Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations

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Background: The present article has been written to convey concepts of anaesthetic care within the context of an Enhanced Recovery After Surgery (ERAS) programme, thus aligning the practice of anaesthesia with the care delivered by the surgical team before, during and after surgery.
Methods: The physiological principles supporting the implementation of the ERAS programmes in patients undergoing major abdominal procedures are reviewed using an updated literature search and discussed by a multidisciplinary group composed of anaesthesiologists and surgeons with the aim to improve perioperative care.
Results: The pathophysiology of some key perioperative elements disturbing the homoeostatic mechanisms such as insulin resistance, ileus and pain is here discussed.
Conclusions: Evidence-based strategies aimed at controlling the disruption of homoeostasis need to be evaluated in the context of ERAS programmes. Anaesthesiologists could, therefore, play a crucial role in facilitating the recovery process.

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Editorial comment: what this article tells us
Complications after surgery are still a major problem. Enhanced Recovery after Surgery (ERAS) programmes may minimise some of the negative impact of surgery on organ function and this article describes the pathophysiology and the role of the anaesthesiologist in this context.

Despite steady advances in anaesthetic and surgical techniques over the years, post-operative complications remain one of the major drawbacks of surgery, not only for the specific patient involved but also for their surgical care team and the health care system in general. Rarely do patients die on the operating table during the surgical procedure, but rather from the pathophysiological response to surgery and its complications. The progressive understanding of the physiological basis of surgical injury has been the rationale underpinning the research efforts of interdisciplinary teams, incorporating surgeons, anaesthesiologists and nurses (among others) to minimise the surgical stress response and thereby improve outcomes. However, one of the immediate challenges to improve the quality of perioperative care is not to discover new knowledge, but rather to integrate what we already know into clinical practice. To this end, the concept of "fast-track surgery" was introduced in the 1990s by Henrik Kehlet. It was demonstrated that by applying evidence-based perioperative principles to open colonic surgery, the post-operative length of hospital stay could be reduced to 2–3 days.[1,2] Realising that the surgical journey involves many professional competencies, a more integrated, multiprofessional, multidisciplinary approach was needed, whereby a decision taken early in the course of the treatment plan would impact on later developments and influence the choices available for recovery further down the line. Unfortunately, large gaps still exist between what the evidence suggests should happen and what actually happens in practice.[1,3]

Compared with traditional perioperative care, the Enhanced Recovery After Surgery (ERAS) programme represents a fundamental shift in the process of care, by including multiple interventions that attenuate surgical stress, maintain physiological function and expedite return to baseline.[4] While each intervention has a small effect, all together they have a stronger synergistic impact (Fig. 1).

The ERAS Society recently published three guidelines on perioperative care focused on colonic,[5] rectal/pelvic[6] and pancreatic and gastric resection.[7] Previous versions of such guidelines have been shown to impact on daily practice.[4,8]

Gustafsson and coworkers[9] showed that with better compliance to an evidence-based ERAS protocol, outcomes improved: ERAS programme patients treated with less than 50% compliance had a complication rate of almost 50%, while those following the protocol more closely (90% compliance) had fewer than 20% complications. Similar improvements have been reported in a meta-analysis of randomised trials.[10]

The aim of this article was to review the pathophysiological basis of some key elements which form the basis of the ERAS programme. The second article, which follows, is more hands on and practical, and is meant to propose recommendations for anaesthetic protocols in the ERAS setting. Obviously, such an approach is based on best available evidence and should not to be seen as set in stone, as there are areas of challenge for the anaesthesiologist beside several aspects of controversial nature that require more research and development. The current papers are the joint effort of a wide range of professionals involved in the improvement of perioperative care working for the ERAS Society.

Methods

The present narrative review has been written following several meetings of a group of anaesthesiologists and surgeons, and after reviewing the literature between 1990 and 2014 on specific perioperative topics. The intention of the authors was to convey concepts of pathophysiology within the context of the ERAS programme, aligning the practice of anaesthesia with the

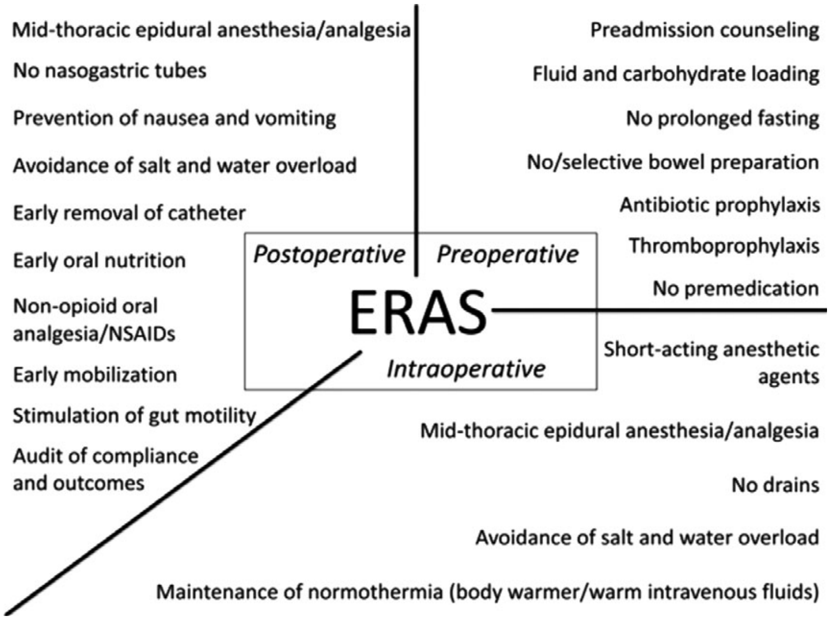

Fig. 1. ERAS elements. Reproduced from Varadhan KK et al. with permission.[105]

care delivered by the surgical team before, during and after surgery.

The role of the anaesthesiologist in implementing ERAS

Implementing ERAS programmes requires a multidisciplinary approach and within this philosophy, it is vital to avoid a 'silo mentality' and this applies most emphatically to the anaesthesia member of the team. Indeed in many institutes/countries, there is a drive towards anaesthesiologists fulfilling the role of perioperative physicians.

In the pre-operative phase, the anaesthesiologist may well run a formal pre-admission anaesthesia clinic for the assessment of patients deemed at high risk by either the surgeon or the pre-admission nurse. Activities may include formal risk assessment, optimisation or referral to other specialties such as cardiology or the frailty clinic. In the post-operative phase, the anaesthesiologist has a role in patient supervision in PACU/HDU to optimise opiate sparing, avoid excessive fluid loading and intervene early with complications such as delirium. Such a role can be extended onto the ward as a key member of the acute pain team. Finally, at a strategic level, the anaesthesiologist can contribute to team leadership, protocol compliance, audit and ongoing team education.

Preparing the patient for surgical stress

The world's population has increasing longevity, with average life expectancies rising yearly. A large proportion of the elderly population requires surgery for various reasons. The physiological changes associated with ageing are responsible for decreased reserve, impaired functional status, thus leading to poor capacity to withstand the stress of surgery. Co-morbidities associated with the elderly include hypertension, ischaemic heart disease, stroke, hypercholesterolaemia, chronic obstructive airway disease and diabetes. Although age per se does not preclude surgery, the presence of coexisting diseases has a greater impact on post-operative morbidity and mortality than age alone.[11] Furthermore, the burden of obesity, cancer and surgery represents a major stressor on organ systems with possible sequelae for cancer spread and declining functional ability. Smoking, alcohol, anaemia, poor nutritional status and poor glycaemic control can further impact adversely on post-operative infection rate, immune function and tissue healing. Pre-operative anxiety, emotional distress and depression have been shown to be associated with higher complication rates, greater post-operative pain, cognitive disturbances and delayed convalescence.

Fitness can be subdivided into coexisting medical problems and physical fitness. Pre-existing health factors such as myocardial infarction, heart failure, stroke, peripheral vascular disease and impaired kidney function can increase the risk of post-operative complications. There is also sufficient evidence that patients with poor physical conditions and low anaerobic threshold have greater post-operative morbidity and mortality.[12] In patients with cardiopulmonary disease, a 6-min walking distance (6MWD) < 350 m predicts mortality.[13] Similarly, in colorectal surgery patients, the 6MWD (which has a weak inverse correlation with sarcopenia) was found to correlate well with peak oxygen consumption in predicting post-operative cardiopulmonary complications.[14]

Risk assessment, optimisation of pre-existing organ function and education are essential ERAS elements for the preparation of patients facing surgery. The multidisciplinary team involved in the process includes anaesthesiologists, surgeons, internists, nutritionists, physiotherapists, nurses and, when needed, psychologists. Besides increasing physiological reserves and pharmacological optimisation, patients and caregivers need to be educated about the surgical process and empowered. The whole patient journey, starting with evaluation, then optimisation of physical, mental, nutritional functions (prehabilitation), then moving through surgery and the hospital episode and finishing with recovery, should be explained well in advance to facilitate active participation, comprehension and allay anxiety. Ideally audiovisual material should be made available. As patient expectation plays a role in determining post-operative outcome, clear information about the process of care has to be delivered to caregivers as well as the patients.[15]

Why it is important to control surgical stress and maintain homoeostasis

For every action, there is a reaction and the reaction to surgical stress is the metabolic response to injury. Preventing stress and thus minimising this response represents the central mechanism around which the concept of enhanced recovery is based. This response encompasses all elements associated with surgery such as anxiety, fasting, tissue damage, haemorrhage, hypothermia, fluid shifts, pain, hypoxia, bed rest, ileus and cognitive imbalance. Such significant changes in metabolic and physiological homoeostasis represent a threat to the body and mind that need to be treated for a successful return to pre-operative conditions. Evidence suggests that this phenomenon, if left untreated, can lead to increased morbidity and mortality. Therefore, it makes sense to provide not only a rational basis for accelerated recovery but also to minimise the potential risk of organ dysfunction leading to complications and decreased long-term survival.[16]

The “stress response” is represented by hormonal and metabolic changes that result in haematological, immunological and endocrine responses, and its extent parallels the degree of tissue injury, being further amplified with post-operative complications. The interaction between the endocrine and inflammatory response is characterised by an elevation in counter-regulatory hormones (cortisol, growth hormone, glucagon and catecholamines) induced by activation of hypothalamic–pituitary–adrenal axis, and an initial predominance of pro-inflammatory cytokines followed by anti-inflammatory cytokines. Following tissue injury, the systemic inflammatory response is activated and mediated mainly by pro-inflammatory cytokines such as interleukins, IL-1 and IL-6. The effects of these mediators on target organs (such as hypothalamic thermoregulation or hepatic acute phase protein production) are modulated potentially by other components of the stress response (e.g. glucagon, cortisol or adrenaline). Local change impacts not only on the generalised inflammatory state but also on homoeostatic, metabolic and circulatory organs. An example of surgical stress-induced organ injury is represented by the occurrence of myocardial injury after non-cardiac surgery (MINS). MINS is where myocardial injury occurs causing a raised peak troponin T level of > 0.03 ng/ml (even without symptoms or a full definition of myocardial infarction) and it is an independent predictor of 30-day mortality.[17] In a recent large cohort study of over 15,000 patients, 8.0% of patients suffered MINS with around 58% of these patients not fulfilling the universal definition of myocardial infarction and only 15.8% of patients with MINS experienced an ischaemic symptom. Although it is not known which ERAS elements can specifically reduce MINS, it has been recently demonstrated that when all the ERAS elements are used cardiovascular complications are reduced.[18]

The more extensive the surgical wound, internal organ manipulation and tissue dissection, the greater is the stress response. This concept not only applies to physiological/metabolic changes but also to changes in the innate immune system. This combination of catecholamine release and hyper-inflammation followed by immunosuppression can contribute, among other things, to a state of insulin resistance.[19,20]

A main reason for the effectiveness of the ERAS protocols is that many of the different treatments building the protocol reduce the stress responses to the injury caused by the operation and thus help to maintain homoeostasis.

Metabolic homoeostasis

Normal metabolism is governed by anabolic and catabolic hormones in interplay. Any major injury including surgery disrupts metabolic homoeostasis and cause insulin resistance. Insulin resistance can be defined as a condition, whereby a normal concentration of insulin produces a subnormal biological response.[19] Studies have demonstrated a significant correlation between the degree of the patient's insulin sensitivity on the first post-operative day and length of hospital stay ($r = 0.53$, $P = 0.0001$).[20] In a multifactorial analysis, the degree of insulin resistance, the magnitude of surgery and blood loss were the three independent factors explaining more than 70% of the variation in length of stay. More importantly, a significant association was shown between the magnitude of insulin resistance and complications. For every decrease in intraoperative insulin sensitivity by 20%, the risk of serious complications was more than doubled after open heart surgery.[21]

The relevance of insulin resistance to outcomes is also reflected by the clinical problems associated with its metabolic sequelae, the catabolic changes in glucose and protein metabolism also known as "diabetes of the injury". In non-diabetic patients undergoing major abdominal procedures, blood glucose (BG) values > 7 mmol/l are frequently observed. Evidence is mounting that hyperglycaemia is a predictor of mortality and complications, and that even a moderate increase in blood glucose may be associated with a worse outcome.[22–24] Patients with fasting blood glucose concentrations > 7 mmol/l or random blood glucose concentrations > 11.1 mmol/l on general surgical wards showed a 18-fold increased in-hospital mortality, a longer hospital stay and a greater risk of infection.[25] Post-operative protein catabolism is characterised by a net loss of functional and structural body protein. Metabolically healthy patients lose between 40 and 80 g of nitrogen after elective open abdominal operations, equivalent to 1.2–2.4 kg wet skeletal muscle.[26] Also, protein losses after abdominal surgery are 50% greater in insulin resistant patients than in those who are not.[27] More recent studies indicate a linear relationship between insulin sensitivity and protein balance in parenterally fed patients undergoing open heart surgery.[28] Loss of lean tissue delays wound healing, compromises immune function and diminishes muscle strength. The ensuing muscle weakness inhibits coughing, impedes mobilisation and prolongs mechanical ventilation if patients are on intensive care thereby complicating convalescence and causing morbidity.

Subjects with altered metabolic and inflammatory states such as elderly, diabetics and patients with cancer undergoing surgery can be exposed to a greater stress response, profound catabolic state as result of poor reserve, thus leading to post-operative complications and delayed functional recovery.[29–31]

Plasma glycosylated haemoglobin A (HbA1c) is an indicator of blood glucose control over the previous 3–4 months. Observations made in 273 diabetic and non-diabetic patients undergoing open heart surgery demonstrated a significant correlation between the quality of pre-operative glycaemic control as reflected by HbA1c levels and insulin sensitivity during cardiac surgery ($r = 0.527$, $P < 0.001$).[21] In addition, diabetic patients with HbA1c > 6.5% had a greater incidence of major complications ($P = 0.010$), and minor infections ($P = 0.006$). Such patients received more blood products, and spent more time in the ICU ($P = 0.030$) and the hospital ($P < 0.001$) than metabolically normal patients.[21] These findings are in agreement with the results of other observational studies indicating worse outcomes after cardiac, abdominal and vascular procedures in the presence of increased HbA1c concentrations.[32–34]

ERAS interventions reducing insulin resistance

Several ERAS interventions are directed to reduce surgical stress and modulate perioperative insulin sensitivity directly and indirectly.

Pre-operative carbohydrate loading and adherence to pre-operative fasting guidelines

The idea of pre-operative carbohydrate treatment instead of overnight fasting came from animal studies showing that coping with stress is much improved if animals sustain trauma in the fed rather than fasted state.[35] Overnight treatment with intravenous glucose was shown to attenuate the decrease in muscle insulin sensitivity.[36] A similar effect was later shown for oral carbohydrates solutions tailored for pre-operative use.[37] The administration of such pre-operative oral carbohydrates raises insulin sensitivity by 50%,[38] and this carries through to the post-operative period resulting in 50% less insulin resistance. Carbohydrate loading also shifts cellular metabolism to a more anabolic state.[39] This allows for better use of any nutritional care post-operatively, with less risk of hyperglycaemia and improved retention of protein and preservation of lean body mass.[40] Studies conducted in relatively small patient populations suggested better outcomes with pre-operative complex carbohydrates given orally up to 2 h before anaesthesia and surgery,[41,42] However, a meta-analysis[43] and a recent Cochrane analysis[44] of all available data from randomised controlled trials suggest that in major abdominal surgery there is clinical impact as evidenced by faster recovery[43,44] (reduced length of stay by 1–1.5 days[43]). However, for minor surgery the benefit is mainly in patient well-being,[41] and in other types of surgeries the data remain sparse.[44] Many National and International Anaesthetic Societies recommend a 6-h pre-operative fast for solids and a 2-h fast for clear liquids, including carbohydrate drinks.[44–47]

Epidural anaesthesia

Another way of minimising post-operative insulin resistance is to use epidural anaesthesia. Ample evidence has accumulated in open surgery to identify the peripheral and central nervous system as a common pathway triggering the catabolic responses to tissue trauma. Blockade of these pathways by epidural anaesthesia and local anaesthetic blocks prevents the increase in circulating counter-regulatory hormones, thereby minimising insulin resistance and limiting protein catabolism[48] and hyperglycaemia.[49] The physiological effects of epidural anaesthesia may serve as a rationale for improved respiratory and cardiovascular outcomes after general, urological and vascular procedures as reported by meta-analyses and randomised controlled trials.[50,51]

Early post-operative feeding

A further additional potentially beneficial way to maintain metabolic homoeostasis is early feeding. Early recommencement of post-operative nutrition has been shown to benefit the patient.[52] However, most of the available data are from patients undergoing surgery in a traditional care programme, and very little is known about the effects of nutrition in a modern ERAS programme. One small study showed that after major colorectal surgery, in patients given pre-operative carbohydrates and thoracic epidural anaesthesia, complete enteral feeding initiated immediately after the operation normalised glucose levels and was associated with abolition of the catabolic response to surgery such that there was no net loss of body nitrogen (protein).[53] This suggests that it is possible to overcome most of the metabolic response to injury when post-operative feeding is combined with pre-operative carbohydrates and epidural anaesthesia.

