces superior pain control, LOSH is not reduced [7].

For open midline laparotomy, EDA has been established as the ideal. EDA using local analgesics (e.g. lidocaine) and low-dose opioids has shown to be superior to intravenous opioid-based alternatives, regarding outcomes such as postoperative pain [7,8] (superior analgesia in the first 72 h following surgery), PONV and pulmonary complications [7]. In this context, EDA was also associated with improved postoperative pulmonary function, decreased risk of pneumonia, improved arterial oxygenation, reduced insulin resistance and a lower rate of postoperative ileus [8].

In laparoscopic surgery, studies regarding colorectal surgery have shown that different epidural blockage levels produce different effects on gastrointestinal function: low-thoracic epidural wasn't associated with benefits, on the contrary, mid-thoracic epidural showed significantly earlier return of flatus, defecation and tolerance of oral diet, when compared to intravenous opioid analgesia [7]. Another study [14], comparing spinal analgesia, PCA with intravenous morphine, and low thoracic epidural anesthesia concluded that patients with the latter had a longer LOSH [7].

EDA causes an extended sympathetic block, which may compromise tissue perfusion. The adequate use of vasopressors to prevent this side effect, provided that the patient is not hypovolemic [7], allows for EDA to be safely used and to its full potential [8]. This adverse effect appears to be attenuated using a combination of low-dose local analgesics and opioids [7]. Other concerns regarding EDA lie with the fact that up to one-third of epidurals are dysfunctional, possibly due to catheter misplacement, inadequate dosing or pump failure. To ensure that the catheter is well placed, sensory blockage should be tested previously to anesthesia induction [8].

Perioperative transversus abdominis plane (TAP) blocks have been used in laparoscopic colonic surgery, alongside intravenous paracetamol, to cover lower abdominal incisions. TAP blocks have the disadvantage of being short-acting and that no significant RCT has yet compared the use of TAP with epi- or subdural analgesia [7]. There is limited information regarding the use of this technique in rectal surgery and gastrectomy [8,9].

Subarachnoid long-acting local anesthetics and opioids have been successfully used for colonic and colorectal resection [9]. A recent study [15], in the context of laparoscopic colorectal surgery, concluded that this anesthetic technique allows for earlier mobilization and hospital discharge, when compared to EDA [7].

4. Fluid management: Normovolemia is essential for an adequate organ perfusion. Overload of salt/water and hypovolemia both increase postoperative complication rates [8]. Use of goal-directed fluid therapy using minimally invasive cardiac output monitoring, such as the esophageal Doppler (ED), can help optimize fluid management [7,9]. Use of ED in major surgery has demonstrated reduced LOSH and complication rate [8,9], faster return of bowel function, less PONV, and lower incidence of acute kidney injury [7]. Balanced crystalloids have proved to be superior to 0.9% saline solution for the maintenance of the electrolyte balance, and should therefore be preferred [7-9].

Attention to arterial pressure values is especially important when epidural anesthesia is administered, due to its effect on vascular tone [7]. Once normovolemia has been established, vasopressors such as neosynephrine or low doses of norepinephrine [9], should be used to avoid intraoperative hypotension and secure adequate organ perfusion.

Fluid shifts should be minimized by avoiding bowel preparation, maintaining preoperative hydration, as well as minimizing bowel handling and exteriorization outside the abdominal cavity [7,9]. Overload of fluids increases the risk of pulmonary interstitial edema, postoperative hypoxia and cardiopulmonary complications, and exacerbates gastrointestinal edema, which may delay recovery of gut function [16].

In colorectal surgery, assuring an adequate gut perfusion is highly important for the integrity of the anastomosis. It depends on mean arterial pressure and cardiac output, since the splanchnic circulation isn't capable of autoregulation [7,9].

Postoperative intravenous fluids should be minimized to avoid fluid excess. The enteral route should be preferably used [7].

