

Review

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Enhanced recovery after rectal surgery: what we have learned so far

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How to cite this article: Tebala GD, Gordon-Dixon A, Imtiaz M, Shrestha A, Toeima M. Enhanced recovery after rectal surgery: what we have learned so far. *Mini-invasive Surg* 2018;2:32. <http://dx.doi.org/10.20517/2574-1225.2018.37>

Received: 8 Jun 2018 **First Decision:** 27 Aug 2018 **Revised:** 31 Aug 2018 **Accepted:** 3 Sep 2018 **Published:** 28 Sep 2018

Science Editor: Gordon N. Buchanan **Copy Editor:** Cai-Hong Wang **Production Editor:** Zhong-Yu Guo

Abstract

Enhanced recovery after surgery (ERAS) protocols are gradually becoming the gold standard in the perioperative management of rectal patients. It is a multimodal and multidisciplinary approach that has the great merit to involve and empower the patient and bring him or her back to the centre of the strategy of care. If applied correctly, ERAS can improve the postoperative recovery, reduce the rate of complications and reduce the postoperative length of stay, in patients who had extensive pelvic dissection. The factors within ERAS and their application do not represent rigid schematizations but fluid concepts that may undergo substantial changes as soon as new evidence becomes available. The ERAS principles must be adapted to the specific environment and each team is expected to set up their own programme and quality control criteria. In this comprehensive review, the latest evidence and trend on enhanced recovery after rectal surgery have been critically appraised and presented.

Keywords: Laparoscopic surgery, rectal surgery, enhanced recovery after surgery

INTRODUCTION

The enhanced recovery after surgery (ERAS) programmes have been introduced in the 90s to improve the outcome of patients undergoing major surgery^[1,2]. The concept at the basis of ERAS is to apply the best and most recent evidences of the literature to set up standardized perioperative protocols to improve the postoperative recovery and, only as an obvious consequence, to reduce the length of hospital stay (LOS)^[3-5]. Unfortunately, the name initially used for these new protocols - "Fast Track" - sounded like a suggestion



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to discharge surgical patients too early and probably unsafely and many patients regarded it only as a way to reduce the costs for the hospital, without any benefit for them who, on the contrary, were exposed to serious risks at home for being discharged prematurely. At the same time, many doctors were concerned regarding the possible medico-legal risks, if complications occurred in patients after their early discharge.

On the contrary, the more recent and positive denomination of ERAS evokes a significant improvement of the experience of the patient undergoing major surgery. ERAS protocols aim at optimising the postoperative recovery as they “reduce surgical stress, maintain postoperative physiological function, and enhance mobilization after surgery”^[6].

In fact, it has been demonstrated that elective patients treated with ER protocols recover better and quicker with respect to those treated under the traditional protocols. Time to first flatus, time to full oral intake and time to full mobilisation are reduced within an ERAS protocol with respect to the traditional postoperative care, and this leads to improvements in patient satisfaction and reduction of costs^[4].

General morbidity and specific medical complication rates after surgery are reduced, although the rate of surgical complications doesn't seem to be affected^[7-11]. On a physiological level, the control of insulin-resistance index and the reduction of the levels of cortisol and cytokines with respect to the “traditional” management demonstrate that ERAS yields a reduction of the postoperative stress response and hence the risk of complications^[12].

As a consequence, postoperative LOS is reduced as well^[12,13]. The UK national audit results published in 2015 confirmed that adherence to ERAS pathway is weakly but significantly associated with overall reduction of LOS. The weakness of this association may raise the hypothesis that it is more than single elements of ERAS acting directly on LOS and that ERAS as a whole, yields a mentality change that leads to better postoperative recovery^[14], also in very elderly patients^[15].

Instead of increasing the risk of complications, as initially feared, early discharge seems to be a protective factor towards complications^[12]. Although we feel this may be considered an over optimistic message, it is obvious that discharging a patient early in their postoperative course would allow him or her to recover completely in their own environment, thus decreasing the risk of hospital-acquired infection and other complications linked to prolonged hospitalisation, including psychological issues.

Clearly, it is important that every system is in place to make sure that patients are adequately followed up at home in their early postoperative period, even if by phone only, and they have a clear pathway to access senior review if and when needed.

Furthermore, ERAS allows an early warning for eventual complications. In fact, a patient who does not recover as expected in the postoperative period - delayed recovery of their bowel function, altered vital signs and parameters, difficulty with mobilization - is likely to be developing a complication and this should prompt the early start of the diagnostic-therapeutic pathway to rule out or treat eventual complications. On the contrary, a patient who clinically recovers quickly and completely, whose bowel works normally (no need to wait a full bowel motion, but just the first flatus), his vital signs are normal and pain is easily controllable can be discharged very early (even on the same day if the safety network is in place) with very low risk of complications and readmission.

However, we would expect that a number of patients would develop complications after their discharge and might need to be readmitted. This does not represent a failure of the ERAS pathway, as the outcome of complicated and readmitted patients is not different from the outcome of complicated in-patients who did

not need readmission^[16].