Glycaemic control

The therapeutic administration of insulin is an obvious choice to overcome perioperative insulin resistance and improve outcome. Normoglycaemia and whole body protein stores can be preserved by insulin therapy suggesting that insulin sensitivity rather than insulin responsiveness is reduced during and after surgery.[54] Although the safety and efficacy of glucose control in the ICU has been debated, trials have consistently shown that in post-operative patients[55] and in trauma patients[56] improved glucose control with insulin in the intensive care situation has proven beneficial by avoiding complications as long as the deleterious effects of hypoglycaemia are avoided. In the ward situation, intensive insulin treatment is more dubious and hard to control and, therefore, measures should be taken to minimise the insulin resistance and thereby avoiding the need of insulin.[53]

Magnitude of surgery and homoeostasis

Minimising the total surgical injury is the principal aim of minimally invasive surgery (MIS), and with optimal surgical techniques the benefits are not just from the reduction in wound size. This concept can be categorised into primary and secondary injury due to surgery. The primary injury is direct trauma to the abdominal wall or tissue damage from mobilisation of tissues or trauma to organs themselves. There is also indirect injury during surgery from bleeding or the physiological effects from anaesthetic techniques (intermittent positive pressure ventilation, drugs causing local vasomotor changes causing local blood flow changes) and the physiological effects of patient positioning combined with the abdominal pressure of the CO_2 pneumoperitoneum. The rationale behind minimising the access wound in particular is to reduce the activation of neuro-humoral pathways that affect recovery adversely. Reducing neuro-humoral stimulation may be achieved by reducing access trauma and internal trauma associated with the surgery.

Trauma to the abdominal wall may be reduced by changing the orientation of the incision such that it traverses fewer myotomes and dermatomes. Where open surgery is performed, transverse incisions may reduce post-operative pain and improve outcomes but the evidence for this is not clear.[57–59] The length of the access incision can be reduced using laparoscopic techniques that will reduce both the total additive length of the incisions and the maximum length of any one incision. Additionally, modern ports used for access work by splitting muscle fibres rather than dividing them, which is also less traumatic.

The intra-abdominal part of the operation is usually similar whether performed with open access or laparoscopically, but differs in a number of ways which might reduce trauma. This is witnessed by good evidence that overall blood loss is less[60] and adhesions are reduced following laparoscopic colorectal surgery.[61] A number of factors may contribute but the reduction of the size of peritoneal injury, the reduced serosal injury and the reduced blood loss will all reduce the tendency to form adhesions. The use of modern energy sources such as ultrasonic technology may also be a factor both in reducing blood loss but also reducing the collateral damage associated with other techniques. The techniques that have been developed with laparoscopic surgery also dictate the necessity to dissect carefully within bloodless plains where possible which may have a benefit in reducing collateral injury and reducing stimulation. This results in a reduction in secondary injury reducing the cytokine, hormonal and neural responses to surgery. The benefits of MIS are further enhanced by reducing consequential problems from fasting and immobilisation as there is a more rapid return of gut function and improved mobilisation.

The benefits from using MIS has to be balanced against the fact that to perform MIS the carbon dioxide (CO_2) pneumoperitoneum and patient position may have detrimental physiological effects which can be compounded if the duration of surgery is long. The initiation of CO_2 pneumoperitoneum triggers a sympathetic response and major changes in blood flow and respiratory mechanics. In fluid optimised patients, there is a rise in aortic afterload with resulting decrease in stroke volume and resultant reduction in oxygen delivery which can affect outcome.[62] This response usually lasts for 20–25 min until adaptation occurs but in some patients cardiac output remains low.[55] Studies to look at reducing the physiological impact of CO_2 pneumoperitoneum by using special ports or deep neuromuscular block to facilitate good surgical exposure at lower pressures are ongoing.

Such graded interaction between minimal access surgery and ERAS is reflected in an additive effect in reduction of length of stay.[63] Thus MIS with its reduction in both primary and secondary injury has become a major component of ERAS.

Surgery and fluid balance

Following the initiation of injury, the release of catabolic hormones and inflammatory mediators facilitate salt and water retention to preserve intravascular volume, maintain blood pressure and vasoconstriction, and provide gluconeogenic substrates for metabolism and cell function. Body temperature decreases to minimise oxygen utilisation, and blood is shunted away from "non-vital" organs such as the gut, skin and muscle to maintain perfusion in vital organs like the heart, brain and kidney. Gene and protein expression of mediators of inflammation and insulin resistance, such as IL-6, AKT-1, FOXO-1, and PDK4 are increased within hours of the incision at the site of the injury (rectus abdominis muscle) and, to a lesser extent, distant from the site of the injury (vastus lateralis muscle).[64] There is also a consistent suppression of muscle mitochondrial complex activity and a decrease in ATP production rates over the same time period.[65] These changes are associated with an increase in intestinal permeability. Blood rheology is also altered with the initiation of a hypercoagulable state.

Teleologically, mammals have developed very efficient mechanisms to conserve salt and water in the face of fluctuations in water supply, scarcity of salt and reductions in plasma volume. On the other hand humans have not, until recent times, been exposed to salt excess and our mechanism for excreting this is correspondingly inefficient, depending on a slow and sustained suppression of the renin–angiotensin–aldosterone axis.[66,67]

Salt and water overload has been shown to impact on anastomotic integrity. Furthermore, ileus and increasing post-operative complications leading to prolonged hospital stay have been reported when maintenance of patients in a state of near-zero fluid balance is not achieved.[66,68] Generally, it has been shown that post-operative complications are increased when the weight gain in the post-operative period exceeds 2.5 kg (indicative of a 2.5 l cumulative fluid overload).[69]

The maintenance of fluid and electrolyte balance and tissue perfusion is achieved directly with several modalities within the ERAS programme and indirectly by overall modulation of the hormonal and inflammatory response. The principle of maintaining a patient in the zone of normovolaemia is to maintain a normal intravascular volume and avoid gaining weight due to excessive administration of fluid. Adequate preoperative hydration and avoidance of bowel preparation aim to keep the patient close to normovolaemia prior to surgery. Physiological interventions during anaesthesia such as intermittent positive pressure ventilation, vasoactive drugs and regional anaesthetic techniques can all affect vasomotor tone and intravascular volume. Due to the venous capacitance vessels, there is a range (sweet spot) within which normovolaemia, cardiac output and tissue perfusion can be adequately maintained. The experienced anaesthesiologist can keep the patient in this zone of normovolaemia throughout the operative and immediate post-operative periods. The use of additional monitoring devices such as pulse pressure variation (PPV), stroke volume variation (SVV), oesophageal Doppler and pulse contour wave analysis can all provide the anaesthesiologist with additional useful information to help guide fluid therapy, even though routine use of advanced hemodynamic monitoring and cardiac output optimisation has not shown to consistently improve post-operative outcomes.[70–73] This is more important when the physiological situation is challenging such as haemorrhage, poor cardiac function or vasodilatation secondary to drugs, regional analgesia or sepsis. Optimal control of intravascular volume, cardiac output and oxygen delivery combined with perfusion pressure maintains optimal oxygen and nutrient delivery to the cells as well as reducing extracellular fluid flux. Maintenance of normothermia maintains central and peripheral perfusion and effective circulatory volume. This makes it easier for the anaesthesiologist to avoid the patient becoming relatively hypovolaemic with resultant hypoperfusion of tissues with development of acidosis and lactataemia. The early establishment of oral intake of fluids as soon as possible after surgery allows the body to control homoeostasis.

Figure 2 shows 2 patient pathways with fluid shifts during and immediately after surgery. One patient is in an ERAS surgical protocol and the other in a traditional surgical pathway. The patient undergoing surgery within a traditional pathway has prolonged starvation and bowel preparation causing dehydration. The patient is hypovolaemic prior to the start of surgery and at the start anaesthesia, and intermittent positive pressure ventilation and drugs have a further negative effect causing splanchnic hypoperfusion. Intravenous fluid infusion restores the intravascular volume, however the prolonged continuation of intravenous fluids post-operatively for several days can lead to relative hypervolaemia and gut oedema with resultant ileus. The patient within the ERAS programme starts surgery within the 'green zone' of normovolaemia and is maintained there by the anaesthesiologist monitoring stroke volume and keep intravascular volume optimised which in turn reduces fluid shifts. Intravenous fluids are maintained at appropriate rates in the immediate post-operative period to maintain normovolaemia, but are then stopped with the commencement of oral intake thus avoiding salt and water overload. It is obvious that the controversy on perioperative fluid balance will continue as more research is carried out in patients at risk where careful administration of fluids and appropriate monitoring are taken into account.

Surgery and gut dysfunction

Major abdominal surgery induces an immuno-inflammatory response, which is accompanied by the production of reactive oxygen species (ROS) at the site of injury causing direct cellular injury by damaging lipids, proteins and DNA. Similarly, the hypothalamic peptide corticotropin-releasing hormone appears to interact with the inflammatory components and inhibit bowel function. The resulting impaired vascular permeability together with excessive fluid administration can lead to fluid overload, interstitial oedema and therefore delayed recovery of gastrointestinal function and impaired anastomotic healing.[68]

The causation of post-operative ileus is multifactorial and a number of risk factors have been identified (Fig. 3). These include increasing age, male gender, low pre-operative serum albumin, acute and chronic opioid use, previous abdominal surgery, pre-existing airways and vascular disease, long duration of surgery, emergency surgery, blood loss and salt and water overload. Most of these factors increase the inflammatory response, and inflammation and oedema play a major role in reducing intestinal smooth muscle contractility.[74] ERAS principles are aimed at reducing perioperative stress and inflammation and, hence, can reduce the duration of ileus and accelerate recovery of gut function post-operatively.

A number of strategies have been suggested to prevent post-operative ileus and some are more effective than others. These have been reviewed extensively recently and are summarised in Table 1.[74]

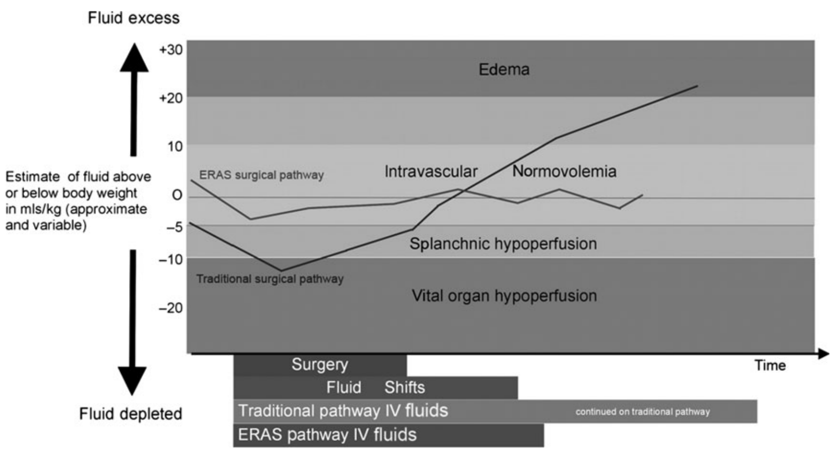

Fig. 2. Perioperative fluid administration with and without an ERAS surgical pathway: risk of perioperative fluid excess and tissue hypoperfusion.[104] Reproduced from Minto G et al. with permission.

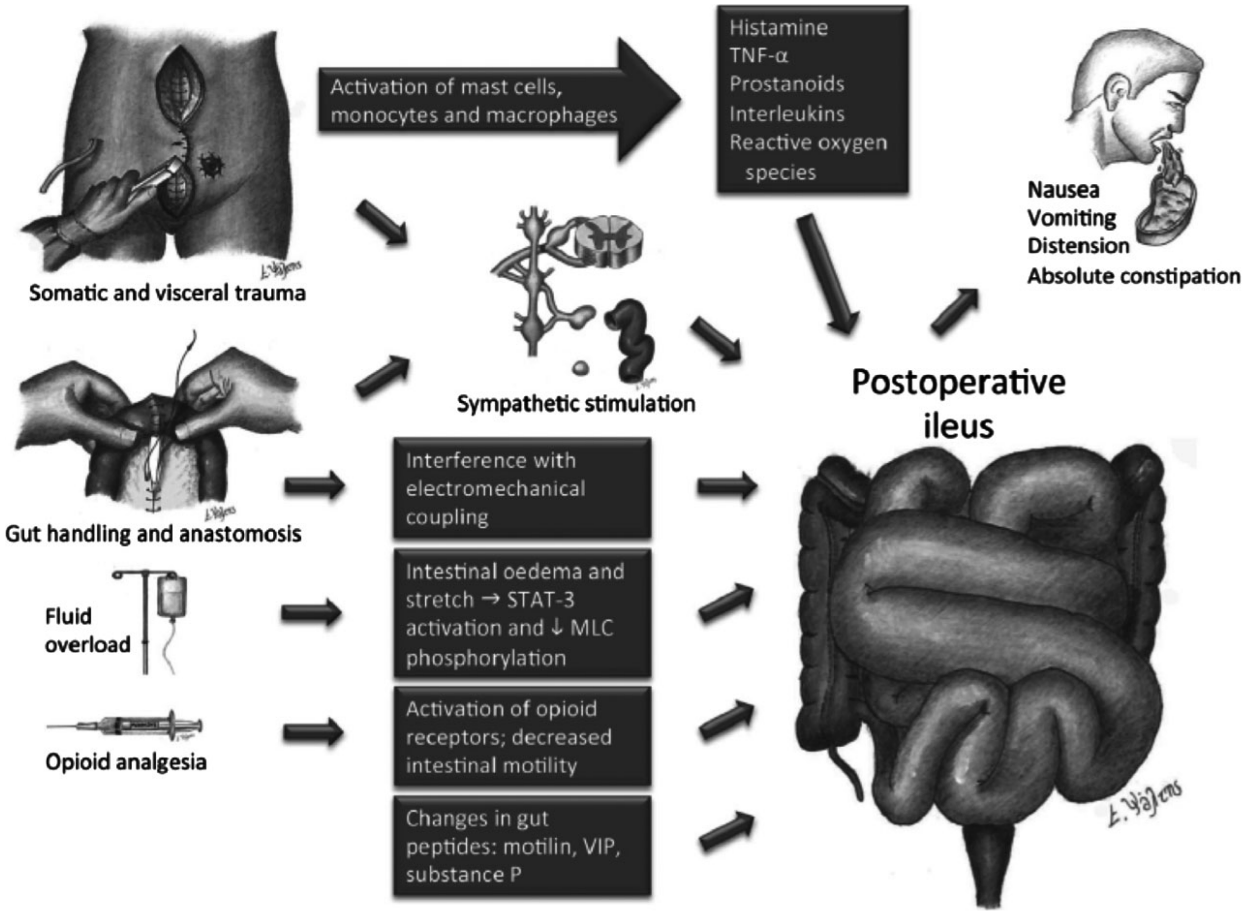

Fig. 3. Pathogenesis of post-operative ileus. MLC, myosin light chain; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor; VIP, vasoactive intestinal polypeptide. From Bragg et al. with permission.[74]

Alvimopan is a peripherally acting μ-opioid receptor antagonist, which does not cross the blood–brain barrier readily. A meta-analysis examining the effect of alvimopan vs. placebo on POI after major abdominal surgery found that alvimopan accelerated recovery of gastrointestinal function by 1.3–1.5 days at a dose of 12 mg/day and 6 mg/day respectively.[75] The time to readiness for discharge was also reduced correspondingly.[75] However, alvimopan is expensive ($1000 for 15 doses) and is not readily available outside the United States.

Surgery and anaesthesia are responsible for initiating nausea and vomiting in the post-operative period. More specifically, abdominal distension, bowel manipulation, intracellular fluid overload, and opioids stimulate peripherally (gut) and centrally located receptors that activate the central coordinating site for nausea and vomiting which is located in an ill-defined area of the lateral reticular formation in the brain stem.[76,77] This "vomiting centre", as it is traditionally called, is not so much a discrete centre of emetic activity as it is a "central pattern generator" (CPG) that sets off a specific sequence of neuronal activities throughout the medulla to result in vomiting.[78–80] A particularly important afferent is the chemoreceptor trigger zone (CTZ), which is located at the base of the fourth ventricle in the area postrema, outside the blood–brain barrier, and plays a role in detecting emetogenic agents in the blood and cerebrospinal fluid (CSF).[78] Five distinct receptor mechanisms have been identified in the CTZ that are involved in nausea and vomiting. They are serotonergic, dopaminergic, histaminergic, muscarinic and neurokinin-1 type. A variety of different pharmacological agents, acting on one

Table 1 Strategies to prevent post-operative ileus. From Bragg et al.[74] with permission.