5. Nasogastric intubation: Strong evidence supports that routine nasogastric (NG) decompression, following gastrectomy and colorectal surgery, should be avoided. NG tubes placed during surgery (to evacuate air), should be removed before reversal of anesthesia [7-10]. Gastroesophageal reflux is increased during laparotomy if NG tubes are used [9], as well as complications such as fever, atelectasis and pneumonia [7,9]. The avoidance of NG tubes was associated with a faster return of bowel movements [7-9]. LOSH and gastric discomfort also showed data supporting no NG decompression [7].

6. Maintenance of normothermia: Numerous meta-analysis and RCTs have related hypothermia (definition <36°C), during major

abdominal surgery, with higher rates of would infections, cardiac complications, bleeding, pain sensibility [7,9] and transfusion requirements [8]. Warming in the preoperative period is especially beneficial for patients who will be exposed due to prolonged anesthetic procedures [7,8]. Temperature maintenance during procedure can be achieved by using forced-air warming blankets, heating mattresses, circulating water garment systems [7]; evidence supports that the latter offers superior temperature control than forced-air warming systems [8]. Also, intravenous fluids should be warmed prior to administration [7]. Patient core temperature should be monitored and maintained in an adequate range [7,9]. Heating or humidifying the carbon dioxide used for insufflation in laparoscopic surgery has not improved temperature maintenance or pain scores postoperatively [7].

7. Urinary drainage: Bladder drainage (BD) is used during and after major abdominal surgery to monitor urine output and prevent urinary retention [7]. Increased BD duration is associated with increased rates of urinary tract infection (UTI) [7]. Early removal is recommended, ideally ≤ 24 h postoperatively [8,9]. If EDA is used, there is an increased risk of urinary retention [17], but, after 24 h of catheterization, this risk is low [9].

Several RCTs have reported that suprapubic catheterization, compared to transurethral, causes less discomfort and is associated with lower rates of UTI, however, the duration of catheterization in these studies was ≥ 4 days [7-9]. This method is recommended for patients with increased risk of prolonged postoperative urinary retention [9].

Postoperative items: 1. Perianastomotic Drainage: ERAS Society Guidelines for perioperative care in elective gastrectomy, colonic and rectal surgery agree that abdominal drains should be avoided to reduce drain-related complications and reduce LOSH [7-9]. Studies presented in the gastrectomy guidelines state that, after gastrectomy, there is no significant difference in postoperative course, namely in time to first bowel movement, oral intake of light diet or LOSH between patients in whom drains were and were not used. In fact, it is even defended that drainage increases LOSH, postoperative morbidity, time to oral intake and causes more frequent reoperations [8].

In colorectal surgery, it was costume to drain the abdominopelvic cavity to prevent accumulation of fluids and anastomotic leakage. However, studies have found that the use of drains after colorectal surgery doesn't affect the rate of anastomotic dehiscence or overall outcomes [7,9]. ERAS Society Guidelines for perioperative care in elective colonic surgery state that drainage systems are a setback to independent mobilization [7].

2. Analgesia: Adequate postoperative pain management may reduce the extent of surgery-induced immunosuppression and inflammation. Patients who experience adequate analgesia, demonstrate decreased levels of pro-inflammatory cytokines and increased lymphocyte activity [6]. Postoperative analgesia is based on a multimodal regimen that aims to avoid the use of opioids [7], due to their multiple adverse effects, which may prolong the LOSH [12].

When EDA is used in abdominal surgery, it should be maintained for at least 48h and, after a successful stop test, replaced by oral analgesia. If necessary, EDA may be prolonged [8]. In the context of colorectal surgery, the aim is to remove the catheter ≈ 48-72 h postoperatively, by the time the patient has had bowel movements [7,9]. In rectal surgery, there is extensive tissue dissection and many patients will even have preoperative pain which may be neuropathic, partially due to neoadjuvant treatments, which will difficult pain management and require a multi-pharmacological approach that includes, for example, the combination of EDA with systemic opioids [9].

A RCT [18], for patients submitted to gastrectomy in gastric cancer context, concluded that patient-controlled EDA is more effective in pain control, and in reducing stress response, than patient-controlled intravenous analgesia, enabling a faster return of normal bowel activity [8].