ERAS is by its own nature a multidisciplinary approach, where the paradigm of surgical treatment has been shifted from the surgeon to the team, consisting of surgeons, anaesthetists, physiotherapists, dietitians, physician assistants and specialist nurses. Adherence to the protocols is crucial to get the positive effects of ERAS in terms of better recovery, fewer complications, reduced LOS, reduction of costs and increased patient satisfaction^[17].

Although ERAS principles are gradually spreading to every surgical specialty, due to local or national arrangements, the initial and still greatest interest is in colorectal surgery^[12]. Within this specific field, a further division has been done between colonic^[6] and rectal^[18] surgery. Although this differentiation sounds to us a bit forced - as any excessive subspecialisation - we cannot deny that some issues specific to rectal surgery still exist and will be highlighted in the present review. With respect to colonic surgery, extraperitoneal rectal surgery is often associated with higher risk of complications due to (1) critical blood supply to the rectal stump and the proximal colonic stump in anterior resection due to anatomical reasons; (2) more difficult surgical technique and longer operation time; (3) previous pelvic radiotherapy; and (4) more frequent need for covering stoma. For these reasons, postoperative length of stay is usually longer after rectal resection with respect to colonic resection.

The ER protocols have 3 fundamental steps: (1) preoperative; (2) intraoperative; and (3) postoperative [Figure 1]. This artificial division does not reflect into the reality, as the three components overlap and interlace very often and one influences the others.

PREOPERATIVE STAGE

The preoperative phase of the ERAS protocols is crucial for the success of the whole treatment. For this reason, the full potential of ERAS can be obtained only in elective patients, as those needing an emergency operation may miss this important step. To try and extend the benefits of ER also to patients admitted as emergencies, one of the Authors endorsed a staged approach in patients with acutely complicated colorectal cancer, with an initial damage control procedure followed by an elective resection after the patient has been stabilized and fully investigated and prepared^[19].

However, quite recently, emergency operations have been included into ER protocols, as it was felt that emergency patients can benefit from some of the improvements yielded by ERAS^[20].

Preoperative counseling

One of the great advantages of ERAS is that the patient has been brought back to the centre of the whole experience and has been empowered to take care of him/herself and their recovery. The first meetings with the patient before their surgery are paramount to ensure the correct application of the ERAS protocol.

During the first encounters, after discussing diagnosis and treatment, the patient is offered to be included into the ERAS programme. Actually, the advantages of ERAS versus the traditional perioperative protocols have already been extensively demonstrated, so in our opinion there is no need to consider ERAS as a “special” measure and the ERAS principles must be considered at the basis of the standard and routine management of surgical patients. Placing special attention on ERAS - with specific paperwork - makes it appear as if it is still a sort of “experimental” treatment needing a “special” consent - which is clearly not the case.

It is true, however, that patients must be accurately informed before the operation, which is best practice anyway, of the kind of management they can expect before, during and after surgery. All the elements must be discussed, including bowel and systemic preparation, DVT and antibiotic prophylaxis, surgical