Intervention	Mechanism	Benefit
		++
Salt and fluid overload	↓ gut oedema and stretch	±
Carbohydrate loading	↓ insulin resistance	–
Routine nasogastric tubes	Prophylactic drainage of stomach	+
Intravenous lidocaine	Anti-inflammatory; opioid-sparing	+
Coffee	Stimulatory effect	+
Chewing gum	Stimulatory effect	++
NSAIDs	Anti-inflammatory; opioid-sparing	++
Early enteral nutrition	Anabolic; ↓ insulin resistance; stimulatory	++
ERPs	Multimodal effect	++
Laparoscopic surgery	↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction	++
Alvimopan	μ-opioid receptor antagonist	++
Mid-thoracic epidural anaesthesia	↓ inflammatory response ↓ sympathetic stimulation ↓ opioid requirement	+/±
Early mobilisation	? anabolic effect	+
Nicotine	Colonic prokinetic	+
Daikenchuto	Anti-inflammatory on acetylcholine receptors	+
Magnesium sulphate	Anaesthetic effect	±
Prokinetics	Prokinetic effect	

or more of the five major neurotransmitter categories are routinely used for the prophylaxis and/or treatment of PONV.[81]

Opioids, although not neurotransmitters, may have a significant effect on PONV, exerting both excitatory and inhibitory effects on the gastrointestinal system (e.g. inhibition of gastrointestinal motility). There are at least three different types of opioid receptors – μ, d and k. Exogenous opioid receptor agonists (e.g. morphine) affect intestinal motility by modulating cholinergic transmission. When administered peripherally, exogenous opioid receptor agonists decrease gastrointestinal motility and delay gastric emptying by inhibiting central μ-receptors.[82]

Risk factors for PONV are based on characteristics relating to the patients, anaesthetic or type of surgery. Specific risk factors for PONV in adults are female gender, history of PONV or motion sickness, use of opioids and non-smoking status. Although the relationship between patient-related risk factors and PONV are clear and well studied, such a relationship with type and duration of surgery is less clear. Nevertheless, a simplified risk scoring system for PONV incorporating the four risk factors have good predictability and is recommended for risk-based PONV prophylactic therapy.[81]

Surgery and nociception

Surgical incision and manipulation of tissues lead to cell disruption releasing a variety of intracellular chemical mediators. These include potassium, adenosine, prostanoids, bradykinin, nerve growth factors, cytokine and chemokine which activate and sensitise (peripheral sensitisation) peripheral nociceptors $A\delta$ and c-fibres to mechanical stimuli (primary hyperalgesia). These pro-inflammatory substances and the release of substance P and calcitonin gene-related peptide from the peripheral branches of nociceptors also sensitise silent $A\delta$ nociceptors in the adjacent non-injured tissues (secondary hyperalgesia). Repeated and prolonged stimulation of peripheral nociceptors in the injured area and in the surrounding non-injured tissues lead to an increase firing of neurons at the level of the dorsal horn of the spinal cord, mediated by the activation of Na-methyl-D-aspartate (NMDA) receptors (central sensitisation). Clinically, these pathophysiological changes could manifest with hyperalgesia, allodynia, and even persistent postsurgical pain. Descending sympathetic inhibitory pathways also play an important role at the level of the spinal cord by modulating transmission of noxious inputs. The response to nociception contributes to activate and potentiate the stress response associated with surgery. Activation of the hypothalamic–pituitary–adrenal axis (HPA), sympathetic stimulation and systemic release of pro-inflammatory cytokines are major determinants of post-operative insulin resistance, that if not attenuated potentially lead to multiorgan dysfunction (Fig. 4). Acute surgical pain can, therefore, be

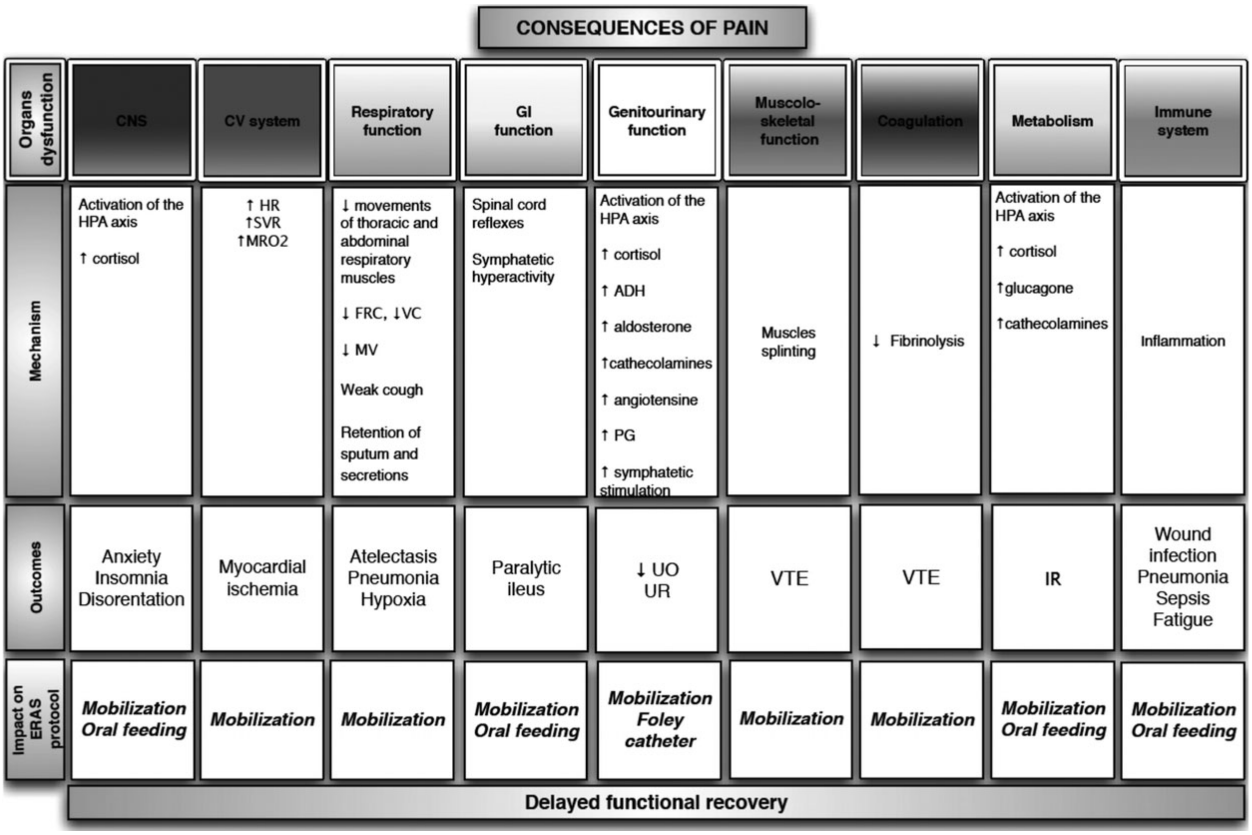

Fig. 4. Post-operative pain: physiological consequences and impact on outcomes and ERAS protocol. CNS, Central Nervous System; HPA axis, Hypothalamic–Pituitary–Adrenal axis; CV, Cardiovascular; HR, Heart Rate; SVR, Systemic Vascular Resistance; MRO2, Metabolic Rate of Oxygen; FRC, Functional Residual Capacity; VC, Vital Capacity; MV, Minute Ventilation; GI, Gastrointestinal; ADH, Antidiuretic Hormone; PG, Prostaglandins; UO, Urinary Output; UR, Urinary Retention; VTE, Venous Thromboembolism; IR, Insulin Resistance. Reproduced from Cologne K et al. with permission.[106]

somatic, visceral or neuropathic depending on the type of surgery and on the surgical approach.[83,84] The scientific rationale for multimodal analgesia is based on the multifactorial nature and complexity of surgical pain pathways. The purpose of multimodal analgesia is to control pain with different classes of medications acting on multiple sites.[85] In the context of the ERAS programme, the adaptation of multimodal analgesic strategies aims not only to improve post-operative pain control and reduce surgical stress but also to attenuate the multiorgan dysfunction induced by unrelieved pain, reduce opioid side effects, facilitate early resumption of oral diet and early mobilisation and ultimately accelerate surgical recovery (Fig. 4). Ten years ago ERAS programmes relied extensively on thoracic epidurals and NSAIDs as the cornerstones of analgesia. For colorectal surgery at least, there has been a sea change away from open surgery and towards laparoscopic techniques whenever possible. Equally, there have been concerns raised about a possible adverse influence of NSAIDs on anastomotic integrity.[86] These two factors have led to the increased use of spinals/TAP blocks or intravenous lidocaine and decreased use of epidural anaesthesia/NSAIDs.[87,88] It has to be said that while the physiological effects of epidural blockade on surgical stress have been well validated, the same cannot be said for lidocaine i.v. infusion and local anaesthetics techniques such as TAP blocks.

Surgery and cognitive dysfunction

Surgical trauma provokes a neuroinflammatory response resulting in either transitory and reversible or persistent impairment of cognition.[89] While some patients develop post-operative delirium (POD), characterised by inattention, disorganised thinking and altered level of consciousness, others develop post-operative cognitive dysfunction (POCD) which is chronic by nature and characterised by deficit in attention, concentration, executive function, verbal memory, visuospatial abstraction and psychomotor speed.

The international study on post-operative cognitive dysfunction (ISPOCD 1) study published in the lancet in 1998 demonstrated long-term POCD in elderly patients undergoing non-cardiac surgery.[90] However, the second study published in 2003 (ISPOD2) found no significant difference in the incidence of cognitive dysfunction 3 months after either general or regional anaesthesia.[91] Accordingly, there is no evidence to suggest any causative relationship between general anaesthesia and long-term POCD.

A possible pathogenic mechanism is of inflammatory nature whereby pro-inflammatory cytokines increased significantly in the systemic circulation and the central nervous system.[92] Pre-existing factors can contribute to POCD, such as advanced age, metabolic syndrome, education, vascular dementia and attention deficit disorders. Sleep disruption, poor analgesia, anaesthetic medications such as benzodiazepines can further exacerbate POCD.

Due to the complexity of the pathogenic mechanism and the multifactorial nature of POD and POCD, attempts are made to identify vulnerable patients and interventions which promote resolution of neuroinflammation. In this context, strategies such as minimally invasive surgery, guiding anaesthetic depth with BIS monitoring,[93,94] adequate pain relief, limited use of benzodiazepines[95,96] and opioids, a quiet environment to facilitate sleep and accelerated discharge home have been proposed as effective measures which need to be confirmed in large trials.

Surgery and post-operative deconditioning

Prolonged bed rest for up to several weeks in hospital was standard surgical practice until the 1940s, probably originating from fears of wound infection or dehiscence and the idea that rest would promote tissue healing.[97] Individuals confined to bed experience a linear decline in exercise capacity, as a result of reduced maximal stroke volume and cardiac output with VO_2max decreasing at a rate of about 1% every 2 days.[98] Complications of prolonged bed rest include skeletal muscle atrophy and weakness, bone loss, decreased insulin sensitivity, thromboembolic disease, microvascular dysfunction, atelectasis and pressure ulcers.[99,100] The negative effects of bed rest can occur after a relatively short period. Decreases in insulin sensitivity can also be detected after as little as 3 days of bed rest; even just 1 day of physical inactivity (sitting) can reduce insulin sensitivity significantly.[101] In older patients, deconditioning occurs by day 2 of hospitalisation.[102]

Post-operative fatigue (POF) is a well-recognised condition characterised by tiredness, lack of concentration which can impact on patient's quality of life. It can occur for several weeks after abdominal surgery and the duration is related to the intensity of surgery.[103] It appears that cancer has some influence on the development of post-operative fatigue. Beside the reported unpleasant and distressing symptoms, objective measures of POF have been identified, such as increased exercise-induced heart rate, elevated production of pro-inflammatory cytokines, decline in cardiorespiratory effort, weight loss, muscle weakness and anorexia. Patients need more energy to perform a given physical task. The psychological aspects of POF have been studied in depth, and it appears that while early symptoms of fatigue can be due to somatisation, late fatigue is secondary to cognitive-behavioural factors. Pre-operative anxiety and depression has been reported to be predictive of the development of fatigue.

ERAS pathways are not specific in relation to the type of exercise to be conducted after surgery as there is no evidence at present to support the use of one plan over another. There is a need to emphasise the importance of an early structured mobilisation plan with daily written targets for time out of bed or distance walked, beginning as early as the day of surgery. POF has a multimodal aetiology and, therefore, requires multimodal intervention. Some improvement in POF has been reported with implementation of combining therapeutic strategies, however more data are required.

Conclusions

Understanding the pathophysiology of the surgical stress response enables clinicians to identify the therapeutic interventions which are incorporated into the ERAS pathway aiming at accelerating the recovery process by targeting some key elements, insulin resistance, disruption of homoeostasis and nociceptive stimulation. There is some evidence that the ERAS synergistic approach is effective and physiologically makes sense, although this is not always translated into clinical outcome. Many aspects need more clarification as the literature is conflicting as ERAS principles continue to evolve and more research is required. ERAS is evidence-based, however translation into clinical care is lagging. It requires continuing professional development, additional debate, interdisciplinary involvement, patient education and regular revalidation. Ultimately, ERAS can lead to major improvements in the quality of patient care, better patient outcomes as well as economic benefits for the whole health care system. This implies that anaesthesiologists play a crucial role in development and the deployment of the programme.

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Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice

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Dr Olle Ljungqvist is founder, shareholder, board member Encare AB, Sweden; board member Nutricia A/S The Netherlands; he also receives speaker's honoraria from Fresenius Kabi, B/Braun, Nutricia, Merck. Dr Dileep N Lobo has received speaker's honoraria and unrestricted research funding from Fresenius Kabi, Baxter & BBraun, and has served on advisory boards of AbbVie & Baxter.

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Background: The present interdisciplinary consensus review proposes clinical considerations and recommendations for anaesthetic practice in patients undergoing gastrointestinal surgery with an Enhanced Recovery after Surgery (ERAS) programme.

Methods: Studies were selected with particular attention being paid to meta-analyses, randomized controlled trials and large prospective cohort studies. For each item of the perioperative treatment pathway, available English-language literature was examined and reviewed. The group reached a consensus recommendation after critical appraisal of the literature.

Results: This consensus statement demonstrates that anaesthesiologists control several preoperative, intraoperative and postoperative ERAS elements. Further research is needed to verify the strength of these recommendations.

Conclusions: Based on the evidence available for each element of perioperative care pathways, the Enhanced Recovery After Surgery (ERAS ®) Society presents a comprehensive consensus review, clinical considerations and recommendations for anaesthesia care in patients undergoing gastrointestinal surgery within an ERAS programme. This unified protocol facilitates involvement of anaesthesiologists in the implementation of the ERAS programmes and allows for comparison between centres and it eventually might facilitate the design of multi-institutional prospective and adequately powered randomized trials.

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Editorial comment: what this article tells us

This consensus paper includes a number of recommendations to enhance recovery in patients undergoing gastrointestinal surgery. Preoperatively, optimization of medical disease and cessation of smoking and alcohol intake are emphasized. Prevention of nausea and vomiting is important. Careful titration of anaesthetics and ensuring full recovery of neuromuscular blockade are recommended. During surgery, there should be normal values of arterial oxygen level, intraoperative temperature and glucose concentration. The article also includes recommendations regarding fluid therapy, opioid-sparing analgesia and mobilization.

Over 234 million major surgical procedures are performed globally each year[1] and despite advances in surgical and anaesthetic care, morbidity after abdominal surgery is still high[2]. Fast-track or enhanced recovery after surgery (ERAS) clinical pathways have been proposed to improve the quality of perioperative care with the aim of attenuating the loss of functional capacity and accelerating the recovery process[3].

The ERAS pathways reduce the delay until full recovery after major abdominal surgery by attenuating surgical stress and maintaining postoperative physiological functions. The implementation of the ERAS pathways has been shown to impact positively in reducing postoperative morbidity, and as a consequence, length of stay in hospital (LOSH) and its related costs[4–9].

In recent years, several studies have highlighted the impact of the anaesthetic management on postoperative morbidity and mortality[10–13]. In view of the evidence that many elements of the ERAS programme published by the ERAS Society in 2009 are of related to anaesthetic care, it is imperative that guidelines on perioperative care include recommendations approved by an interdisciplinary team comprising anaesthesiologists and surgeons[3].