In the context of laparoscopic surgery, the duration of postoperative pain that requires major analgesics is much shorter than for open surgery, which allows for discharge as soon as 23 h following surgery [7]. The faster recovery associated with this technique, allows for toleration of early feeding, which implies that analgesic requirements can be met through oral multimodal analgesia, avoiding the need for regional blocks or strong analgesics [7].

Multimodal analgesia with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) has shown to spare opioid use by 30% [9]. Paracetamol may be administered up to 4 times a day, in an intravenous preparation of 1 g. Clinical trials, in colorectal surgery, have related the use of NSAIDs (diclofenac and celecoxib) with an increased risk of anastomotic dehiscence [7,9]. Nowadays, there isn't enough evidence supporting that NSAIDs should be abandoned, more studies regarding this question are needed [7]. No medication has yet been recommended for routine use [7,9], however, there are several ongoing studies on opioid alternatives for the relief of postoperative pain [7].

3. Control of glucose: In surgical stress context, there is a generalized catabolic, hyperglycemic response that leads to insulin resistance [4,5]. Insulin resistance is associated with increased morbidity and mortality after major gastrointestinal surgery [7,8]. Hyperglycemia is a major predictor of adverse post-surgical outcomes, exerting inflammatory action and possibly increasing predisposition to infection. Hypoglycemia is equally dangerous as this state adversely affects the circulatory and both the autonomic and central nervous systems [19].

Several ERAS items attenuate insulin resistance, the most obvious ones being: no preoperative fasting and MBP; oral CHO treatment and stimulation of bowel movements through optimal fluid balance; avoidance of systemic opioids; early mobilization; and lessening of the overall stress response by using EDA whenever possible [7,8]. These treatments have the added advantage of not carrying risk of hypoglycaemia [7].

Treatment of hyperglycemia in postsurgical patients in the intensive care unit (ICU) may require the need for insulin, however, this carries the risk of hypoglycemia and, therefore, should only be used when strictly necessary [7]. The optimal target glucose levels remain uncertain [7-9].

4. Prevention of nausea and vomiting: PONV following a standard anesthetic procedure using inhalational anesthetics and opioids, and without any PONV prophylaxis, affects up to 30% of all surgical patients. PONV is an important cause of delay in postoperative feeding and recovery [9]. There are several PONV scoring systems (e.g. Apfel score) stratifying patients from low-to-high risk groups. These scoring systems serve to help guide antiemetic prophylaxis, and in several RCTs have proven to reduce PONV, however, they still haven't been widely implemented in routine practice [7]. Multimodal regimens should be adopted in patients with ≥ 2 risk factors undergoing major

colorectal surgery or gastrectomy [8,9]. A multimodal approach to PONV includes antiemetic medication and non-pharmacological techniques, as the avoidance of inhalational anesthetics and of increased propofol doses in induction/maintenance, minimal preoperative fasting, carbohydrate loading and adequate hydration [7].

5. Perioperative nutritional care: An early resumption of normal oral feeding following major abdominal surgery is associated with a decreased rate of infectious complications and faster recovery, however early feeding seems to be associated with an increased risk of vomiting [9].

An RCT, in colorectal surgery context, that combined preoperative treatment with oral CHO, EDA and early oral feeding showed an improved nitrogen equilibrium whilst maintaining normal glucose concentrations, without the need for insulin administration [7].

ERAS Society guidelines for patients submitted to rectal surgery, recommend that this group of patients begin oral ad libitum diet 4h after surgery [9], whilst ERAS Society guidelines for patients who underwent colonic surgery state that, in the postoperative phase, patients can drink and eat normal hospital food, immediately after recovery from anesthesia [7]. Early oral diet has been shown to be safe in patients with a non-diverted colorectal anastomosis [9], not affecting the risk of anastomotic dehiscence [7]. There is doubt if normal food intake is enough to prevent postoperative weight loss and, therefore, it is recommended that patients be offered oral nutritional supplements to maintain adequate protein and energy intake [7].