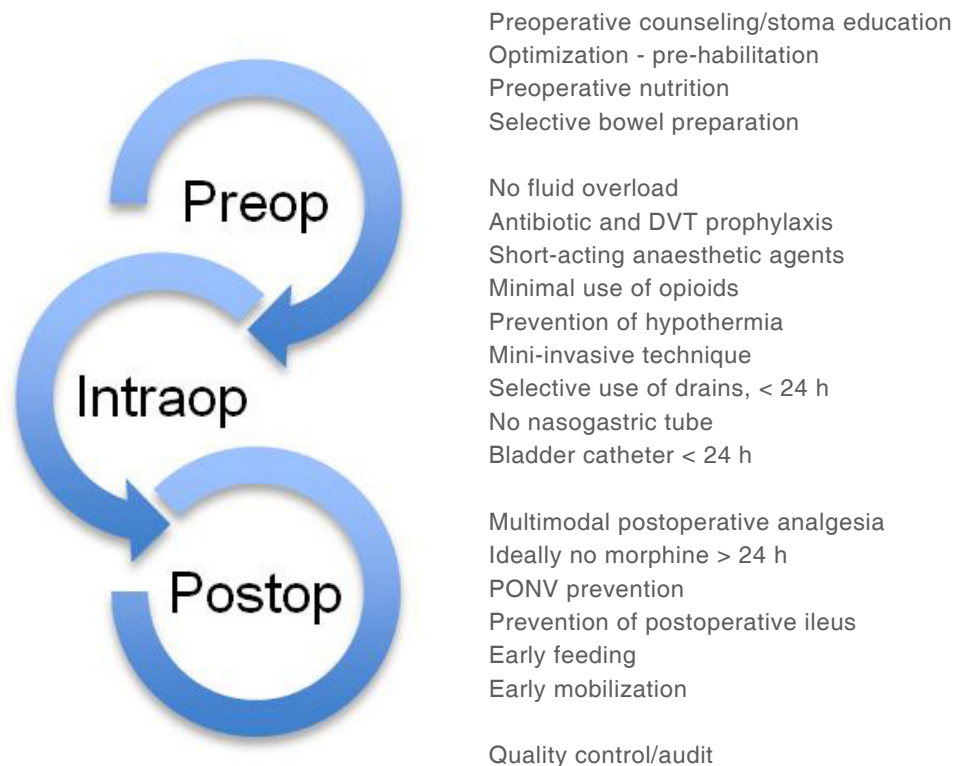


Figure 1. ERAS flowchart

technique, postoperative diet, mobilization/rehabilitation and pain control. In particular, the discharge must be prepared well in advance, in the preoperative period, and all the systems must be put in place for a safe return home. Involvement of the patient and their family (not only providing information) is crucial. A recent non-blinded randomized controlled trial from Norway clearly showed the value of extensive counseling within an ERAS programme in colorectal surgery. Patients who received repeated information preoperatively showed a more efficient engagement in some elements of the ERAS programme such as early feeding and early mobilization after surgery, thus reducing their LOS by 2 days with respect to the patients who received only standard information^[21].

In our practice, the patient has at least 3 important meetings before surgery: (1) with the consultant surgeon, who communicates the diagnosis, offers and discusses the treatment and introduces ERAS; (2) with the anaesthetist, who provides preoperative optimization of the patient, discusses the pre, intra and postoperative anaesthesiological management and explains the ERAS in more detail; and (3) with the colorectal nurse who is responsible for a holistic approach and oversees some particular elements of the ERAS protocol. Sometimes the colorectal specialist nurse can be in charge of the ERAS protocol as well as the preoperative stoma teaching and site marking. In fact, the creation of a stoma is itself a contributory factor of prolonged LOS, therefore with the ERAS protocol we should aim at reducing the impact of stomas on the postoperative recovery. Stoma education is more effective if initiated in the preoperative period^[22]. It is mandatory that that criteria and pathway for discharge are discussed with the patient at this stage^[23].

Optimization

During the preoperative meetings, all the comorbidities are fully investigated and the patient is optimized for surgery, including quitting smoking and alcohol, rebalancing their sugar levels and addressing their nutritional needs. Clearly, the optimization process needs time, and the ERAS Society guidelines suggest that

preoperative counseling must take place 4 weeks before surgery^[18].

Despite some less than enthusiastic report^[24], pre-habilitation is becoming a key factor in increasing the functional capacity of the patient before an operation^[25,26]. It has been defined as a multimodal protocol involving not only nutritional assessment and support, but also physical exercise. Typically, patients considered for prehabilitation are recruited in a 3 or 4-week supervised physical training associated with unsupervised home exercises. This schedule has been demonstrated to be beneficial to improve the cardio-pulmonary exercise test scores^[27,28] and to significantly reduce LOS and length of recovery^[28,29]. The effect of prehabilitation as opposed to standard rehabilitation is more evident in sedentary people^[30].

It is clear that this protocol is time-consuming and may delay curative surgery for cancer. In particular in the countries, such as the UK, where cancer targets exist and require the operation to be performed as soon as possible after the diagnosis, prehabilitation has not been diffusely accepted yet due to the fears that a prolonged preoperative interval would impair survival^[31]. However, a recent prospective study from UK has demonstrated that time from diagnosis to surgery - either 4, 8 or 12 weeks - does not impact on survival, so the regulatory pathways can safely be changed to accommodate prehabilitation^[32]. A few prospective trials are still ongoing and are targeted at assessing the value of physical prehabilitation in patients scheduled for colorectal surgery^[28,33-35]. We are looking forward to evaluating their results. However, it should be universally clear by now that prehabilitation should be included in every ERAS protocol, possibly adding also anxiety-reduction techniques which may benefit both the psychological and physical wellbeing of patients undergoing major rectal surgery^[36].

Preoperative nutrition

One of the new concepts highlighted by ERAS is that a correct preoperative nutrition can improve post-operative recovery by reducing the effects of surgical stress. As malnutrition is a negative prognostic factor for LOS and complications^[37], nutritional assessment and support have been included in the prehabilitation programme.

It has been demonstrated that the traditional long fasting before the operation has no advantages in terms of possible risk of inhalation^[38] and, on the contrary, can be detrimental due to the risk of increasing the physiologically stress-related insulin-resistance^[39]. Randomized controlled trials demonstrated that the administration of a specific sugary fizzy drink before the operation could reduce postoperative insulin-resistance, other than hunger, thirst and anxiety^[23]. The preoperative sugar load would improve the metabolism of proteins and nitrogen and reduces the detrimental catabolic effects of surgical stress on the muscular mass and the healing process^[40,41], thus reducing the risk of complications and expediting the recovery.

Recent recommendation of the American Society of Anesthesiologists is that patients should have free access to fluids up to 2 h before surgery and to solid food up to 6 h before surgery, thus resembling a “normal” nutritional pattern^[42]. Particular attention has been suggested - at least initially - to diabetic patients, where sugary drinks can potentially derange their glycaemia. Moreover, patients with complicated type 2 diabetes are known to have an increased risk of delayed gastric emptying, so - at least theoretically - the ERAS recommendations must be applied with special care.