As a follow-up of the previous manuscript[14] where the pathophysiological basis of the ERAS were analysed, this article represents an effort of the ERAS Society (www.erassociety.org) to present a consensus review of clinical considerations, including recommendations, for optimal anaesthesia care for patients undergoing gastrointestinal surgery within the ERAS programme. It is not the purpose of this manuscript to provide detailed information about each single ERAS element and for each type of gastrointestinal surgical procedure. Most of the ERAS elements have been already discussed extensively, specifically for different types of surgical procedures, as well the quality of evidence supporting each ERAS element[15–19]. It must be acknowledged that evidence supporting some of the ERAS elements still remains controversial.

Methods

An interdisciplinary group of physicians, anaesthesiologists and surgeons who are experts in the field of ERAS programmes were invited to participate in the preparation of this consensus statement.

Literature search

The authors met in October 2012 and the topics for inclusion were agreed upon and allocated. The principal literature search utilized MEDLINE, Embase and Cochrane databases to identify contributions related to the topic published between January 1966 and May 2014. Medical Subject Headings (MeSH) terms were used, as were accompanying entry terms for the patient group, interventions and outcomes. Key words included "'anesthesia'', "anaesthesia", "analgesia", "surgery", "'enhanced recovery'' and "'fast track''. Reference lists of all eligible articles were checked for other relevant studies. Conference proceedings were not searched. Expert contributions came from within the ERAS Society Working Party.

Study selection, assessment and data analyses of the identified trials

Based on the literature search, titles and abstracts were screened by individual reviewers to identify reviews, case series, non-randomized studies, randomized control studies, meta-analyses and systematic reviews that were considered for each individual topic. Discrepancies in judgment were resolved by the senior author and during committee meetings of the ERAS Society Working Party.

Recommendations
Recommendations were made by the panel based on the evidence supporting each ERAS element. Specifically, "Strong recommendations" indicate that the panel was confident that the desirable effects of adherence to a recommendation outweighed the undesirable effects. "Weak recommendations" indicate that the desirable effects of adherence to a recommendation probably outweighed the undesirable effects, but the panel was less confident. Recommendations were based on the balance between desirable and undesirable effects, and on values and preferences.

Part A. Preoperative ERAS elements

An ERAS approach to preoperative evaluation

Pre-admission risk stratification
Risk scoring systems have been used to try and identify which patients are at higher risk of death and complications from major surgery. Up to 80% of postoperative deaths come from this high-risk group[20]. It is imperative not only to provide patients with an overview of the risk of surgery but also to select those patients for further investigation and optimization and decide which perioperative care pathway the patients should be on for resource allocation. In a major retrospective study in the USA, Khuri et al. analysed data on 105,951 patients undergoing a variety of different specialty major surgical procedures. The striking result was that if patients had a major complication within 30 days of surgery then it reduced median survival by 69% at 8 years[21]. Therefore, identification for risk factors for any major complication of surgery is also important.

Scoring systems for surgery. Many different scoring systems, some of them procedure-specific, have been developed for patients undergoing surgery. The purpose of this section is to give an overview of the most common scoring system use in clinical practice beside the well known American Society of Anesthesiologists (ASA) physical status score.

POSSUM scores: in 1991, Copeland et al. described the POSSUM (Physiological and Operative Severity Scoring for the enUmeration of Mortality and morbidity) scoring system for general surgical patients[22]. This is a two part scoring system based on physiological assessment (12 variables) and operative severity (six variables). Each variable has a 1–4 point range depending on severity. The system predicts 30-day risk for mortality (matrix for the 50% prediction of risk of mortality: specificity = 99.3% and sensitivity = 54.1%) and morbidity (matrix for the 50% prediction of risk of morbidity: specificity = 92.4% and sensitivity = 52.1%). The Portsmouth POSSUM (P-POSSUM) better predicts postoperative mortality[23], as the original POSSUM logistic regression equation overpredicts mortality especially in low-risk patients. POSSUM has been also modified slightly for different specialties such as colorectal[24], oesophageal[25] and vascular surgery[26] to try and improve sensitivity and specificity for these specialties.

Assessing cardiac risk in non-cardiac surgery—Cardiovascular risk can be predicted by multivariate risk incidences that include clinical and surgical criteria, and biological markers[27–29]. These tools have been incorporated in the recent ACC/AHA 2014 guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery.[30]

The Lee index—The Lee Index is a modification of the original Goldman cardiac risk index[31]. It comprises six independent clinical determinants of major perioperative cardiac events:

1. History of ischaemic heart disease (IHD)
2. History of cerebrovascular disease
3. Heart failure
4. Preoperative insulin treatment for diabetes mellitus
5. Serum creatinine > 177 μmol/l
6. High-risk type of surgery

All factors contribute 1 point equally to the index, and for patients with an index of 0, 1, 2 and 3 points the incidence of major cardiac complications is estimated at 0.4%, 0.9%, 7% and 11% respectively.[31]

Cardiovascular Risk Calculator—A similar tool to determine the postoperative probability of myocardial infarct or cardiac arrest has been validated by Gupta and colleagues in 211,410 patients undergoing surgery. It contains five independent predictors[28]:

1. Type of surgery
2. Dependent functional status (inability to perform activities of daily living in the 30 days before surgery, partially independent or totally independent)
3. Abnormal serum creatinine
4. American Society of Anesthesiologists class (ASA)
5. Increasing age

More recently there has been increasing awareness that perioperative myocardial injury does not always present with any of the typical ischaemic features of chest pain, electrocardiogram changes, rhythm disturbance or heart failure. The VISION study measured troponins and showed a spectrum of results with 44% of troponin rises fulfilling the criteria for myocardial injury without fulfilling a traditional definition of perioperative myocardial infarction[32].

Assessment of functional capacity. Estimating functional capacity is an important start of assessing a patient. Functional capacity is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate at rest. Climbing one flight of stairs demands 4 METs and strenuous activity such as playing tennis or swimming is > 10 METS. The inability to perform 4 METS indicates poor functional capacity and is associated with an increased incidence of postoperative cardiac events.[33] The presence of good functional capacity, even in the presence of stable IHD or other risk factors is associated with a good outcome.[34] As patients poorly estimate their functional capacity, it is important to obtain an independent assessment using dynamic testing.

Dynamic Tests

Walk Tests—(2 min, 6 min, shuttle) All these tests measure the distance covered over a set period of time by the patient. They have been validated in clinical practice and are easy to administer.[35,36] Norms according to age and gender have been created. Although they correlated with cardiopulmonary testing, they have not been used to determine whether to operate or not on patients undergoing high-risk surgery.

Cardiopulmonary Exercise Testing (CPET)—This is a dynamic non-invasive objective test that evaluates the ability of a patient's cardiopulmonary system to adapt to a sudden increase in oxygen demand. The ramped exercise test is performed on a cycle ergometer with ECG monitoring and analysis of expired carbon dioxide and oxygen consumption, the later being directly related to oxygen delivery and a linear function of cardiac output when exercising. With increasing exercise, oxygen consumption will eventually exceed oxygen delivery. Aerobic metabolism becomes inadequate to meet the metabolic demands and blood lactate rises reflecting supplementary anaerobic metabolism. The value for oxygen consumption at this point is known as the anaerobic threshold (AT), expressed as ml/kg/min VO_2 peak/max can also be measured. Both values have been used to try and predict the risk of complications. Older's original work in colorectal patients showed that if a patient's AT was less than 11 ml/kg/min, the patients was at higher risk of complications which was increased if there was the presence of ischaemic heart disease.[37,38] Snowden et al. showed that an AT cut-off value of 10.1 ml/kg/min predicts complications better than an algorithm-based activity assessment (Veterans Activity Questionnaire Index [VASI]).[39] Similarly, in patients undergoing pancreatic, hepatic and vascular surgery and AT < 10 ml/kg/min predicts complications and early postoperative death[40–43]. VO_2 max has also been studied to predict outcome and has been shown to be a sensitive marker for cardiopulmonary complications in patients undergoing oesophageal resection[44]. Despite its high sensitivity, the specificity of the CPET is not high enough to identify patients with a significant preoperative risk correctly, as patients with low ATs can still undergo major surgery without complications.

Risk of acute kidney injury (AKI). Approximately 1% of patients undergoing non-cardiac surgery develop AKI, and it is associated with higher morbidity and mortality. Eleven preoperative risk factors (age 56 years or older, male sex, emergency surgery, intraperitoneal surgery, diabetes mellitus necessitating oral therapy, diabetes mellitus necessitating insulin therapy, active congestive heart failure, ascites, hypertension, mild preoperative renal insufficiency and moderate preoperative renal insufficiency) have been identified as independent predictors of AKI in patients undergoing non-cardiac surgery. The risk of developing postoperative AKI can be stratified in five classes based on to the presence of these risks factors (General Surgery Acute Kidney Injury Risk Index).[45]

Summary and recommendations: preoperative scoring tools and functional capacity tests can be used to identify patients at risk of complications and to stratify perioperative risk (Table 1).

Recommendation grade:
POSSUM: strong
Lee Index: strong
Cardiovascular Risk Calculator: strong
Walk tests: strong (to predict postoperative morbidity, but not to decide if operate or not)
CPET: strong
General Surgery Acute Kidney Injury Risk Index: strong

Optimization of pre-existing health conditions

Alcohol. Alcohol abusers (defined by the World Health Organization as ingesting more than 36 g of ethanol or equivalent of 3 standard drinks/day) have an increased risk of perioperative bleeding and wound infection. Furthermore, alcohol impairs the metabolic stress response, cardiac and the immune function. The risk increases proportionately with the amount of alcohol ingested with an increased perioperative risk of 200–400% when ingestion exceeds 5 drinks or 60 g of ethanol per day. A minimum of 4 weeks abstinence is needed to reduce these risks, but 8–12 weeks may be needed for patients to return to normal. However, it is often a challenge to maintain abstinence in these patients even with replacement medical therapy. Patients with end stage liver failure due to cirrhosis are at extremely high risk and will need expert care for all types of procedures[46,47].

Smoking. Smokers often have comorbidities due to smoking such as chronic obstructive airways disease, emphysema, peripheral vascular and ischaemic heart disease and cerebrovascular

Table 1 Scoring systems for surgery.

Test	Predicting	Scoring	Evidence level	Recommendation
P-POSSUM	Mortality and Morbidity	12 physiological and 6 operative variables	High	Strong
Lees index	Perioperative cardiac complications	6 preoperative clinical factors	Moderate	Strong
Cardiovascular Risk Calculator	Myocardial Infarct or Cardiac Arrest	4 preoperative clinical factors and 1 operative variable	Moderate	Strong
Shuttle Walk Test	Perioperative complications	Aerobic fitness	Moderate	Moderate
Shuttle Walk Test	Screening tool to proceed to CPET/echocardiography etc.	Aerobic fitness	Moderate	Strong
Cardiopulmonary Exercise testing (CPET)	Perioperative complications	Aerobic exercise – AT and VO_2 max	Moderate	Strong
Cardiopulmonary Exercise testing (CPET)	Selecting patient's suitability for surgery	Aerobic exercise – AT and VO_2 max	Moderate	Moderate
General Surgery Acute Kidney Injury Risk Index	Acute Kidney Injury	11 preoperative clinical factors	Moderate	Moderate

AT, anaerobic threshold; VO_2, maximum oxygen consumption.

disease that can increase the risk of perioperative complications independently. Smokers without these comorbidities still have an increased perioperative risk, mainly due to poor wound and tissue healing which can lead to wound infection[48] as well as cardiopulmonary complications such as chest infection. Studies have been undertaken to assess whether short-term abstinence from smoking can improve outcome. The cessation of smoking for 4 weeks prior to surgery has been shown to improve wound healing.[48–50] The use of nicotine replacement therapy (NRT) and counselling facilitate preoperative smoking cessation.[49] Other pharmacological interventions are also available. Varenicline, in combination with two preoperative 15-minute standardized counselling sessions, started 1 week before surgery and followed up for 12 weeks, was shown to improve long-term smoking abstinence (RR 1.45, 95% CI 1.01–2.07, $P = 0.04$) but not reduce postoperative complications in comparison with placebo. However, nausea occurred more frequently in patients treated with varenicline (13.3% vs. 3.7%, $P = 0.004$).[51] Antidepressants such as bupropion also seem beneficial to improve smoking cessation, but limited data are available in the perioperative setting.[52,53]

Preoperative anaemia. Haemoglobin is one of the main determinants of oxygen delivery. Preoperative anaemia is common and is an independent predictor of mortality and postoperative complications.[54,55] Haemoglobin levels should be corrected preoperatively, as it is common to expect a drop of haemoglobin concentrations due to blood loss and to the dilution effect of intravenous fluids. Correction of preoperative anaemia should take in consideration its aetiology.[56,57] Iron, folate, vitamin B_{12} supplements and/or erythropoietin should be used when appropriate. Medical management of preoperative anaemia takes time and should be planned at least 3–4 weeks before elective surgery. Although preoperative blood transfusion corrects anaemia rapidly and could be used in severely anaemic patients and/or in patients undergoing surgery with expected profound blood loss, caution should be used as it has been associated with increased mortality and morbidity.[58–60] These effects seem to be dose-dependent.[58] The risk of transfusion-related complications and the effect of blood transfusion on the immune system must be also considered.[56,57,61] Evidence suggesting that normalizing preoperative haemoglobin levels prior to surgery reduces postoperative morbidity and mortality is lacking and studies evaluating the role of preoperative anaemia optimization are warranted.[57,62] Implementation of perioperative blood management protocols can reduce the risk of allogenic blood transfusions.[56,57]

Cardiovascular risk reduction. It is not the intent of this manuscript to discuss in detail perioperative cardiovascular strategies to reduce cardiovascular risk. These interventions are extensively discussed in the recent ACC/AHA 2014 guidelines.[30]

Asthma, COPD and diabetes. Chronic conditions such as asthma, chronic obstructive airways disease[63], diabetes mellitus[64] malnutrition[65–67] and frailty[68] should be optimized prior to surgery.

Summary and recommendation: cessation of smoking and alcohol intake at least 4 weeks before surgery is recommended. Encouraging patients is not enough; pharmacological support and individual counselling should be offered to every patient who smokes and to alcohol abusers undergoing elective surgery. Optimization of medical conditions, such as cardiovascular diseases, anaemia, chronic obstructive airways disease, diabetes, nutritional status and frailty and should follow international recommendations.

Recommendation grade:
Smoking cessation: high
Nicotine replacement therapy and counselling: high
Alcohol cessation: low
Medical optimization: strong

Pre-anaesthetic medications

Patients undergoing major surgery are, as expected, anxious. Anxiety has also been shown in many studies to be the most common predictor for postoperative pain and positively correlates with postoperative pain intensity.[69] Furthermore, preoperative pain is also a significant predictor for postoperative pain.[70] Therefore, education and counselling, and preoperative analgesic and anxiolytic medication must be specifically addressed during the preoperative assessment of the patient. Short-acting anxiolytics and analgesics can be administered to facilitate regional anaesthetic procedures and insertion of intravascular lines, provided they are used in adequate doses based on age and patients' comorbidities.[71] Short-acting benzodiazepines should be avoided in older patients (age > 60).[72] Long-acting sedatives and opioids should be avoided as they may hinder recovery, thus impairing postoperative mobilization and direct participation, resulting in prolonged length of stay.[71]

Summary and recommendation: long-acting anxiolytic and opioids should be avoided as they may delay discharge. Short-acting benzodiazepine should be avoided in the elderly.

Recommendation grade: strong

Preoperative fasting and carbohydrate loading

Although fasting guidelines of various anaesthesia societies support the safety of allowing clear fluids up to 2 h and solid food up to 6 h before the induction of anaesthesia, patients scheduled for elective surgery are commonly asked to fast from midnight. The evidence supporting this practice, with the belief to ensure an empty stomach before the induction of anaesthesia and decrease the risk of aspiration is lacking.[73] On the contrary, it has been shown that fasting from midnight increases insulin resistance, patient's discomfort and potentially decreases intravascular volume, especially in patients receiving mechanical bowel preparation.[74] In fact, functional intravascular deficit after fasting time, as indicated by guidelines[75] or after 8 h fasting[76] is minimally affected in patients undergoing elective surgeries without mechanical bowel preparation.[75,76] Results from two Cochrane meta-analyses have shown that gastric content of patients following anaesthesia fasting guidelines is the same or lower of the gastric content of patients fasting after midnight.[77,78] Imaging studies have further supported the safety of allowing clear fluids up to 2 h before the induction of anaesthesia, showing complete gastric emptying with 90 min.[79] Recently, the European and American Anesthesia Society have revised their fasting guidelines and have not changed their previous recommendations.[80,81] Preoperative treatment with oral complex carbohydrates (CHO) (maltodextrin) with a relatively high concentration (12.5%), with 100 g (800 ml) administered the night before of surgery and 50 g (400 ml) 2–3 h before induction of anaesthesia, reduces the catabolic state induced by overnight fasting and surgery. Indeed, overnight fasting before surgery inhibits insulin secretion and promotes the release of catabolic hormones such as glucagon and cortisol. By increasing insulin levels preoperative treatment with oral CHO reduces postoperative insulin resistance, maintains glycogen reserves, decreases protein breakdown and improves muscle strength.[82] Faster surgical recovery and better postoperative well-being still remains controversial[83,84]. Delayed gastric emptying should be suspected in patients with documented gastroparesis, patients on prokinetic agents such as metoclopramide and/or domperidone, patients scheduled for gastrointestinal operations such oesophageal, gastric, fundoplication, paraesophageal hernia repair, gastro-jejunostomy, in patients who underwent previous Whipple's procedure, in patients with achalasia and in patients with neurological diseases with dysphagia. Patients with diabetes with neuropathy and, less clearly, obese patients[85] are considered to have delayed gastric emptying. However, gastric emptying after 300 ml of clear fluids 2–3 h before the induction of anaesthesia in obese patients has been shown to be similar to those of lean patients[86,87] and gastric emptying after CHO administration in patients with uncomplicated diabetes is normal.[88,89] The clinical relevance of preoperative CHO drinks in these specific populations remains to be established.