Patients subjected to total gastrectomy are probably at a greater risk of malnutrition and cachexia at the time of surgery [8]. All patients with risk of malnutrition/nutrient deficit should receive special nutritional considerations. In severely malnourished patients, supplements have a greater effect if initiated 7-10 days preoperatively [7]. A prospective observational study [19,20] of an ERAS program for colorectal surgery concluded that malnourished patients were at risk for delayed recovery of gastrointestinal function, prolonged LOSH and increased postoperative morbidity.

No trial has reported adverse effects from the attempt of introducing early introduction of oral feeding in patients who underwent gastrectomy [8]. ERAS Society [8] recommendations for gastrectomy state that patients should be offered drinks and food at will from postoperative day (POD) 1, with the advice to begin cautiously and increase intake according to tolerance. Malnourished patients or patients unable to meet 60% of daily requirements by POD6, should be given nutritional support.

In several studies in the context of traditional care, immunonutrition diets (special preparations to enhance immune function in surgical patients) have shown to reduce the rate of complications and shorten LOSH, but results are heterogeneous. Evidence suggests that it is more effective in malnourished patients. There are no RCTs conducted in the ERAS setting [7].

6. Stimulation of gut movement and prevention of postoperative ileus: Postoperative ileus is one of the most common occurrences after abdominal surgery, causing delayed recovery, increased LOSH and medical costs [21]. The elimination of ileus, allows for earlier initiation of enteral nutrition, which is essential to reduce risk of infection [5]. Strategies to reduce the risk of postoperative ileus, included in the ERAS pathway, are balancing fluids, avoiding nasogastric tubes [7,9], opioid analgesia, and PONV [2,9].

EDA, compared with intravenous opioid analgesia is highly effective in reducing ileus occurrence [7]. Laparoscopic colonic resection is also associated with a faster return of gut movement, when compared to laparotomy [7,9].

Use of oral laxatives such as oral magnesium oxide or bisacodyl has demonstrated, in different RCTs, a 1-day reduction in time to first defecation. Other outcomes (toleration of oral food, LOSH, morbidity and mortality) weren't altered. In colonic resection, administration of oral laxatives has been associated with faster normalization of gastrointestinal transit [7,9]. No RCTs to this matter have been conducted specifically in rectal surgery, so further studies are needed [9]. Oral alvimopan, approved for clinical use in postoperative ileus, has shown to accelerate gastrointestinal recovery, whilst reducing the LOSH in patients who underwent open colonic resection, having postoperative opioid analgesia [7]. Current recommendations state that oral laxatives should only be used when opioid analgesia is administered [7]. It is not yet known if stimulant laxatives are associated with an increased risk of anastomotic dehiscence, further studies are necessary [9].

Chewing gum is a safe strategy that seems to have a positive effect on postoperative duration of ileus after gastrointestinal surgery [7], reducing time to first bowel movement by 1-day [9]. This strategy has shown no impact on LOSH [9]. Efficacy on colorectal surgery has been demonstrated, but RCTs specifically concerning gastrectomy are lacking [8].

8. Early mobilization: Prolonged bed rest is a risk factor for several complications, such as thromboembolism, prolonged ileus, increased insulin resistance, loss of muscle and strength, pulmonary depression and reduced tissue oxygenation [7,9]. Early mobilization should be encouraged since the first postoperative day, but for a limited number of hours [7-9].

Available RCTs show no direct clinical advantage of early mobilization, however disadvantages of prolonged immobilization are well supported [7].

Postdischarge Items: 1. Audit of compliance and outcomes: Auditing of compliance and outcomes is the last phase of the ERAS protocol. Regular auditing and standard measuring is essential to determine clinical outcome and confirm the adequate implementation of the protocol. It is crucial though to distinguish an unsuccessful implementation from lack of aimed results [8].

Auditing ERAS protocols has three main dimensions: measurement of clinical outcomes such as LOSH, complication and readmission rates; evaluation of patient experience and functional recovery; assessment of degree of compliance [7].

The ERAS Society has created an online interactive software, the ERAS® Interactive Audit System, to facilitate protocol implementation. This tool not only collects data on the patient, treatment and outcomes, but also provides relevant feedback on clinical outcomes that are important for the patient and the healthcare team [7].