Immuno-nutrition has been recently introduced as a way to reduce complications and improve recovery. The SONVI Study compared an immune-enhancing pre and postoperative nutrition with the traditional hyper caloric hypernitrogenous supplement within an ERAS programme and found that the number of infective complications was significantly reduced in the treated group^[43]. Immuno-nutrition will be further discussed.

Nutritional supplements are mandatory in malnourished patients and preoperative enteral or parenteral feeding should be considered in patients who are not meeting the nutritional requirements.

Bowel preparation

Mechanical bowel preparation (MBP) has always been one of the cornerstones of colorectal surgery and lower gastrointestinal endoscopy, but it may be associated with dehydration and electrolyte imbalance, in particular in high risk patients (advanced age, renal impairment, liver failure). A Cochrane systematic review published in 2005 indicated that MBP does not prevent anastomotic complications and therefore should be avoided^[6,44]. Although it was clear that this review was poorly significant due to high heterogeneity, it was suggested that no patient scheduled for colorectal resectional surgery should have his/her bowel prepared. A RCT trial published in 2010 and a new Cochrane review published in 2011 found that, although bowel preparation would make no difference in colonic surgery, it may be beneficial - and hence used selectively - in patients undergoing rectal surgery^[45,46]. More recent studies seem to give contrasting results.

Two recent meta-analyses on this subject, one conducted in the USA and the other in Europe, propose a totally different approach. Yost *et al.*^[47] from Massachusetts found that MBP associated with oral antibiotics can reduce the risk of anastomotic leak, wound infection and postoperative sepsis, and facilitate the manipulation of the bowel in laparoscopic surgery. On the contrary, the systematic review by Leenen *et al.*^[48] from the Netherlands arrives to the conclusion that MBP does not decrease the incidence of leak, but admits that the study is flawed by the small size of the sample and the heterogeneity of the studies reviewed. Already in 2015 a retrospective study on prospectively collected outcome data from the National Surgical Quality Improvement Program on 8442 patients showed that MBP almost halves the risk of anastomotic leak, ileus and surgical site infection^[49].

The different approach to this issue between the two sides of the ocean reflects in the official guidelines. The 2012 guidelines of the European ERAS Society clearly state, that MBP should be avoided in colonic and rectal surgery^[6,18]. On the contrary, the 2017 ASCRS/SAGES guidelines advocate the use of MBP with oral antibiotics^[23]. This difference can be explained, at least partially, by the fact that the US review took into account more recent evidences, clearly not available 5 years before, but also by the different cultural, and probably financial attitude. Although local guidelines must be developed and validated, it is undeniable that at the moment this is still matter for debate and a definitive answer is yet to come. We feel that with the current status of evidence the ultimate choice must stay with the consultant in charge, as some surgeons may feel more confident to operate on a completely empty and deflated bowel, mostly in laparoscopy, whereas others do not see the presence of a non-prepared bowel as a limitation or increasing difficulty. The role of oral antibiotics associated with MBP is gaining popularity after the studies of Alverdy and his team in Chicago^[50] and the ERAS guidelines of the ASCRS/SAGES^[23].

INTRAOPERATIVE STAGE

Intra and postoperative fluid therapy

The traditional liberal infusion of fluids during and after a major operation, either by open or laparoscopic surgery, has been demonstrated to be one of the causes of prolonged postoperative ileus, probably due to the tissue oedema or sodium excess, and other perioperative complications, therefore it has been suggested to have a more restrictive fluid regimen^[51,52]. The so called “goal-directed fluid therapy” has been considered as the first choice to correctly titrate the amount of fluids to be infused during and after a surgical operation^[53]. Invasive and non-invasive monitoring systems have been used to utilize cardiac output as a guide for fluid infusion^[18,54], but currently most teams prefer to adopt a more “empiric” system, with a low volume of intraoperative infusions followed by free oral fluid in the immediate postoperative period,

at least in elective patients with no important comorbidities. Obviously, cardiac output remains the best indicator of volemia (and oxygen delivery), but pulse, blood pressure and urine output are generally considered good enough to guide fluid infusion in rectal surgery. The growing diffusion of laparoscopic surgery, which entails reduced evaporative fluid loss and reduced blood loss with respect to open surgery, has helped significantly to reduce the amount of volume to be infused. However, the recent RELIEF trial failed to demonstrate a higher rate of disability-free survival and pointed out an increased risk of acute renal failure in patients with restricted fluid infusion^[55]. Although this interesting study is gradually contributing to switching the paradigm of restrictive fluid infusion, we can reasonably admit that at the moment the pathophysiology of fluid infusion during surgery is not yet completely understood and we may still decide case by case on empiric bases until more definitive evidence becomes available.

The vast majority of published articles do not differentiate between colonic and rectal surgery, but rectal surgery is more easily associated with dehydration or hypovolemia due to increased duration of surgery, bowel preparation and possible blood loss in the pelvis, therefore a less restrictive fluid infusion may be advisable.