Summary and recommendation: Intake of clear fluids should be allowed until 2 h before induction of anaesthesia. Solids should be allowed until 6 h. Preoperative treatment with oral CHOs can be administered safely except in patients with documented delayed gastric emptying or gastrointestinal motility disorders and as well in patients undergoing emergency surgery.

Recommendation grade:
Adherence to fasting guidelines (avoid overnight fasting): strong
Administration of preoperative CHOs: strong
Administration of preoperative CHOs in diabetic and obese patients: weak

Part B. Intraoperative and postoperative ERAS elements

Preventing and treating postoperative nausea and vomiting

Despite significant advances in our knowledge of PONV and the introduction of new agents, the overall incidence of PONV is currently estimated to be 20–30%. In high-risk patients, the incidence in still as high as 70%,[90] and it is one of the most unpleasant experiences in the perioperative period.[91]

There are many risk factors that predispose patients to PONV.[92] The most widely used scoring system was developed by Apfel et al.,[93] who created a simplified scoring system using only four risk factors – female gender, a history of motion sickness or PONV, non-smoking status and the use of postoperative opioids.[92]

The multimodal approach to PONV within an ERAS programme contains the use of antiemetics and a total intravenous anaesthesia with propofol instead of inhalational agents. Avoidance of nitrous oxide is also important.[94] Other factors like the reduction of preoperative fasting, carbohydrate loading and adequate hydration[95,96] and high inspired oxygen concentrations[97] may influence the prevalence of PONV. The use of regional anaesthetic techniques and the use of non-steroidal anti-inflammatory drugs (NSAIDs) as opioid-sparing strategies may have an additional indirect influence on the prevalence of PONV.

Classes of antiemetics (serotonergic, dopaminergic, cholinergic and histaminergic) are based on the antagonism of different kinds of central receptors that are all involved in the pathophysiology of PONV and all have shown to be superior to placebo in the prevention of PONV.[98] Newer drugs as the neurokinin-1 receptor antagonists show encouraging results in initial trials.[99] Unfortunately, none of the available pharmacological agents when used alone are effective in reducing the incidence of PONV by more than 25%. Antiemetic combinations are recommended for patients at higher risk of PONV. Combination therapy is more effective than monotherapy, and for high-risk patients, combination with 2–3 antiemetics in addition to propofol based total intravenous anaesthetic (TIVA) has the greatest likelihood of reducing PONV.

Examples of antiemetic drugs are serotonin antagonists like ondansetron 4 mg i.v. or dopamine antagonists like droperidol 0.625–1.25 mg i.v. given at the end of surgery or a transdermal patch of scopolamine placed the evening prior to or 2 h before surgery. Dexamethasone 4–5 mg i.v. after induction of anaesthesia has also been shown to be effective, but its immunosuppressive effects on long-term oncological outcome are unknown. Higher doses of dexamethasone have no additional effect and are associated to sleep disturbances. It should not be used in diabetic patients requiring insulin and not given prior to induction of anaesthesia due to perineal pain.

If PONV is present postoperatively, rescue therapy should be with an antiemetic from a different class unless the elapsed time from the previous antiemetic administration is greater than 6 h,[100] After prophylactic administration of 4 mg ondansetron re-dosing for established PONV was shown to be no more effective than placebo.[101]

Summary and recommendation: Aggressive PONV prevention strategy should be included in an ERAS protocol.[102] All patients with 1–2 risk factors should receive as PONV prophylaxis a combination of two antiemetics. Patients with 3–4 risk factors should receive 2–3 antiemetics and total intravenous anaesthesia (TIVA) with propofol and opioid-sparing strategies should be encouraged.[93,102]

Recommendation grade: strong.

Standard anaesthetic protocol and depth of anaesthesia monitoring

Although there are no studies comparing general anaesthetic techniques for gastrointestinal surgery, it is sensible to assume that within the ERAS protocol efforts have to be made to minimize the impact of anaesthetic agents and techniques on organ function, and to facilitate rapid awakening from anaesthesia thus accelerating recovery of the patient's gastrointestinal and motor functions. As such particular attention can be drawn to the type of agents used and the monitoring of vital functions.

Traditionally the anaesthesiologist has relied on clinical signs to try and ensure appropriate depth of anaesthesia and avoidance of awareness but also avoiding overdose and the resultant depression of a patient's physiological status. Depth of anaesthesia can now be measured by many devices but in terms of clinical evaluation the data on Bispectral Index (BIS) far exceeds other devices.[103] Recent focus has been on using depth of anaesthesia monitoring not just to avoid awareness during surgery but also to titrate the minimum amount of anaesthetic necessary to avoid complications.[103–116] This appears to have particular significance in the elderly population with cognitive dysfunction.[117] Unfortunately BIS is not infallible. Many things can affect the BIS value, in particular neuromuscular relaxation, which is commonly used in anaesthesia. The specificity seems to be lower when using total intravenous anaesthesia (TIVA).[106] There is also a lag time between EEG interpretation and the displayed BIS value.

When compared with clinical signs alone, BIS obtains lower rates of awareness during surgery.[112–114,116] Anaesthetic depth guided by BIS may also help reduce the amount of drug given,[107,116] with more rapid immediate recovery although the time to discharge home appears to be unaffected[116]. In Myles' study, 138 patients needed to have BIS monitoring to avoid one case of awareness.[112] Avidan's studies[104,105] have demonstrated that maintaining anaesthetic depth with an end tidal concentration (EATC) between 0.7 and 1.3 MAC equivalents can prevent intra-operative awareness as effectively as anaesthesia guided by a BIS value between 40 and 60. The use of nitrous oxide, a N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to reduce the risk of awareness[118] with one study showing an NNT of 46,[119] however, there were two cases of awareness in the ENIGMA study in patients having nitrous oxide.[120] Recent studies have highlighted that patients with BIS levels < 45 under anaesthesia (reflecting increased suppression of brain activity) have an increased risk of death by up to 1.24-fold (95% CI 1.06–1.44).[121] Subsequent analysis suggests this may be a reflection of elderly patients who have multiple problems and cognitive dysfunction and may have a reduced life expectancy prior to surgery more likely to have low BIS values. More studies are needed to clarify this point. There is increasing interest in anaesthetic drugs and analgesic techniques. (e.g. morphine and thoracic epidural analgesia) and their effect on cancer outcome but there is currently not enough consistent data to support making specific recommendations.[122,123]

Summary and recommendation: anaesthetic depth should be guided either maintaining an end tidal concentration of 0.7–1.3 MAC or BIS index between 40 and 60 with the aim not only to prevent awareness but also to minimize anaesthetic side effects and facilitate rapid awakening and recovery. Avoid too deep anaesthesia (BIS < 45), especially in elderly patients

Recommendation grade: strong

Neuromuscular blockade (NMB) and neuromuscular monitoring

This section discusses the importance of neuromuscular blockade and neuromuscular monitoring, and their potential implications specifically in the context of an ERAS programme. Neuromuscular blockade agents (NMBA) paralyse skeletal muscles, allowing optimal conditions for surgery. The level of NMB needed to obtain optimal surgical conditions can differ depending on the surgical approach. A deep NMB might be particularly useful when a laparoscopic approach is used.[124,125] A recent systematic review showed that during certain laparoscopic procedures deep NMB (e.g. Post-Tetanic Count 1 or more; but Train of Four (TOF) Count of 0[126]) provide better surgical conditions than moderate NMB[125], but limited evidence is available to support this practice.[126] Moreover, the use of deep NMB during laparoscopic procedures, especially in countries where sugammadex is not available, may increase the risk of residual paralysis.[126] Although moderate NMB certainly facilitates surgical work, the use of NMB might not be always necessary for patients undergoing open abdominal surgery. Indeed, an adequate level of anaesthesia without muscle relaxants can produce a good to excellent surgical field in approximately two-third of patients undergoing radical retropubic prostatectomy.[127] In the light of these considerations, the hypotheses that optimal NMB can potentially attenuate surgical stress by shortening the duration of surgery, and that it can facilitate the use of low pneumoperitoneum pressures, thereby reducing postoperative pain remain appealing, especially in the context of an ERAS programme. However, this needs to be tested in larger high-quality trials.

At the end of surgery, it is important to restore neuromuscular function to preoperative levels and avoid residual muscle paralysis which can be responsible for respiratory insufficiency, hypoxia, aspiration into the lungs as well as distress for the patient.[128] Similarly, it might impair early mobilization. To avoid residual muscle paralysis long-acting NMBA should not be used.[128] Hypothermia also influences neuromuscular function directly and prolongs duration of action and recovery time of NMBA significantly.[129] Maintenance of normothermia is, therefore, essential to prevent residual paralysis.[129]

The use of NMBA must be guided by adequate assessment of neuromuscular block and appropriate monitoring. In healthy volunteers, it has been demonstrated that there is risk of pharyngeal dysfunction or aspiration if TOF < 0.9.[130] Furthermore, three clinical trials[131–133] have demonstrated that there is a greater proportion of hypoxaemic events and prolonged stay in the recovery room if TOF < 0.9. Even more experienced anaesthesiologists cannot clinically identify the degree of residual curarization.[134] Several studies have shown that clinical tests and qualitative (visual or tactile) assessment of neuromuscular function (TOF, double burst suppression or tetanic stimulation) are not reliable and sufficient to detect residual curarization,[128] even when sugammadex is used.[135] Quantitative methods such as mechanomyography and acceleromyography provide more accurate information.[136] Although mechanomyography remains the goal-standard to measure neuromuscular function, its use in clinical practice remains limited[136]. On the contrary, acceleromyography can be used easily to measure neuromuscular function and avoid residual paralysis.[136]

There are three ways to avoid residual paralysis:

1. Waiting for a spontaneous recovery of neuromuscular function identified by a TOF>0.9. This approach might not be convenient for brief surgical procedures, as the effect of some NMBA can last longer than 4 h, even after a single dose administered at the beginning of surgery.[137] Side effects of reversal agents are avoided.
2. Administering cholinesterase inhibitors. Side effects of cholinesterase inhibitors and antimuscarinic agents have to be considered.
3. Administering sugammadex. Sugammadex selectively revers the neuromuscular block induced by steroidal NMBA. Abrishami et al. demonstrated that sugammadex reverses neuromuscular block (rocuronium-induced) faster than neostigmine and independent of the depth of the neuromuscular block.[138] Sugammadex can be used at different dosages, 2, 4 or 16 mg/kg to reverse moderate, deep or recently induced block, respectively. Sugammadex reverses neuromuscular block 3–4 times faster than neostigmine, and the neuromuscular block is completely reversed after 5 min.

Summary and recommendations: It remains controversial if deep neuromuscular blockade during laparoscopic surgery improves operating conditions. Neuromuscular function should be always monitored when using NMBA to avoid residual paralysis. Long-acting NMBA should be avoided. When NMBA are administered neuromuscular function should be monitored by using a peripheral nerve stimulator to ensure adequate muscle relaxation during surgery and optimal restoration of neuromuscular function at the end of surgery. A TOF ratio of 0.9 must be achieved to ensure adequate return of muscle function and thus preventing complications.

Recommendation grade: Monitoring neuromuscular function: strong.

Reversing neuromuscular blockade: strong.

Use of inspired oxygen

Oxygen is a highly reactive gas which is ubiquitous in anaesthetic practice. In cellular physiology the controlled oxidation of glucose to carbon dioxide with the concurrent reduction of oxygen to water is the basis for aerobic metabolism and production of energy. Therefore, one of the highest priorities of the anaesthesiologist is to try to ensure a patient does not become hypoxic to avoid interruption of cellular metabolism.

Oxygen is widely available in anaesthesia and has traditionally been added to increase the inspired fraction of oxygen above 21% to overcome hypoxia under anaesthesia caused by physiological changes such as pulmonary shunt. Although increasing the FiO_2 is necessary to overcome hypoxia there has been increasing recognition that hyperoxia can cause damage due to the production of oxygen free radicals.

However, it has been suggested that high inspired oxygen concentration protects against the risk of surgical site infections. The PROXI trial, a multicentre RCT, found no differences between patients treated with a FiO_2 30% vs. 80% in terms of SSI or pulmonary complications.[139].A meta-analysis including the PROXI trial showed that two subgroups of patients benefitted from high inspired oxygen therapy – those undergoing general anaesthesia and colorectal surgery.[140] However a high-heterogeneity was found among the studies included.[140] The latest meta-analysis including new nine RCTs (5001 patients) found a marginal reduction of SSI in patients undergoing colorectal surgery treated with high concentrations of oxygen vs. normal oxygen concentrations (RR 0.77, 95% CI 0.59–1.00, $P = 0.03$). The study also found that high oxygen concentrations reduce the incidence of late (24 h postoperatively) nausea and vomiting, but only in patients receiving volatile anaesthesia without antiemetic prophylaxis.[97] Based on these data, it still remains unclear if high concentrations of oxygen protects against the risk of SSI.

On the con side was the long-term follow-up of patients included in the PROXI trial. This study showed a reduction in survival in patients with cancer who had received the higher inspired oxygen concentration.[141] Unfortunately, the authors failed to report why patients died earlier than patients receiving normal inspired oxygen concentrations. Both this study and the analysis of outcomes of patients following cardiac arrest, which show a poorer neurological outcome in patients receiving a higher FiO_2,[142,143] suggest that there can be harmful effects from receiving high inspired concentrations of oxygen.

Therefore, higher inspired oxygen concentrations of 80% may reduce surgical wound site infection especially in patients with colorectal cancer, but there may be deleterious effects on long-term cancer outcomes. To reduce wound infection to a minimum the importance of other contributing factors such as maintaining patient's body temperature, cardiac output, glycaemic control, prophylactic antibiotics and minimizing surgical contamination should also be considered.

The short-term use of high inspired oxygen concentrations is widely practised in anaesthesia to overcome hypoxic episodes and to pre-oxygenate (de-nitrogenate) the lungs prior to the induction of anaesthesia. Edmark and colleagues looked at differing inspired concentrations (60%; 80%; 100%) of oxygen for 5 min prior to the induction of anaesthesia.[144] Computed tomography showed an increase in atelectasis in the 100% inspired oxygen group although patients took longer to desaturate. The use of 80% oxygen in a subgroup of the PROXI study and in a recent meta-analysis also did not demonstrate any increased risk of pulmonary complications.[97,145]

Summary and recommendations

1). The inspired fractional concentration of oxygen should be titrated to produce normal arterial oxygen levels and saturations. Prolonged periods of high inspired oxygen concentrations which result in hyperoxia should be avoided.

Recommendation grade: strong

2). 100% inspired oxygen concentrations can be used for pre-oxygenation prior to anaesthesia or for short periods to overcome hypoxia.

Recommendation grade: strong

Preventing intraoperative hypothermia

Perioperative hypothermia, defined as a core temperature below 36°C is a common adverse consequence of anaesthesia and surgery.[146] The prevalence of inadvertent hypothermia ranges from 50% to 90%[147] independently whether patients undergo laparoscopic or open surgery.[148] Older adults are more prone to heat loss, whereas obesity has a protective effect.[149]

Hypothermia in most patients undergoing general anaesthesia is the result of an internal core-to-peripheral redistribution of body heat that usually reduces core temperature by 0.5–1.5°C in the first 30 min after induction of anaesthesia.[150]

Several meta-analyses and RCTs have demonstrated that preventing inadvertent hypothermia during major abdominal surgery significantly reduces wound infections,[151,152] cardiac complications,[151,153] bleeding and transfusion requirements,[153,154] and improves immune function,[151] the duration of post-anaesthetic recovery[155] and overall survival.[156] Therefore, it makes sense to prevent the loss of body heat as also recommended by the ERAS society.

Use of active warming devices is highly recommended in all cases lasting more than 30 min[151] and this can be achieved by using different warming devices (forced air warming systems, circulating water garments or warmed i.v. solutions). Combined strategies, and among the others preoperative warming, should be considered in vulnerable groups such as older patients with cardiorespiratory diseases, and surgery of long duration.[147] Rewarming should be performed to a core temperature of 35.5–36.0°C before emergence from anaesthesia, and every effort should be made to avoid shivering by using meperidine 0.25–0.5 mg/kg. Alternatively clonidine 1–2 μg/kg i.v. can be used.