Systematic audit has shown to improve compliance and clinical outcomes [8], and helps to understand where there is space for modifications and improvements.

Outcomes

Colonic surgery

A comprehensive medical record review, developed by Haverkamp et al. [22] for laparoscopic colectomy, stated a significant difference in LOSH in patients who received the ERAS perioperative care (median: 4 days *vs.* 6 days, p<0.007). Time to return of bowel function was 1 day less in the ERAS group (p<0.001). No significant differences were noted in postoperative procedure-related complications, 30-day morbidity and mortality, readmission and reoperation rates. Haverkamp et al. [22] suggest that these results are the effect of the combination of the ERAS protocol with laparoscopic colectomy. The design of this study is limited by the fact that it lacks both blinding and randomization, but results are in agreement with data from other studies.

Bakker et al. [23] studied, over the course of 8 years, the impact that adherence levels to ERAS protocols had on LOSH, following colon cancer resection, concluding that they relate inversely. Years with high adherence to protocol had a shorter LOSH than years with low adherence (5.7 days *vs.* 7.3 days, p<0.001). It was noted, however, that there was a variation in the percentage of laparoscopic resections over the 8 years, which may have influenced results on LOSH. Cakir et al. [24] also reported that strict adherence to the ERAS protocol resulted in lower LOSH and improved outcomes in colon surgery for malignancy. In colorectal laparoscopic surgery, Pisarska et al. [25] reported consistent findings by showing that improvement of protocol compliance leads to better treatment results and convalescence parameters, even when groups with high and very-high compliance rate are compared. Pisarska et al. [25] only analyzed short-term results, whereas Gustafsson et al. [26] demonstrated that the risk of 5-year cancer-specific death in colorectal cancer is lower by 42% in groups with ≥ 70% compliance in comparison to <70%. Although this last study demonstrates a striking relationship between adherence to protocol and cancer survival, this may not imply a cause and effect association between them – the study doesn't present evidence of mechanisms behind this effect. Several other studies have demonstrated that an improved adherence to the ERAS protocol, is associated with lower LOSH and improved clinical outcomes following colorectal surgery [27-30].

Rectal surgery

Recently, two cohort studies comparing ERAS and conventional perioperative care reported similar results: Teeuwen et al. [31] studied results in open rectal surgery, and Huibers et al. [32] in laparoscopic total mesorectal excision for rectal cancer. Both studies showed significantly shorter LOSH in the ERAS group [(median: 8 days *vs.* 12 days, p<0.005) and (median: 7 days *vs.* 10 days, p<0.001), respectively], with no significant difference in mortality, morbidity, and readmission rates between groups. Functional recovery was also faster in the ERAS groups, with reduced time to first bowel movement (p<0,001, for both studies). Teeuwen et al. [31] noted a trend towards more readmissions in the ERAS group, however this difference was not significant (17.1% *vs.* 7.3%; p<0.203). While these studies demonstrated a benefit in terms of LOSH in the ERAS group, caution must be exercised in interpreting these results due to their lack of randomization, which gives room for potential bias and confounding.

Colorectal surgery

In a RCT, Mari et al. [33] demonstrated that the ERAS protocol, applied to colorectal laparoscopic procedures, reduces the surgical stress response by diminishing levels of important proinflammatory elements, more specifically IL-6 and C-reactive protein. This attenuates the liver's protein synthesis switch from physiological to acute phase inflammatory proteins, allowing for an earlier liver function resumption.

Ren et al. [34] concluded, in a 597-patient RCT, that the ERAS protocol attenuates the surgical stress response, by reducing the postoperative insulin resistance index, and cortisol and cytokine levels in the ERAS group, comparing with the control group (p<0.001). The ERAS group had decreased LOSH (5.7 ± 1.6 days *vs.* 6.6 ± 2.4 days) in comparison with the controls. This study, however, modified one item of the ERAS protocol: traditional Chinese herbal medicine with acupuncture was used to promote gut motility, instead of common drugs such as magnesium oxide. It is not known to what extent this may have influenced results.