Our attitude is to reasonably limit the intraoperative infusion to maintain adequate tissue perfusion during the operation and to allow the patient to consume free or clear fluids as soon as he or she is awake and comfortable in the recovery room after surgery. Invasive monitoring of the cardiac dynamics increases the risks, delays the mobilization and raises the costs of surgery, but it may be necessary in selected cases, mostly in unprepared patients.

Antibiotic prophylaxis and DVT prophylaxis

It has been widely demonstrated that systemic antibiotic prophylaxis reduces the risk of postoperative infections^[56]. Both ultra-short term prophylaxis (a single dose before surgery) and short term prophylaxis (a preoperative dose plus 24 h coverage after surgery) revealed effective. It is still a matter for debate what antibiotics should be used. Clearly, they must be active on aerobic and anaerobic so usually a combination of two antibiotics is needed, but the choice is usually left with local policies and protocols. The first dose should be administered within 1 h from skin incision. Apparently, the association of intravenous and oral antibiotic is more effective than intravenous alone^[57]. Much debate has been done recently on the use of intraluminal antibiotics in association with mechanical bowel preparation (see dedicated paragraph), which would be able to reduce the risk of ileus and leak.

DVT prophylaxis has been one of the pivots of the traditional perioperative management for decades. It is well known that the correct administration of low-molecular-weight heparin and the use of thromboembolism deterrent stockings (TEDS) would decrease the risk of DVT and pulmonary embolism. Obviously, this best practice has been integrated into the ERAS protocols.

Anaesthesia

Open rectal surgery usually needs a long abdominal incision, a wide pelvic dissection and sometimes also a perineal incision with severe disruption of the pelvic floor. The laparoscopic approach reduces the trauma of the midline laparotomy, even if often a small laparotomy may still be needed, but increases the operative time and adds the further pathophysiological trauma of a steep Trendelenburg position.

The ERAS principles pertaining to anaesthesia are: (1) short-acting agents to expedite the postoperative recovery; and (2) optimal pain control with minimal use of opioids. Intraoperative pain relief can be obtained with a blended approach with epidural analgesia (see postoperative analgesia) and short acting opioids. Remifentanyl can reduce the surgical trauma and the stress response. Muscle relaxation is essential in

laparoscopic surgery of the pelvis - much more than in open surgery - to allow a complete distension of the abdomen without contrasting the CO₂ insufflation and to facilitate the pelvic dissection^[23].

Prevention of hypothermia

It is well known that hypothermia is one of the killers of the surgical and trauma patient, also due to its negative effect on coagulation. It has been demonstrated, and is considered best practice, that prevention of hypothermia through the administration of warm fluids and the use of a thermic blanket can reduce bleeding, surgical site infection and cardiac complications.

Hypothermia can also be detrimental in terms of prolonging the admission and delaying oral feeding, but its direct relation with postoperative ileus has not been proved^[58]. It has been suggested to monitor body temperature during and after surgery^[18].

Surgical technique

The ERAS being mostly a perioperative policy, the surgical technique is pretty much unchanged with respect to the traditional protocols. However, if we want to get the whole range of benefits of ERAS, it is clear that the surgical technique must be as less invasive as possible. Therefore, the higher benefits of ERAS can be obtained in patients operated by laparoscopy^[2,5]. Although pelvic dissection is always traumatic, in particular when coupled with perineal dissection, the laparoscopic approach associated with ERAS would reduce postoperative ileus and overall physiologic recovery^[18]. Numerous and strong evidence^[59,60] confirmed that laparoscopic surgery for rectal cancer is feasible, safe and effective and adds the benefits of the minimally-invasive approach to the care of patients with rectal malignancies. The combination of laparoscopic surgery with the ERAS approach improves the already outstanding results of each of the two taken singularly; therefore we strongly believe that laparoscopic surgery must be considered one of the core items of ERAS also in pelvic benign and malignant conditions.

Use of drains

If one of the principles of the surgical technique under an ERAS protocol is to be respectful of the particular pathophysiology of the patient, it necessarily follows that all those items that can delay his or her recovery should be avoided. The presence of one or more drains in the pelvis can impair the patient's early mobilization, without reducing the incidence or the severity of anastomotic leaks^[61,62]. A large retrospective study from Holland and a meta-analysis from Italy showed that in patients who had total mesorectal excision the use of drain can be beneficial^[63,64], but this finding was not confirmed by the GRECCAR 5 randomized controlled trial^[65].

Nasogastric tube

The traditional use of a nasogastric (NG) tube to prevent postoperative vomiting and gastric distension has been demonstrated to be detrimental to an expedited recovery as it may be one of the causes of respiratory complications. A Cochrane meta-analysis demonstrated that bowel motility recovers quickly without a NG tube, with no increased risk of inhalation^[66]. NG tubes should be reserved to those patients who develop postoperative ileus^[23].