Summary and recommendation: Intraoperative hypothermia should be avoided by using active warming devices.

Recommendation grade: strong.

Surgical techniques

The short-term benefits of laparoscopic vs. open surgery for abdominal surgery have been well established in the literature to date and include shorter length of stay, reduced postoperative morbidity, earlier passage of flatus and less narcotic analgesic requirements.[157] However, long-term outcomes have shown equivalence between laparoscopic and open surgery.[158] The fact that laparoscopic practice has improved since these trials were initiated, further consolidates the role played by this technique as the preferable one for abdominal surgery. In the context of an enhanced recovery programme, the multicentre randomized LAFA study has shown positive benefits when laparoscopic resection is optimized within an ERAS protocol.[5]

The main goal of enhanced recovery strategy should not be based on the choice of laparoscopic vs. open, but less surgical invasiveness as the surgical technique should minimize wound trauma, tissue distraction and bleeding.

A recently updated Cochrane review comparing transverse with midline laparotomy incisions for abdominal surgery found less postoperative opiate analgesic use with transverse incisions[159] but no differences in visual analogue pain scores reported by patients. Pooled data for spirometry after the operation showed that a transverse incision had less effect on vital capacity and FEV_1. However, these benefits on pulmonary function did not result in reduced pulmonary complications or hospital stay. A trend towards a lower incidence of wound dehiscence was shown in the transverse incision group. Finally there was a reduction in incisional hernias with transverse incisions, but the studies showed a high variety of time to follow-up.

A number of new minimally invasive surgical technologies have emerged over the past decade. A recent meta-analysis of non-randomized controlled trials has indicated that robotic total mesorectal excision (TME) did not reduce operation time, length of hospital stay, time to resume regular diet, postoperative morbidity or mortality[160] and is a technique that requires evaluation through high-quality randomized research. While single-incision laparoscopic resections may improve recovery, no robust data have yet appeared and these techniques are at an early stage in their development.[161] Furthermore, transvaginal and transrectal specimen extraction to avoid abdominal wounds has been described, but with little data on short- and long-term results.[162,163] At this stage, no recommendation can be made on these procedures. However, the negative intraoperative pathophysiological consequences (e.g. head-down-position, longer operation time) have to be balanced to the benefits of the minimal-invasive approaches and the use of an ERAS protocol.

Summary and recommendation: Laparoscopic surgery for gastrointestinal resections is recommended when the expertise is available. Transverse incisions for colonic resections should be preferred.

Recommendation grade:
Laparoscopic approach: strong;
Transverse incisions: low.

Nasogastric intubation

There is strong evidence that routine nasogastric decompression following elective laparotomy should be avoided.[164] Prophylactic nasogastric tubes placed during surgery (to evacuate air) should be removed before reversal of anaesthesia. Fever, oropharyngeal and pulmonary complications are more frequent in patients with nasogastric tubes.[164–166] Even death and other serious complications resulting from nasogastric tubes are reported.[167,168] Avoidance of nasogastric decompression is associated with an earlier return of bowel function[164–166,169] while gastroesophageal reflux is increased during laparotomy if nasogastric tubes are placed.[170] Even in gastroduodenal and pancreatic surgery, there appears to be no evidence of a beneficial effect from the prophylactic use of nasogastric tubes.[164,171] However, the incidence of vomiting has been shown to be higher in patients without nasogastric tubes.[164–166] Nevertheless, the benefits of routinely avoiding nasogastric intubations overcome the risks.

Delayed gastric emptying can occur in a small proportion of patients, leading to vomiting and fatal aspiration if not treated promptly by inserting a nasogastric tube.[172,173] The recognition and avoidance of this complication is essential. Teams should be taught to positively identify these changes, particularly when patients are failing to progress between 2 and 5 days after surgery.

Summary and recommendation: Prophylactic use of nasogastric tubes is not recommended for patients undergoing elective colorectal surgery, while its use in patients undergoing gastrectomy and oesophagectomy is still debatable. Patients with delayed gastric emptying after surgery should be treated by inserting a nasogastric tube.

Recommendation grade: strong.

Intraoperative glycaemic control

Blood glucose levels increase during and after elective surgery with the magnitude of hyperglycaemia depending upon the patient's metabolic state (fasting, fed, diabetes), the type of anaesthesia and analgesia and the severity of surgical tissue trauma.[174]

Strong evidence indicates that even moderate increases in blood glucose are associated with adverse outcomes.[175–177] Patients with fasting glucose levels > 7 mmol/l or random blood glucose levels > 11.1 mmol/l on general surgical wards showed an 18-fold increased in-hospital mortality.[175]

More recent observations suggest that the quality of preoperative glycaemic control also is important. In fact elevated HbA1c levels have been found to be predictive of complications after cardiac and abdominal surgery.[178–181]

Mere associations between two variables, i.e. glycaemia and clinical outcomes, do not prove a direct cause–effect relationship. At present there is insufficient evidence to demonstrate superiority of strict glycaemic control (blood glucose levels within a normal and narrow range) over conventional management in surgical patients. As in the ICU situation, it remains a balance between the benefits of bringing down glucose levels vs. the risks of hypoglycaemia. For the surgical patient on the ward, there is also the issue of the nursing staffing and their capacity to monitor patients on intensive insulin treatment to take into account. A review of the effect of glycaemic control on the incidence of surgical site infections was inconclusive, mainly because of the small number of studies ($n = 5$), the heterogeneity in patient populations, the route of insulin administrations, the definition of outcomes measures and the fact that glycaemic targets were different and/or were not achieved.[182] Hence, to date, the optimal glucose level for enhancing clinical outcomes is unknown.

This uncertainty is reflected by the diversity of recommendations issued by Medical Associations concerning blood glucose control in critically ill and surgical patients.[64,183–185] Overall most of the Associations recommend treatment of random blood glucose concentrations > 10 mmol/l. A large randomized controlled trial of aggressive preservation of normoglycaemia vs. conventional glycaemic control is necessary to identify target blood glucose concentrations in patients undergoing major surgery.

In the meantime, it is important to emphasize that there are a range of elements in the ERAS protocol that will reduce insulin resistance and hence reduce the risk of hyperglycaemia and that should be employed.[186] These include preoperative carbohydrates, an active mid thoracic epidural, early feeding and good pain control.

Summary and recommendation: Glucose concentrations should be kept as close to normal as possible without compromising safety. Employing perioperative treatments that reduce insulin resistance without causing hypoglycaemia is recommended.

Recommendation grade: strong.

Perioperative haemodynamic management

Preoperative period: preoperative hydration deficit can vary according to patients' comorbidities, preoperative fasting and use of preoperative mechanical bowel preparation (MBP). The avoidance of prolonged preoperative fasting,[80,81] MBP[187,188] and as well the administration of preoperative carbohydrate (CHO) drinks[83] have substantially reduced intraoperative fluid requirements. However, when MBP is indicated fluid and electrolytes derangements occur even if patients are encouraged to drink.[74,189,190] The replacement of preoperative intravascular deficits should be based on individualized intraoperative fluid administration strategies[75] rather than administering fluid based on anecdotal "textbook recipes".

Intraoperative period: intraoperative fluid therapy aims to administer balanced crystalloid solutions to cover the needs derived from the salt–water homoeostasis. This is in contrast to volume therapy where goal-directed boluses of intravenous solutions are administered to treat objective evidence of hypovolaemia, and consequently improve intravascular volume and circulatory flow.

Intraoperative fluid therapy should aim to maintain a near-zero fluid balance[191] and substantial weight gain of more than 2.5 kg should be avoided.[192]. Intraoperative fluid requirements can be met with a basal crystalloid infusion rate of 3 ± 2 ml/kg/h (also called restrictive approach[11]).[192–194] Crystalloid excess increases the risk of pulmonary complications,[193] prolonged ileus[192,195,196] and delayed recovery.[197]

Crystalloid isotonic balanced solutions should be preferred and 0.9% saline solutions avoided.[198,199] Hyperchloraemia caused by the use of 0.9% saline solutions has been associated with kidney dysfunction[200–202], prolonged hospital stay and increased 30-day mortality (OR = 1.58, 95% CI 1.25–1.98).[200]

Intraoperative volume therapy should be performed by bolus administration of an intravenous solution based on objective measures of hypovolaemia. Goal-directed fluid therapy (GDFT) aims to maintain central normovolaemia by utilizing changes in stroke volume measured by a minimally invasive cardiac output monitor to optimize the patients on their individual Frank–Starling curve.[96,203]

Trans-oesophageal Doppler (TOD)-guided GDFT has been shown to reduce the length of hospital stay and postoperative complications in several RCTs of patients undergoing non-cardiac surgery[96,204–206] and in a hospital quality improvement project.[207] Similarly, GDFT based on pulse contour analysis and aiming to minimize stroke volume variations during the respiratory cycle of mechanically ventilated patients has also shown to decrease morbidity and accelerate recovery[203,208–210]. These findings are in agreement with the results of 2 recent meta-analysis[209,211].

However, the benefits of GDFT seem to be offset by the optimization of perioperative surgical care. In fact, in two recent RCTs, TOD-guided GDFT showed no benefits on postoperative outcomes in low-risk patients treated within an ERAS protocol.[191,212]. These results could be also explained by a judicious fluid management in patients not treated with GDFT, as the amount of intravenous fluid received in patients randomized in these patients was significantly less than the amount received by the same population in previous studies.[213]

The benefits of GDFT become more clinically meaningful in high-risk patients[214,215], and in patients undergoing surgery associated with larger intravascular fluid loss (blood loss and protein/fluid shift)[213,216]. In the largest multicentre RCT (734 patients), Pearse et al. found a non-significant trend towards decreased complications (36% vs. 43.4% respectively, $P = 0.07$) and 180-day mortality (7.7% vs. 11.6% respectively, $P = 0.08$) in high-risk patients receiving GDFT compared with patients receiving usual care.[215] Auditing internal data (amount of intraoperative fluid given, surgical loss, complications, mortality, length of stay and readmission rate) is essential to determine if GDFT should be implemented as routine strategy to improve postoperative outcomes.[213]

Colloidal solutions have been mainly used to optimize stroke volume during GDFT.[96,204–206] Colloids improve circulatory flow to a greater extent,[217,218] produce better blood volume expansion and less interstitial space overload than crystalloids[219] and could reduce the incidence of postoperative nausea and vomiting and postoperative pain.[220] Recently, Yates et al. showed that in moderate–high-risk patients GDFT with colloid boluses does not accelerate the recovery of bowel function, reduce complications or impair haemostasis compared with crystalloids.[221] Recent data have suggested that the use of large volumes of colloids administered post-resuscitation in critically ill patients can increase the risk of death and acute kidney injury (AKI) in critically ill patients,[222,223] but these results have not been consistently reproduced in the perioperative setting.[224,225] A recent study has found a dose-dependent association between the volume of HES administered and the development of AKI. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has recommended that HES should only be used for the treatment of hypovolaemia caused by acute blood loss when crystalloids alone are not considered sufficient and that it should be used at the lowest effective dose for the shortest period of time. It also states that treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The committee also observed that there is a lack of robust long-term safety data in patients undergoing surgical procedures and in patients with trauma.[226] Moreover, the use of large volumes of colloids (2605 ± 512 ml) hydroxyethyl starch (HES) 130/0.4 during major urological procedures has shown to impair haemostasis and increase surgical blood loss compared with crystalloids.[227] Nevertheless, crystalloid-based GDFT can significantly increase the risk of fluid overload.[227]

Arterial hypotension should be treated with vasopressors when administering intravenous fluid boluses fails to significantly improve the stroke volume (stroke volume > 10%).[13,203] Inotropes should be considered in patients with reduced contractility (Cardiac Index < 2.5 l/min) to guarantee adequate oxygen delivery.[203]

Postoperative period. Early oral intake of fluids and solids following abdominal surgery should be encouraged[171,228,229]. If oral intake is tolerated, routine intravenous fluid administration should be discontinued after PACU discharge and restarted only if clinically indicated. In the absence of surgical losses to cover physiological needs patients should be encouraged to drink 25–35 ml/kg of water per day (1.75–2.75 l for an average person).[11] After ensuring the patient is normovolaemic, hypotensive patients receiving epidural analgesia should be treated with vasopressors.[230,231]

Summary and Recommendation: The goal of perioperative fluid therapy is to maintain fluid homeostasis avoiding fluid excess and organ hypoperfusion. Fluid excess leading to perioperative weight gain more than 2.5 kg should be avoided, and a perioperative near-zero fluid balance approach should be preferred. The need of GDFT should be determined based on clinical and surgical factors. GDFT should be adopted especially in high-risk patients and in patients undergoing surgery with large intravascular fluid loss (blood loss and protein/fluid shift). Inotropes should be considered in patients with poor contractility CI < 2.5 l/min). 0.9% saline and saline-based solutions should be avoided, with balanced solutions preferred. Colloids should be used to treat objective evidence of hypovolaemia. In patients receiving epidural analgesia, arterial hypotension should be treated with vasopressors after ensuring the patient is normovolaemic. In the absence of surgical losses, postoperative intravenous fluid should be discontinued and oral intake (1.5 l/day) encouraged.

Recommendation grade: GDFT: Strong in high-risk patients and for patients undergoing surgery with large intravascular fluid loss (blood loss and protein/fluid shift)

GDFT: low in low-risk patients and in patients undergoing low-risk surgery

Perioperative near-zero fluid balance: moderate

Use of advanced haemodynamic monitoring: strong in high-risk patients and for patients undergoing surgery with large intravascular fluid loss (blood loss and protein/fluid shift)

Balanced crystalloids vs. 0.9% saline

Healthy volunteer studies have suggested that the excretion of an acute saline load is slower when compared with balanced crystalloid infusions[232–234], and saline tends to overload the interstitial space to a greater extent, with a tendency to result in more oedema than balanced crystalloids.[232] Mechanisms for excreting this saline excess are inefficient, depending on a slow and sustained suppression of the renin–angiotensin–aldosterone axis.[219] In addition, 0.9% saline produces a hyperchloraemic acidosis, which along with renal oedema, can lead to a reduction in renal blood flow and renal cortical perfusion, even in healthy human volunteers.[232]

There are two relatively small randomized clinical trials in humans comparing 0.9% saline with Ringer's lactate in the perioperative period, showing that 0.9% saline caused more side effects.[235,236] One of these studies, involving patients undergoing renal transplantation, had to be stopped prematurely because, compared with none in those receiving Ringer's lactate, 19% of patients in the saline group had to be treated for hyperkalaemia and 31% for metabolic acidosis.[235] In the other study, involving patients undergoing abdominal aortic aneurysm repair, those receiving saline needed more blood products and bicarbonate therapy.[236] Three recent large observational studies[200–202] have suggested that 0.9% saline, because of the high chloride content, may cause harm, especially to the kidney. In a study using a validated and quality assured database, evaluation of outcomes in 2,788 adults undergoing major open abdominal surgery who received only 0.9% saline and 926 who received only a balanced crystalloid on the day of surgery and showed that unadjusted in-hospital mortality (5.6% vs. 2.9%) and the percentage of patients developing complications (33.7% vs. 23%) were significantly greater in the 0.9% saline group than in the balanced crystalloid group.[202] Patients receiving 0.9% saline had significantly greater blood transfusion requirements and more infectious complications, and were 4.8 times more likely to require dialysis than those receiving balanced crystalloids. Another recent study provides support for chloride-restrictive fluid strategies in critically ill patients.[201] In an open-label prospective sequential manner, 760 patients consecutively admitted to intensive care (30% of whom were admitted after elective surgery) received either traditional chloride-rich solutions (0.9% sodium chloride, 4% succinylated gelatin solution or 4% albumin solution) or chloride-restricted (Hartmann's solution, Plasma-Lyte 148 or chloride-poor 20% albumin). After adjusting for confounding variables, the chloride-restricted group had decreased incidence of acute kidney injury [odds ratio 0.52 (95% CI 0.37–0.75), $P < 0.001$] and the use of renal replacement therapy [odds ratio 0.52 (95% CI 0.33–0.81), $P = 0.004$]. However, there were no differences in hospital mortality, hospital or ICU length of stay.[201] A third study on 22,851 surgical patients with normal preoperative serum chloride concentration and renal function showed that the incidence of acute postoperative hyperchloraemia (serum chloride > 110 mmol/l) was 22%.[200] Patients with hyperchloraemia were at increased risk of 30-day postoperative mortality (3.0% vs. 1.9%; odds ratio 1.58 (95% CI 1.25–1.98) and had a longer median hospital stay [7.0 days (IQR 4.1–12.3) vs. 6.3 days (IQR 4.0–11.3)] than patients with normal postoperative serum chloride concentrations.[200] Patients with postoperative hyperchloraemia were also more likely to have postoperative renal dysfunction.

There is a strong signal suggesting that 0.9% saline is harmful, particularly in the perioperative period when compared with balanced solutions[199]. However, there are currently no large-scale randomized controlled trails that confirm this finding. Nevertheless, it may be preferable to use balanced crystalloids in the perioperative period and restrict the use of saline to patients who have alkalosis or have a hyperchloraemia secondary to conditions such as vomiting or high nasogastric tube aspirates, and in neurosurgical patients because of the relative hypo-osmolarity of some of the balanced crystalloids.