Zhuang et al. [35], in a meta-analysis of 13 RCTs (total 1910 patients) found that, in comparison to conventional care, ERAS programs in colorectal surgery are associated with significantly lower LOSH (weighted mean difference, -2.44 days; 95% CI, -3.06 to -1.83 days; p<0.00001). No significant differences were found for readmission rates, surgical complications and mortality. This review found several other studies with consistent conclusions in colorectal surgery, reporting that ERAS programs reduce LOSH [36-42]. Shida et al. [43] found these same results in patients operated for obstructed colorectal cancer. Keane et al. [37] added that time to tolerate light diet and first bowel movements were also significantly reduced in the ERAS group.

In a retrospective review, Smart et al. [44], found that deviation from certain ERAS items at the end of POD1 predicted a delayed discharge after colorectal surgery and consequent ERAS failure: sustained intravenous fluid infusion, dysfunctional epidural, failure to mobilize, vomiting demanding nasogastric tube insertion and re-insertion of urinary catheter, were strongly associated with delayed discharge.

In an interesting study, Shida et al. [45], studied if the lower LOSH associated with the implementation of ERAS programs in colorectal cancer patients is compatible with a better outcome from the patients' point of view. To do so, a 40-item quality of recovery score (QoR-40) was used. QoR-40 measures five dimensions: physical comfort, physical independence, emotional state, psychological support and pain, on the preoperatory and on POD 1, 3, 6 and one month later. On POD6 the global QoR-40 was not significantly different from the baseline level (p=0.06), and one month after surgery the score was almost the same as the baseline score (p=1.00).

A meta-analysis developed by Keane et al. [37] for patients undergoing colorectal surgery, concluded that median primary LOSH (duration of postoperative hospital stay until discharge) and total LOSH (primary LOSH plus any additional days during hospital readmission) were significantly shorter in the ERAS group by one (p<0.004) and three days (p<0.003), respectively, than in the conventional care group. In a subgroup analysis for patients undergoing colonic and rectal surgery, it was noticed that in the latter subgroup, differences in length of stay were less pronounced, probably due to special requirements of this group of patients, namely regarding stoma management and urinary catheter removal.

Pędziwiatr [46] investigated if there were differences in short-term outcomes between laparoscopic surgery for colonic and rectal carcinoma, in the context of an ERAS program and concluded that LOSH was significantly lower for patients treated for colonic cancer than for those treated for rectal cancer (median LOSH: 4 *vs.* 5; p<0.0464). No statistical difference was found in postoperative complications between groups, nor in the 30-day readmission rates. The study points out as explanations for this difference the fact that there was a higher percentage of patients with stomas in the rectal group, which may prolong LOSH once these patients require training on how to handle the stoma; and the significantly increased use of MBP and postoperative drainage in the rectal cancer group.

Gastrectomy

Unlike with colorectal surgery, ERAS protocols have been less implemented in gastric surgery, and, consequently, there are less studies in this field.

The works published on this area, show that the ERAS protocol can be safely implemented for gastric cancer surgery [47,48]. Makuuchi et al. [49], in a 300-patient case-control study, concluded that the use of the ERAS protocol for gastrectomy in patients with gastric cancer shortened LOSH by 1 day (p<0.001) without increasing complications. The main reason for the shortened stay being the introduction of oral feeding one day earlier. This approach was safely adopted without increased incidence of anastomotic leakage.

Abdikarim et al. [16], in an RCT conducted in patients submitted to laparoscopic assisted radical gastrectomy, showed that time to first ambulation, oral food intake, and time do defecation were significantly sorter in the ERAS group, compared to the conventional one (p=0.04, 0.003, 0.01 respectively). LOSH was also significantly lower in the ERAS group (6.8 ± 1.1 days *vs.* 7.7 ± 1.1 days, p=0.002). Incidence of complications between groups wasn't significantly different (p=1).

Jeong et al. [50] found that female sex and age (≥ 65 years) were significantly associated with a delay in recovery of oral intake, and that total gastrectomy was significantly associated with delayed achievement of adequate pain control.