Bladder catheter

The use of a bladder catheter (either transurethral or suprapubic) has been part of the traditional perioperative management for decades, as it allows to monitor the urinary output and to deflate the bladder to improve the visualization of the pelvis, either by open or laparoscopic surgery. Moreover, it can be useful if the patient is not yet fully mobile. In rectal surgery, bladder catheter is standard practice due to the risk of urinary function impairment. However, there is no evident advantage in maintaining the catheter beyond

the strict necessity. Several studies, and consequently the ERAS guidelines, suggest taking it out as soon as possible, even within the 1st day^[18,67]. The American guidelines differentiate colonic and rectal surgery and suggest removal of the bladder catheter within day 2 in infraperitoneal rectal resections. Obviously, a longer duration of bladder catheterization may be necessary in patients with increased risk of urinary retention^[18], such as in the presence of epidural analgesia, and in those who had extensive pelvic surgery^[23].

Prevention of postoperative infections

Colorectal surgery patients are more prone to develop infections than any other surgical patients, possibly due to the high potential for bacterial seeding and/or translocation. Whereas specific infective processes such as pneumonia have a clear pathophysiology, it is still not perfectly clear why patients develop surgical site infection (SSI). The traditional view that this may be due to direct contamination during the operation, suspected on the basis that the most common causative bacteria of SSI are enteric in origin (*E. coli*, *B. fragilis*), has been disproved by the fact that cultures of the wound at the end of a surgical operation are not predictive of postoperative infection^[68]. It has been proposed a “Trojan Horse” hypothesis for SSI, whereby virulent bacteria normally quiescent within the gastrointestinal tract are simply transferred to the surgical wound by neutrophils and macrophages activated by the surgical trauma^[69]. The use of oral non-absorbable antibiotic would therefore be beneficial also in reducing the risk of SSI^[23,50].

A similar mechanism has been invoked for the genesis of anastomotic leak. It has been demonstrated long ago that bacteria and not technique are usually responsible for anastomotic leak^[70]. Unfortunately, for some reasons the view that local ischaemia and technical failure are the main causative factor for leak prevailed, despite the clinical evidence that oral antibiotics would decrease the risk of leak^[71], until the more recent evidences^[49] convinced the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons to include oral antibiotics in their ERAS guidelines^[23].

The adoption of a bundle of measures to reduce SSI is a winning entry. A recent systematic review and meta-analysis showed a reduction of the risk of SSI of more than 50% (15.1% vs. 7%). All the studies considered in this review had in common the core elements of the SSI-reduction bundles, namely antibiotic prophylaxis, prevention of hypothermia, hair removal, prevention of hyperglycaemia^[72]. Other interventions have been suggested, such as no fluid overload, skin preparation with chlorhexidine, double gloving or change of gloves and gowns before closing the fascia, lavage of subcutaneous tissue and silver dressing^[23].

POSTOPERATIVE STAGE

Postoperative analgesia

Control of postoperative pain has always been a hot topic, as it is one of the variables that may affect postoperative recovery. The traditional use of morphine has always been quite effective, but at the expense of important side effects, such as prolonged ileus, and potential complications (respiratory, neurologic) and safety issues (drowsiness, dizziness, falls) in high risk patients. Several different analgesia regimens have been proposed, with the aim of minimizing patient discomfort while facilitating his or her recovery and minimizing side effects and complications of drugs. We agree with the American Society for Enhanced Recovery (ASER) that a completely painless surgery is a non-achievable goal^[73], so we should aim at the best possible analgesia that does not impair the patient’s physical recovery. Every analgesic regimen must also take into consideration the kind of surgical approach, as the requirements of pain control may vary according to the size and shape of the abdominal incision and the subsequent surgical trauma.

Opioids have been extensively used in the past to control postoperative pain, but at the expense of heavy

side effects such as constipation, ileus, nausea, urinary retention, over sedation, delirium and delayed discharge. Clearly, this does not fit with the ERAS principles. The further demonstration, that non-opioid analgesia may be associated with less pain, reduced risk of cancer recurrence and longer survival^[74] has convinced the medical community that non-opioids regimens should be considered. The European guidelines suggest using opioids only as rescue analgesia, in particular in laparoscopic surgery. The ASER guidelines suggest a multimodal approach with NSAIDs, paracetamol and/or gabapentin, eventually associated with spinal/epidural analgesia and/or local anaesthetic infusion within the wound. Eventual adjuncts can be steroids, ketamine and tramadol^[73].

It has been demonstrated that the neuro-axial block is able to reduce the surgical stress by interrupting the transmission of the nociceptive stimulus to the brainstem, thus reducing the risk of postoperative ileus^[2,75]. Epidural analgesia is also effective for the pain control in the postoperative period, even if many Authors prefer to limit its use to laparotomic surgery where its benefits are definitely clearer than the risks. Epidural anaesthesia (EA) is associated with very good pain control after colorectal surgery, both laparoscopic and open, but the prolonged block of the sympathetic system, with consequent hypotension and need for continuous fluid infusion, is a major concern. Although the benefits of EA are well known^[76], the use of single-injection intrathecal (spinal) analgesia (IA) with opioid plus or minus local anaesthesia is gaining favor^[77]. The main advantage of IA with respect to epidural is its easiness, as it does not require any further equipment or specific surveillance. The perceived drawback is its potential risk of complications such as respiratory depression. This has been widely contradicted by scientific evidences^[77]. On the contrary, IA is safe and effective, as it is able to control postoperative pain while allowing earlier functional recovery and shorter LOS^[78]. IA is usually performed to provide additional pain control in association with paracetamol and NSAIDs.