Summary and Recommendations: 0.9% saline should be avoided and balanced crystalloids used in the preoperative period. The use of 0.9% saline should be restricted in hypochloraemic and acidotic patients.

Recommendation: strong

Pain management

Multimodal, evidence-based and procedure-specific analgesic regimens should be standard of care, with the aim to achieve optimal analgesia with minimal side effects and to facilitate the achievement of important ERAS milestones such as early mobilization and oral feeding (Table 2).[237,238]

Thoracic epidural analgesia (TEA)

TEA (T6-T11) remains the gold standard for postoperative pain control in patients undergoing open abdominal surgery.[239] It still remains unclear if epidural analgesia improves postoperative outcomes. Although the results of a large multicentre RCT failed to show a significant benefit of using epidural analgesia in association with general anaesthesia in reducing 30-day mortality and postoperative morbidity in high-risk patients[240] a recent meta-analysis of 9044 patients undergoing surgery with general anaesthesia and receiving epidural analgesia (4525 patients) found that epidural analgesia is associated with a 40% reduction of mortality.[241] Initiation of neuroaxial blockade before surgery and its maintenance throughout surgery decreases the need for anaesthetic agents, opioids and muscle relaxants.[242] Compared with parenteral opioids, epidural blockade has shown to provide better postoperative static and dynamic analgesia for the first 72 h,[10], to accelerate the recovery of gastrointestinal function,[243–245] to reduce insulin resistance[246] and impact positively on cardiovascular and respiratory complications.[241,247]. However, hypotension, urinary retention pruritus and motor blockade are common side effects.[248] Although detrusor function can be impaired in patients receiving TEA, a recent RCT has shown that early removal of a urinary catheter (on postoperative day 1) does not increase the risk bladder recatheterization and urinary infection.[249]. Also TEA does not influence the duration of hospital stay.[250]

The same benefits have not been observed after laparoscopic procedures,[59] especially in a context of an ERAS programme.[251–253] However, TEA might still be valuable in patients at risk of respiratory complications, in those with high probability of conversion to laparotomy, or requiring transverse or Pfannenstiel-like incisions.[254] Furthermore, TEA may be useful to facilitate the recovery of bowel function even after laparoscopic colorectal surgery.[243]

Clinical management

Epidural blockade should be tested before surgery or in the immediate postoperative period (post-anaesthesia care unit) to avoid non-functioning epidurals and unnecessary opioid administration.[255] The addition of opioids to local anaesthetic has shown to improve postoperative analgesia.[248,256] Although a paucity of studies have compared the analgesic efficacy of

Table 2 Non-analgesic outcomes and current issues reported after abdominal surgery with different analgesic techniques.

	Analgesia technique	Outcomes	ERAS	Control group	Complications/issues
Laparotomy	TEA (low dose of LA and opioids)	↓ PONV[250]	–	SO	Hypotension, pruritus, bladder dysfunction[248,249]
		↑Recovery of bowel function[244]	–	SO	
		↓Insulin resistance[246]	–	SO	
		↓Respiratory complications[247]	–	SO	
		↑Health-related quality of life[353]	–	SO	
		= LOSH[250]	–	SO	
	IT morphine	Health-related quality of life[354]	✓	SO	Respiratory depression, pruritus, bladder dysfunction[265]
	IVLI	Anti-inflammatory[269]	–	SO	LA toxicity[270]
		↑Recovery of bowel function[269]	–	SO	
		↓LOSH[269]	–	SO	
		= LOSH[254]	✓	TEA	
	CWI LA	↓/↑/= Recovery of bowel function[275–277,355]	✓/–	SO;TEA	Ideal anatomic location not determined[274]
		↓/↑/= LOSH[273,275,276]	–	SO;TEA	
	Abdominal trunks blocks	↓Postoperative sedation[284,289]	–	SO	Timing, dose, volume of LA, technique[297]
		↓PONV[283]	–	SO	
Laparoscopy	TEA	↑/=/↓ Recovery of bowel function[243,253,254]	✓/–	SO;IVLI;IT/TAP	Hypotension, pruritus, bladder dysfunction[248,249]
		↑/= LOSH[253,254]	✓	SO;IT;TAP	
	IT morphine	= Recovery of bowel function[253,268,356]	✓	SO;TEA	Respiratory depression, pruritus, bladder dysfunction[265]
		Facilitate mobilization[356]	✓	TEA	
		↓/= LOSH[253,268]	✓	SO;TEA	
		23-h LOSH after laparoscopic colectomy[357]	✓	–	
	IVLI	Anti-inflammatory[269](↓ IL-6, IL1-R)	–	SO	LA toxicity[270]
		↑/= Recovery of bowel function[254,272]	✓	SO;TEA	
		= LOSH[254]	✓	TEA	
	Abdominal trunksblocks	23-h LOSH after laparoscopic colectomy[286]	✓	SO	Timing, dose and volume of LA, technique[297]
		= LOSH[295]	✓	SO	
		= LOSH, earlier urinary catheter removal[296]	✓	TEA	

↓, decreasing; ↑, accelerating; =, no effect. SO, systemic opioids; TEA, thoracic epidural analgesia; IVLI, intravenous lidocaine infusion; CWI, continuous wound infusion; LA, local anaesthetic; LOSH, length of hospital stay in hospital; (ERAS), study within an ERAS programme.

epidural solutions combining local anaesthetic with lipophilic opioids vs. those containing local anaesthetic combined with hydrophilic opioids, epidural solution containing morphine increase the risk of urinary retention.[257,258] However, the use of low dose of local anaesthetics (bupivacaine 0.1 mg/ml) and lipophilic opioids (e.g. fentanyl 3 μg/ml) seem to provide optimal analgesia with minimal side effects[257]. Epidural morphine (0.02 mg/ml) in adjunct to local anaesthetic can be preferred to lipophilic opioids to increase segmental analgesia spread and could be recommended for long midline incisions.[259] Epidural infusions can be continued for 48-72, gradually reducing infusion rates and until the recovery of gastrointestinal function. Adding adrenaline (1.5–2.0 μg/ml) to epidural mixture of local anaesthetic and fentanyl improves postoperative analgesia, especially during mobilization and coughing, and reduces pruritus and nausea.[248,256,260–262] Evidence on the analgesic efficacy of epidural clonidine is inconclusive and the risk of hypotension and sedation is increased.[263] Hypotension induced by epidural blockade should be treated with vasopressors as first choice provided the patient is not hypovolaemic. Orthostatic hypotension associated with postoperative epidural analgesia does not impair the ability to ambulate.[264] Institutional policies on how to manage epidural side effects, terminate epidural infusions, and how transition to oral multi-modal analgesia are recommended.

Intrathecal (IT) analgesia. IT morphine is a valuable analgesic technique to improve early postoperative analgesia[265] and facilitates surgical recovery.[266] However, compared with systemic opioids, the incidence of pruritus (OR 3.85, 95% CI 2.40–6.15) and respiratory depression (although rare) is increased (OR 7.86, 95% CI 1.54–40.3). Postoperative urinary retention is also slightly more frequent (OR 2.35, 95% CI 1.00–5.51).[265] Hypotension in the first 12 h, especially in a context of an enhanced recovery pathway and a restrictive fluid management, has been also associated with the use of intrathecal hydromorphone (with bupivacaine or clonidine).[267]

In the light of these side effects, in the context of an multimodal analgesic regimen other regional anaesthesia technique could be favoured especially in elderly patients. Behind providing excellent analgesia,[268] IT morphine seems an appealing technique to shorten hospital stay in low-risk patients undergoing laparoscopic colorectal surgery with an ERAS protocol.[253]

Clinical management

Reported IT morphine dosage range between 200 and 250 μg in patients aged ≤ 75 years to μg 150 in patients > 75 years of age. Isobaric or hyperbaric bupivacaine (10–12.5 mg) have been used in conjunction with IT morphine.[253,268]

Intravenous lidocaine (IVL) infusion

In view of its antinociceptive and anti-inflammatory properties, systemic administration of IVL as adjuvant to systemic opioids has been shown to improve postoperative analgesia, reduce opioid consumption and speed surgical recovery.[269,270] Similar benefits have been observed after laparoscopic abdominal surgeries when compared with systemic opioids,[271] but not when compared with TEA[254], and especially in the absence of an ERAS programme.[254,272]

Clinical management

A loading dose of 1.5 mg/kg (IBW) should be initiated 30 min before or at the induction of anaesthesia and continued until the end of surgery or in the recovery room (2 mg/kg/h IBW). The exact duration of the infusion providing optimal analgesia and facilitating also recovery remains unknown. Systemic toxicity is rare, but continuous cardiovascular monitoring is required.[270]

Continuous wound infusion (CWI) of local anaesthetic. CWI of local anaesthetic after open abdominal surgery has been shown to improve postoperative analgesia and reduce opioid consumption,[273,274] however the effect on the recovery of bowel function is unclear.[273,275] Two recent RCTs have compared the analgesic efficacy of CWI of local anaesthetic with TEA but the results are contrasting.[276,277] A recent feasibility study has compared the analgesic efficacy of CWI of local anaesthetic with epidural analgesia after laparoscopic abdominal surgery. Pain intensity was similar among patients receiving epidural and CWI of local anaesthetic.[278]

Despite promising results the analgesic efficacy of CWI of local anaesthetic remains inconclusive and several aspects related to this techniques need to be clarified. For example, although preperitoneal multihole catheters have consistently provided satisfactory analgesia, and subfascial catheters have provided better results than suprafascial catheters,[279] the anatomical location associated with optimal recovery remains undetermined.[274,279] Furthermore, it remains to be established if the analgesic effect observed in different trials is mainly driven by the bolus of local anaesthetic commonly given at the end of surgery or by the infusion of local anaesthetic during the postoperative period.[280]

Clinical management

Preperitoneal continuous infusion of ropivacaine 0.2% (10 ml/h) for 48–72 h has been used in the majority of the studies. Other amide-local anaesthetics have also been used. Systemic opioids are still required to control visceral pain.

Abdominal trunk blocks: transversus abdominis plane (TAP) block and rectus sheath block. Significant reduction of pain intensity and opioid consumption after ultrasound-guided single-shot TAP blocks has been observed but it is limited to the first 24 h after surgery.[281–283] TAP blocks can also be performed by surgeons from the peritoneal cavity before closing the abdominal wall,[284,285] or laparoscopic guided.[286–288] Few studies have reported a reduction of some of the opioids side effects such as nausea and vomiting[283] or sedation,[284,289] but these results have not been reproduced consistently.[281] Continuous infusion or intermittent administration of local anaesthetics through multihole catheters placed in the transversus abdominis plane have been used to improve and prolong opioid-based postoperative analgesia up to 48–72 h after abdominal surgery, but the evidence supporting the analgesic efficacy of TAP-infusion of local anaesthetic remains scarce and inconclusive.[290–292] Niraj et al. found that epidural analgesia did not provide better visual analogue scores during coughing than intermittent local anaesthetic boluses through bilateral subcostal TAP catheters in the first 72 h after upper abdominal surgery.[293] However, epidural failure rate were high (22%) and almost half of the TAP catheters had to be replaced in the postoperative period.

Similar benefits have been reported in abdominal laparoscopic procedures[282,294] and in a context of an ERAS programme.[286,295] Despite facilitating hospital discharge,[286] bilateral single-shot TAP blocks seem to do not reduce hospital stay after laparoscopic colorectal surgery.[295] A recent RCT has shown that the analgesic efficacy of four-quadrant TAP blocks in adjunct to bilateral posterior continuous TAP blocks, was not inferior to TEA after laparoscopic colorectal surgery.[296]

Clinical management

Optimal timing, choice of local anaesthetic, dosing and volumes remain unknown.[297] However, it seems that a minimal volume of 15 ml is required to achieve satisfactory analgesia with single-shot TAP block.[297] Ropivacaine 0.2% (8–10 ml/h) can be infused for 48–72 h trough a multihole catheter. A bilateral infusion (8–10 ml/h each side) is required with a midline incision. Systemic opioids are needed to control visceral pain.

More studies that further validate the analgesic efficacy of TAP blocks are warranted.

Intraperitoneal local anaesthetic (IPLA) . The results of a meta-analysis including eight RCTs have shown that IPLA after open abdominal surgery reduce postoperative pain scores but not opioid consumption. However, in the latest randomized control trial conducted in a context of an enhanced recovery programme, IPLA improved surgical recovery, reduced postoperative pain and opioid consumption in patients undergoing open colectomy and receiving thoracic epidural analgesia.[298]

IPLA has been shown to improve postoperative analgesia, reduce shoulder pain and opioid consumption after laparoscopic gastric surgery[299].

Multimodal analgesia (MMA). A MMA regimen based on routine use of NSAIDs, COX-2 and acetaminophen (paracetamol) (PO or intravenously when available) should adopted if not contraindicated in patients undergoing open and laparoscopic abdominal procedures with the aim to reduce opioid consumption and their dose-dependent side effects that impair recovery.[300] NSAIDs and COX-2 inhibitors have been shown to improve postoperative analgesia, reduce opioid consumption and some of their side effects by 30%.[301] There have been recent concerns about the risk of anastomotic leakage and the use of NSAIDs or COX-2 inhibitors after colorectal surgeries based on experimental, retrospective and case-series studies.[302]. Large RCTs are needed to confirm these results. The risk of anastomotic leakage after bowel surgery was not significantly increased in a recent meta-analysis of six RCTs (480 patients) of patients receiving at least one dose of NSAIDs or COX-2 inhibitors within 48 h of surgery (Peto OR 2.16 [95% CI 0.85–5.53, $P = 0.11$])[303]. This effect seems to be molecule-specific (diclofenac is associated with the highest risk)[302] and class-specific (risk of anastomotic leakage with NSAIDs, OR 2.13 [95% CI 1.24–3.65], $P = 0.006$, risk of anastomotic leakage with selective COX-2 inhibitors OR 1.16 [95% CI 0.49–2.75] $P = 0.741$)[304]. Furthermore, the risk varies with duration of the treatment, and it is higher after 3 days or more of NSAIDs than after 1 or 2 days only[304]. Acetaminophen (paracetamol) has shown to improve postoperative analgesia, have an opioid-sparing effect, but not reduce opioids side effects.[305] However, a recent meta-analysis has demonstrated that intravenous paracetamol reduces the risk of postoperative nausea and vomiting, but this effect seems more related to an improvement in postoperative pain rather than to a reduction in opioid consumption.[306] Concerns have been raised about the cardiovascular risk and delayed bone healing associated with the use of NSAIDs and COX-2 inhibitors[307]. Overall, the evidence is inconclusive[307] and does not support the avoidance of short perioperative NSAIDs and COX-2 inhibitors treatment in patients with low cardiovascular risk.[307,308] High-dose of systemic steroids have also shown promising results[309,310], also in patients not undergoing gastrointestinal surgery.[311,312] Perioperative intravenous ketamine and gabapentinoids have also shown opioid-sparing properties.[313,314] However, the risk of side effects such as dizziness and sedation should be considered. An opioid-free ultimodal analgesic strategy based mainly on analgesic adjuvants would be appealing but more studies are warranted to establish the feasibility, efficacy and safety of such analgesic approaches.[315] Wound infiltration with long-acting multivesicular liposome formulation of bupivacaine as part of multimodal analgesic regimens has also shown promising results.[316,317] It must be acknowledged that most of the following recommendations come from studies not using enhanced recovery after surgery (ERAS) programmes. It might be possible that the well-proven benefits of ERAS programmes might offset the reported advantages of different analgesic techniques.[242] The synergistic effect of combining different analgesic medications remains unknown and the impact of MMA on long- term outcomes still remains to be determined[318].

Summary and Recommendation: Analgesic techniques should aim to not only provide optimal pain control but also to facilitate the achievement of important milestones such as tolerance of oral intake, and early mobilization. Opioid side effects are dose-dependent and delay recovery. Opioid-sparing analgesic strategies, including regional analgesia techniques, should be implemented in a context of a multimodal analgesic regimen. Postoperative pain management should be procedure-specific.

Recommendation grade: MMA: strong

Open abdominal surgery. TEA: strong for using it
IVLI: moderate for using it
CWI: weak for using it
TAP blocks: moderate for using it

Laparoscopic abdominal surgery. TEA: weak for using it
IVLI: moderate for using it
Intrathecal morphine: moderate for using it
TAP blocks: moderate for using it

Postoperative delirium

Postoperative delirium is increasingly recognized in surgical practice, particularly in the elderly population who have pre-existing cognitive dysfunction. While delirium can be a symptom of a surgical or medical complication it is important to be recognized instantly.

The prevalence is underestimated and underdiagnosed if no systematic monitoring is applied.[319] It is defined as a condition of altered consciousness, orientation, memory, thought, perception, behaviour and possibly sleep pattern which develops acutely and shows a fluctuating clinical course.[320] Delirium can be classified into three subtypes: the hyperactive delirium, the hypoactive delirium and a mixed form.[321] Delirium as a symptom of acute cerebral dysfunction should not solely be perceived as a strictly binary phenomenon which is either present or absent. Detection of delirium also at pre-delirium or sub-syndromal levels could prevent further deterioration of cerebral function.