Discussion

It was noted that, for studies evaluating the same operated organ (stomach, rectum or colon), works related to laparoscopic surgery, when compared to laparotomy, showed lower LOSH [37]. Although this tendency was noticed, no definite conclusions can be drawn, nor is this the aim of the present review. It is also important to consider that in studies comparing ERAS to conventional care in terms of outcomes, if laparoscopic surgery is significantly more common in the ERAS group, this may confound results [37,49].

In most patients, achieving total protocol compliance isn't possible. Even in centers that use ERAS protocols on a routine basis, compliance rate round 60-80% [25]. Many studies do not specify the compliance rate of the ERAS protocols and, between the ones who do, there is lack of uniformity in compliance definitions, which are frequently defined by different cutoff points for common analyzed parameters. A good example of this lies in the definition of early mobilization, which is subjectively determined by authors [25]. A lack of standardization may result in bias when trying to evaluate overall compliance rates.

Most studies concerning ERAS protocols in colorectal surgery include heterogeneous groups of patients operated for colonic/rectal disease, creating a potential bias. There is lack of research focusing specifically on the outcomes of rectal and colonic surgery, under ERAS programs. Each group has special postoperative requirements [37]. Namely regarding urinary catheterization. Rectal dissection involves a greater risk of pelvic autonomic neuropraxia, making this group of patients more likely to suffer urinary retention after and anticipated catheter removal. In addition to this, this type of surgery is more likely to require stoma formation. Stoma-related complications are a common cause for delay in discharge. It seems that rectal surgery patients have longer LOSH than colonic surgery patients, but that they equally benefit from the implementation of the ERAS protocols.

All studies that came up in the PUBMED search for this literature review relate to cancer related gastrectomies [16,47-50]. Therefore, further studies are needed to conclude if the ERAS protocols are safe and effective in gastrectomies due to a different etiology.

Teeuwan et al. [31], in a study focused on rectal surgery patients, noticed a trend towards an increased readmission rate in the ERAS group, although the difference was not significant. This raises the question if early discharge is likely to raise readmission rates. An adequate use of proper discharge criteria should prevent increased readmission rates in fast-track surgery. Other than this, several RCTs [16,31,49] studying the impact of the ERAS protocols did not include the discharge criteria in the publication. It is important for the discharge decision to be made according to standardized criteria and by clinicians who are not involved in the study, to secure that this decision is solemnly based on the patients' condition, and not influenced by the fact that the patient was randomized to the ERAS program.

Given that factors such as sex and age influence recovery time after gastrectomy [50], studies with uneven samples for these two aspects, may have achieved lower/higher results that are influenced by these factors, and not solemnly dependent on the implementation of the ERAS protocol.

It would be interesting to know which key elements of ERAS protocols are mainly responsible for the overall reduction in LOSH, although work developed by Watt et al. [51] states that there is limited evidence of the effect of individual ERAS protocol items in reducing the stress response following colorectal surgery.

Using LOSH as a measure of recovery may be problematic, as this value is influenced by several non-clinical factors, including patient expectations, traditions, availability of communitarian or familial support, insurance status and discharge destination [45]. Furthermore, LOSH is largely dependent on discharge criteria, which still lack standardized uniformization.

Conclusions

The ERAS pathway has shown to be safe and to improve outcomes in gastrectomy (due to gastric cancer) and colorectal surgery, by minimizing length of stay in hospital by at least one day as well as time to return of bowel function.

This was achieved without an increase in complications, readmissions, morbidity and mortality rates, whilst maintaining quality of care.

This multimodal approach reaches optimal perioperative management and results when the compliance level is high.

The implementation of the ERAS pathway in colorectal surgery has shown to successfully reduce the stress response to surgery and to help maintain homeostasis perioperatively, information is lacking regarding impact from this point of view in gastrectomy within an ERAS protocol.

Conclusions on which ERAS pathway elements contribute the most to a reduction in postsurgical hospital stay can't be made from this review. It seems that the collective implementation of the ERAS items is what contributes to a significant impact in length of hospital stay, as opposed to the implementation of the ERAS items individually.

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