Peripheral analgesia can also be extremely effective. Transversus abdominis plane infiltration, wound and peritoneal infiltration and rectus sheath block in association with systemic analgesia have all been demonstrated to be able to reduce the use of opioid with respect to systemic analgesia only^[73].

All non-opioid oral analgesic agents have been widely used and have been found to be able to reduce the use of opioids. Their routine use is part of any ERAS programme. Intravenous administration of paracetamol can achieve higher plasma concentrations with respect to the oral administration, but there is no evidence of a clear superiority of intravenous versus oral administration in the clinical settings^[79]. The use of NSAIDs has been recommended on the basis of good efficacy and insufficient evidence of complications^[80]. However, recent evidence suggest caution with the use of non-selective NSAIDs like diclofenac, due to increased risk of anatomotic leak^[81]. Gabapentin and pregabalin can also be used to reduce the requirement of opioids in the postoperative period^[82], and as such their use is recommended by the ASER^[73], but only at high doses. Tramadol^[83], ketamine^[84], magnesium^[85] and steroids^[86] have all been used for postoperative pain control, with some efficacy, but their use has not gained wide acceptance.

Prevention of postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) are common side effects of surgery and anaesthesia and can affect early feeding and reduce patient satisfaction. Recent guidelines suggest a multimodal and quite liberal approach to PONV treatment^[23]. Avoidance of opiates and administration of oxygen can help reducing PONV. Goll *et al.*^[87] demonstrated that 2 h of 80% oxygen are more effective in reducing PONV than ondansetron. However, postoperative ondansetron following preoperative administration of dexamethasone is an effective combination^[23]. It is well known that intravenous anaesthesia with propofol is superior to inhalation anaesthesia^[88], but the role of gabapentin is not yet fully defined^[23].

Prevention of postoperative ileus

Postoperative ileus still remains a major problem after colorectal surgery, and in particular after extensive rectal operations, with a prevalence rate as high as 28%^[89]. Its global impact on LOS overlaps the impact of anastomotic leak^[90]. Its etiology is multifactorial and usually is not related to a substandard surgical technique. Smoking, major laparotomy, ASA classification and duration of surgery were considered independent causative factors^[91,92]. Molecular level evidence has recently demonstrated the role of intestinal microbioma in the regulation of bowel motility^[93], possibly through its action on bowel macrophages, whose activation leads to generalized intestinal nervous plexa dysfunction and paralytic ileus^[94]. This can be taken as a confirmation of the positive role of oral non-absorbable antibiotics in the preparation of the bowel for colorectal surgery^[49], even if the exact mechanism of action and the bacteria species involved in the process are not yet fully understood^[50].

Compliance with ERAS principles is a protective factor against postoperative ileus^[95]. According to ERAS principles, early recovery of bowel peristalsis is based on four cornerstones: (1) mini-invasive technique; (2) restrictive fluid infusion; (3) avoidance of opiates; and (4) early re-feeding.

Multiple RCTs and meta-analyses have demonstrated that early feeding stimulates recovery of bowel function^[23,96]; this is particularly true in younger patients operated on by subspecialist colorectal surgeons using laparoscopic techniques^[97,98].

It is well known that opioids may impair the gastrointestinal motility through a direct action on the mu-receptors of the bowel, causing ileus and constipation. Therefore, the use of peripheral opioid antagonists may reduce the risk of postoperative ileus^[97]. Although this has been incorporated into the American ERAS guidelines^[23], some Authors suggest prudence as definitive evidence is not yet available^[98]. A recent phase 2 study from Scotland confirmed that oxycodone and naloxone reduces time to first bowel motion when compared to oxycodone only within an ERAS protocol in laparoscopic colorectal surgery, but the authors admit that a proper RCT is still needed^[99].

It has been proposed that chewing gum may stimulate bowel motility - via vagal stimulation or gastrointestinal hormones secretion - with an earlier return of intestinal function and reduced LOS^[100], but unfortunately the vast majority of colorectal studies are small sized and of poor quality^[101,102]. A large RCT on 402 patients clearly demonstrated that, although there is no detriment, there is no beneficial effect either^[103]. Although chewing gum has been added to the ERAS Society guidelines^[18], this matter remains unclear.

The use of oral laxatives such as magnesium oxide and disodium phosphate can reduce the time to first bowel motion^[104], but it has not been fully evaluated yet and it is considered a weak recommendation^[18].

Postoperative nutrition

Early studies confirmed that early oral feeding after a colorectal operation does not increase the risk of complications and, on the contrary, can be beneficial in reducing the post-surgical catabolism, improving the immune function, reducing the systemic inflammatory response and reducing bacterial translocation. The ERAS protocols suggest early re-feeding with liberal fluid intake by mouth immediately after surgery, provided that PONV is well controlled, and early return to a normal diet^[18]. In cases where oral feeding is not deemed to be sufficient to get a correct caloric intake, it may be necessary to add oral proteic supplements^[18].

Even if the application of simple rules can yield great results, the implementation of a specific gastrointesti-

nal rehabilitation programme resulted in further reduced morbidity and LOS^[105].

Immunonutrition is associated with reduced rate of complications and reduced length of stay^[106,107]. In fact, it has been demonstrated that the administration of nutritional supplements containing mainly glutamine, arginine, omega-3 fatty acid and ribonucleic acid is able to reduce the inflammation and improve the immune response. The mechanism of action of immunonutrition has not been fully clarified yet. Apparently, its main effect is to reduce bacterial translocation by maintaining the integrity of the intestinal mucosa and reducing its permeability, thus reducing the risk of infectious complications^[107].

The main barrier to a correct postoperative nutrition is patient information^[108], so once again it is important to emphasize the need for patient engagement also in nutritional care at the preoperative encounters^[109].

Early mobilization

Early postoperative mobilization has beneficial effects on the whole postoperative recovery. In fact, it reduces catabolism and bowel recovery and improves ventilator function and bronchial clearance (reducing the risk of pneumonia and atelectasis), reduces the risk of DVT and prevents muscle loss and insulin-resistance. Ultimately, it reduces postoperative LOS, encourages independence and reduces discomfort^[18]. Several different modalities and targets have been proposed^[23], but no specific protocol has been identified. A frequent approach is to allow liberal mobilization as soon as possible after surgery^[23], but in high risk patients, strong support by specialized staff may be needed.

Quality control

Auditing outcome data is the only way to improve the service we are offering. Once an ERAS programme has been started, it is likely that this will become part of the “routine” management of surgical patients. Nonetheless, there is good recent evidence that habituation can lead to over-confidence and the application of some of the ERAS elements can reduce with time^[110,111]. The exact quality indicators of ERAS protocols are yet to be defined, but it is obvious that LOS is not necessarily the main endpoint. Fit-for-discharge as a parameter can be more reliable than LOS^[112]. The ERAS Society recommends also considering morbidity and mortality, need for transfusions, duration of surgery, readmission rate and total cost. We would also add reoperation rate and patient satisfaction as key factors for quality control. Moreover, it must be emphasized that the ultimate aim of rectal resection is to cure a malignant condition; therefore we believe that oncologic outcomes, such as rate of radical resections and rate of adequate lymphadenectomies must also be taken as quality parameters.

Another parameter that must be recorded and audited is the compliance with the elements of ERAS. Engagement of the whole multidisciplinary department is paramount and adherence to the process is crucial to obtain the advantages of ERAS^[17,113].

To the best of our knowledge, adherence to ERAS protocols has never been analysed in relation to the size of the department, however we feel that in a small department it should be relatively easy to implement the necessary changes leading to the full potential of ERAS principles, with respect to a big-size department where engagement of all the relevant people can be tricky and sometimes frustratingly impossible. One of the Authors' past experience with implementing ERAS in a rural hospital has shown that evolutionary changes aiming at improving postoperative recovery in colorectal surgery can be implemented relatively quickly, and the learning curve of the whole team is quite short^[5]. In more sizeable departments, the introduction of the ERAS protocol should be more gradual, focusing initially on prevention of hypothermia, early postoperative feeding, early removal of the bladder catheter and no nasogastric tube^[114]. Actually, the Perioperative Italian Society who released this statement in a very recent publication added no bowel

preparation to the “core” items listed above, but on this subject we favour the American guidelines, suggesting selective bowel preparation. Although a gradual approach can be acceptable, we again agree with the American guidelines that the aim must be a complete and standardised protocol implementation^[23].

Probably never, have such minimal changes in surgical organisation and mindset yielded such a huge return as with ERAS in colorectal surgery^[4].

CONCLUSION

ERAS protocols are largely improving the experience of patients undergoing colorectal surgery but they also represent a huge step forward in team working, hospital dynamics and trust finances, as they reduce LOS, total hospital costs and pharmacy costs, with a contemporary reduction of complications and readmission rates^[115]. In a world where new scientific evidences are published on daily basis it is normal that ERAS principles are still quite fluid, but this is not necessarily a bad thing. Some of the ERAS elements are particularly likely to change in the near future, such as the attitude towards MBP and oral antibiotic, prehabilitation and immunonutrition. We can expect that with increased experience and awareness, LOS will reduce with time and more and more patients will be operated as day cases in the future.

Despite the various attempts at standardisation, ERAS statements remain general principles whose dynamic application must be adapted to the local situation and to the team preferences and must show an ample degree of flexibility. For this reason, every team applying ERAS standards must keep in mind the need for regular audits, quality checks and improvement.

DECLARATIONS

Author's contributions

Literature selection and review, article drafting, and approved the final version: Tebala GD, Gordon-Dixon A, Imtiaz M, Shrestha A, Toeima M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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