Undetected and untreated or delayed treatment of delirium does increase the rate of complications, the length of hospital stay as well as mortality[322,323] and is associated with long-term cognitive dysfunction.[324]

Early detection in the postoperative setting is a prerequisite for finding and treating the underlying causes. Numerous validated Delirium Instruments have been validated for clinical use.[325,326]

Delirium promoting factors such as prolonged preoperative fluid fasting times, deep anaesthesia time as well as disturbing the sleep–wake cycle and the use of sedatives and other delirogenic medications should be avoided.[117,327]

If postoperative delirium is detected, the early symptomatic therapy based on pharmacological and non-pharmacological measures, is associated with a decreased mortality[323]. Psychotic symptoms should be treated with neuroleptics. A systematic review that a low-dose haloperidol therapy compared with a therapy with atypical neuroleptics has a similar effectiveness and side effect rate.[328]

If there is the necessity to apply substances with sedative properties, non-benzodiazepines should be preferred (e.g. alpha-2-agonists) due to international guidelines for sedation. Benzodiazepines are known to be an independent risk factor for delirium and should therefore be avoided if possible.[329]

Summary and recommendation: Preventive measure as avoidance of prolonged fasting, deep anaesthesia, disturbance of sleep–wake cycle or delirogenic medications like benzodiazepines, atropine should be implemented. Systematic delirium screening and symptom-oriented treatment should be performed and potential underlying medical causes should be ruled out.

Recommendation grade: strong.

Attenuation and treatment of postoperative ileus

Postoperative ileus (POI) is defined as a transient reduction of bowel motility that prevents effective transit of bowel content and tolerance of oral intake following surgical interventions.[330] POI has been associated with prolonged hospital stay and higher risk of complications. POI can be classified in primary POI that occurs in the absence of surgical complications, and in secondary POI in the presence of surgical complications such as anastomotic leakage, abscess, peritonitis, etc.[330] Primary POI is considered an inevitable consequence after abdominal surgery. However, its clinical presentation and duration can significantly vary among patients depending on the severity of the gastrointestinal dysfunction. Some patients can be totally asymptomatic and tolerate oral intake in the immediate postoperative period, while others experience gastrointestinal symptoms, cannot tolerate any oral intake for several days and might require insertion of a nasogastric tube (NGT).[330] The definitions of primary POI remains elusive and many clinical trials still utilize personal definitions in view of the difficulty on how to clinically identify patients with a clinically relevant impairment of gastrointestinal dysfunction. In a recent study measuring the gastrointestinal transit after colorectal surgery, Van Bree et al. showed that the combination of tolerance of solid food and passage of stool best correlates with the recovery of gastrointestinal function (area under the curve 0.9, SE 0.04, 95% CI 0.79–0.95, $P < 0.001$), with a positive predictive value of 93% (95% CI 78–99).[331] It also best predicts hospital stay.[331] Others clinical indicators commonly used to assess POI, such as the time to first flatus, poorly correlate with the recovery of the gastrointestinal function.[331] A list of clinical indicators commonly used in clinical practice to evaluate the recovery of the gastrointestinal function is reported in Fig. 1. Non-ileus-related nausea and intra-abdominal surgical complications leading to secondary POI should be excluded.

Due to its multifactorial pathogenesis several perioperative preventive strategies can be implemented to reduce the severity and duration of primary POI.[332] Based on the results of a large retrospective study, it should be also considered that some patients might have a higher risk to develop prolonged primary POI (Table 3). These results need to be confirmed when adopting multiple interventions to attenuate postoperative gastrointestinal dysfunctions as in a context of an ERAS programme.[333] Nasogastric decompression should be considered to prevent complications such as pulmonary aspiration and arrhythmias.[164]

Summary and recommendation: Primary POI is an inevitable consequence after gastrointestinal surgery and its pathogenesis is multifactorial. Multimodal preventing strategies should be adopted to facilitate the recovery of gastrointestinal function.

Recommendation grade: moderate

Early mobilization

Although the tradition of prolonged postoperative bed rest was abandoned over 75 years ago[334] and the dangers of staying in bed acknowledged,[335] modern surgical patients actually spend very little time out of bed.[336] Early "enforced" or "structured" mobilization is a key component of virtually all ERAS programmes.[16,337] Patients cared for with the ERAS paradigms mobilize more and achieve independent mobilization earlier than those cared for without ERAS.[7] Mobilization helps preserve

Table 3 Risk factors, prevention and management of primary POI.

Patients risk factors[333]
- Male
- Cerebrovascular diseases
- Respiratory diseases
- Peripheral vascular diseases

Intraoperative strategies to accelerate the recovery of gastrointestinal function
- Laparoscopic surgery[5]
- Thoracic epidural analgesia[241]
- Opioid-sparing strategies[332]
  - Intravenous Lidocaine
  - NSAIDs/COX-2
  - Ketamine
- Avoid fluid excess and splanchnic hypoperfusion[332]

Postoperative strategies to accelerate the recovery of gastrointestinal function
- Thoracic epidural analgesia[241]
- Opioid-sparing strategies[332]
  - NSAIDs/COX-2
- Opioid antagonists[358]
  - Alvimopam
  - Metiltrexone
- Mobilization[332]
- Laxative[332]
- Gum-chewing[359]
- Administer IV fluids only if clinical indicated (surgical losses, inadequate hydration) (ref)
- Early feeding[332]
- Avoidance prophylactic and routine use of NGT

Treatment of primary POI
NGT insertion[332]

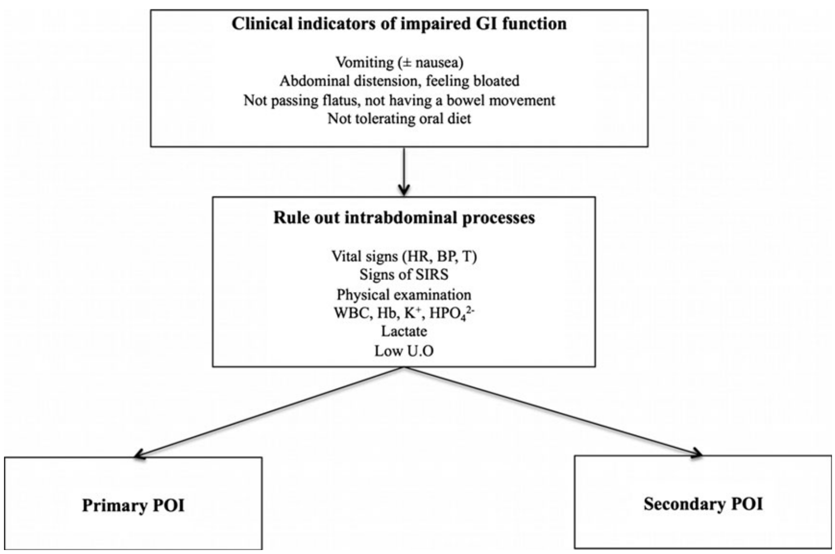

Fig. 1. Identification of patients with primary or secondary postoperative Ileus (POI). SIRS, systemic inflammmatory response; WBC, white blood cell; Hb, hemoglobin; K+, potassium; HPO_4^{2-}, phospate.

muscle function and prevent complications associated with bed rest, but also aligns with the message of empowerment of patients to play an active role in their own recovery after surgery; this term is used instead of "convalescence", which implies a passive process.

Protocols differ between pathways and there is no standard definition of early mobilization which may include exercising in bed, sitting out of bed, standing, walking in the room, walking in the hallway or exercising.[338] Different successful pathways set different mobilization goals using different benchmarks such as time[7] (hours out of bed, hours sitting or walking) or distance (e.g. number of times to walk a hallway or ward).[339] These begin early, on the day of surgery, and increase each day to reach predetermined targets. There are no data to support the use of one plan over another or suggestion of a "dose–response" curve related to outcomes.

Unfortunately, there is little evidence available to guide how to best achieve early mobilization and even within established ERAS programmes adherence to mobilization targets may be quite low, suggesting a need for specific studies in this area.[197] A review of the impact of early mobilization for medical and surgical patients found that the use of a more standardized and structured approach beginning as early as possible had the most favourable results.[340] This begins in the preoperative setting with clear and explicit instructions detailing daily mobilization goals. These instructions are reinforced with written material which improves recall[341] and which is brought by the patient to the hospital. Posters on the ward may help reinforce daily goals.[342] Patients who begin an exercise programme in the preoperative period may also be more likely to be physically active postoperatively.[343] Compliance may be improved by the use of a patient diary[344] or when a pedometer is worn, which has been shown in other contexts to be associated with increased physical activity.[345] Creation of separate ERAS "rehabilitation" wards[344] or having a separate ward dining room may help[337] but are not feasible in all settings. The absence of an in-room entertainment system may promote increased walking.[346] Having an audit tool available recording compliance with mobilization is important to identify and address barriers.

Achieving early mobilization on the ward requires integration between the patient and the various health care providers working in a multidisciplinary fashion form the beginning. Pain and drains inhibit ambulation.[338] Ideally a dedicated pain service is involved in the ERAS team to optimize pain control and reduce side effects.[337] Epidural analgesia provides excellent analgesia after open abdominal or thoracic surgery but it is associated with postoperative hypotension and with lower limb weakness if the epidural block is extended to the lumbar nerve roots.[248] Epidural systems that reduce interference with ambulation should be used if possible. There is a tendency to bed rest patients experiencing orthostatic intolerance or hypotension, and to consider the epidural responsible for this effect. However, in patients with thoracic epidural analgesia hypotension is a relatively common side effect on postoperative day 1 but is often asymptomatic and does not predict the ability to walk.[264] Furthermore, epidural analgesia is not associated with higher risk of orthostatic intolerance or hypotension than systemic opioids.[347] Orthostatic intolerance seems to be more related to an impairment of the autonomic system and to an alteration of the baroreceptor reflex[348,349] rather than to other factors such as hypovolaemia,[350] anaemia and pain.[349] The underlying mechanisms are not yet fully understood.

Most pathways rely on nurses to assist with "enforcing" mobilization[7] with physiotherapists involved in some programmes, suggesting an increased need for resources. Nurses should be involved in the creation of the mobilization plan from the beginning in order for the team to understand potential barriers to ambulation.[351] Although there may be concern from nurses that ERAS will increase their daily workload related to these physical tasks, this has not been shown to be the case, perhaps because of increased patient independence.[352]

Summary and recommendation: Achievement of mobilization goals requires a multidisciplinary approach. Patients should be given written information setting daily targets for ambulation in hospital. Patients should be encouraged to increase their physical activity in the preoperative period. Patients should use a diary or pedometer to record their daily physical activity.

Table 4 ERAS elements: summary and recommendations.

Perioperative element	Summary and recommendation	Recommendation grade
Risk assessment	Preoperative scoring tools and functional capacity tests can be used to identify patients at risk of complications and to stratify perioperative risk.	POSSUM: strong Lee Index: strong Cardiovascular Risk Calculator: strong Walk tests: strong CPET: strong General Surgery Acute Kidney Injury Risk Index: strong
Preoperative optimization	Cessation of smoking and alcohol intake at least 4 weeks before surgery is recommended. Encouraging patients is not enough; pharmacological support and individual counselling should be offered to every patient who smokes and to alcohol abusers undergoing elective surgery. Optimization of medical conditions, such as cardiovascular diseases, anaemia, COPD, nutritional status and diabetes should follow international recommendations.	Smoking cessation: high NRT and counselling: high Alcohol cessation: low Medical optimization: strong Optimize preoperative anaemia reduces morbidity and mortality: moderate
Pre-anaesthetic medication	Long-acting anxiolytic and opioids should be avoided as they may delay discharge. Short-acting benzodiazepine should be avoided in the elderly.	Strong.
Preoperative fasting and carbohydrates (CHOs) loading	Intake of clear fluids should be allowed until 2 h before induction of anaesthesia. Solids should be allowed until 6 h. Preoperative treatment with oral CHOs should be routinely administered except in patients with documented delayed gastric emptying or slow gastrointestinal motility and as well in patients undergoing emergency surgery.	Adherence to fasting guidelines (avoid overnight fasting): strong Administration of preoperative CHOs: strong Administration of preoperative CHOs in diabetic and obese patients: weak
Preventing and treating postoperative nausea and vomiting (PONV)	Aggressive PONV prevention strategy should be included in an ERAS protocol[102]. All patients with 1–2 risk factors should receive a combination of two antiemetics. Patients with 3–4 risk factors should receive 2–3 antiemetics. Total intravenous anaesthesia (TIVA) with propofol and opioid-sparing strategies should be encouraged.	Strong
Standard anaesthetic protocol	Anaesthetic depth should be guided either maintaining an end tidal concentration of 0.7–1.3 MAC or BIS index between 40 and 60 with the aim not only to prevent awareness but also to minimize anaesthetic side effects and facilitate rapid awakening and recovery. Avoid too deep anaesthesia (BIS $<$ 45), especially in elderly patients	Strong
Neuromuscular blockade (NMB) and neuromuscular monitoring	It remains controversial if deep neuromuscular blockade during laparoscopic surgery improves operating conditions. Neuromuscular function should be always monitored when using NMBA to avoid residual paralysis. Long-acting NMBA should be avoided. When NMBA are administered neuromuscular function should be monitored by using a peripheral nerve stimulator to ensure adequate muscle relaxation during surgery and optimal restoration of neuromuscular function at the end of surgery. A TOF ratio of 0.9 must be achieved to ensure adequate return of muscle function and thus preventing complications.	Monitoring neuromuscular function: strong Reversing neuromuscular blockade: strong
Inspired Oxygen Concentration	1) The inspired fractional concentration of oxygen should be titrated to produce normal arterial oxygen levels and saturations. Prolonged periods of high inspired oxygen concentrations which result in hyperoxia should be avoided.	1) Strong 2) Strong

Table 4 (Continued)

Perioperative element	Summary and recommendation	Recommendation grade
	2) 100% inspired oxygen concentrations can be used for pre-oxygenation prior to anaesthesia or for short periods to overcome hypoxia.	
Preventing intraoperative hypothermia	Intraoperative hypothermia should be avoided by using active warming devices.	Strong.
Surgical techniques	Laparoscopic surgery for gastrointestinal surgery is recommended when the expertise is available. Transverse incisions for colonic resections can be preferred.	Laparoscopic approach: strong Transverse incisions for colonic surgery: low
Nasogastric intubation	Prophylactic use of NGTs is not recommended for patients undergoing elective colorectal surgery, while its use in patients undergoing gastrectomy and oesophagectomy is still debatable. Patients with delayed gastric emptying after surgery should be treated by inserting a NGT.	Strong.
Intraoperative glycaemic control	Glucose levels should be kept as close to normal as possible without compromising safety. Employing perioperative treatments that reduce insulin resistance without causing hypoglycaemia is recommended.	Strong.
Perioperative haemodynamic management	The goal of perioperative fluid therapy is to maintain fluid homeostasis avoiding fluid excess and organ hypoperfusion. Fluid excess leading to perioperative weight gain more than 2.5 kg should be avoided, and a perioperative near-zero fluid balance approach should be preferred. GDFT should be adopted especially in moderate–high-risk patients. Inotropes should be considered in patients with poor contractility CI < 2.5 l/min). Colloids should not be used in septic patients and in patients with reduced renal function. Large amount of colloids can impair haemostasis. In patients receiving epidural analgesia arterial hypotension should be treated with vasopressors, ensuring the patient is normovolaemic. In the absence of surgical losses postoperative intravenous fluid should be discontinued and oral intake (1.5 l/day) encouraged.	GDFT: Strong in high-risk patients and for patients undergoing surgery with large intravascular fluid loss (blood loss and protein/fluid shift) GDFT: low in low-risk patients and in patients undergoing low-risk surgery Perioperative near-zero fluid balance: moderate Use of advanced hemodynamic monitoring: strong in high-risk patients and for patients undergoing surgery with large intravascular fluid loss (blood loss and protein/fluid shift)
Balanced crystalloids vs. 0.9% saline	0.9% saline should be avoided and balanced crystalloid solution used in the preoperative period. The use of 0.9% saline should be restricted in hypochloraemic and acidotic patients.	Strong
Pain management	Analgesic techniques should aim to not only provide optimal pain control, but also to facilitate the achievement of important milestones such as tolerance of oral intake, and early mobilization. Opioids side effects are dose-dependent and delay recovery. Opioid-sparing analgesic strategies, including regional analgesia techniques, should be implemented in a context of a multimodal analgesic regimen. Postoperative pain management should be procedure-specific	MMA: strong *Open abdominal surgery* TEA: strong for using it IVLI: moderate for using it CWI: weak for using it TAP blocks: moderate for using it *Laparoscopic abdominal surgery* TEA: weak for using it IVLI: moderate for using it Intrathecal morphine: moderate for using it TAP blocks: moderate for using it
Postoperative Delirium	Preventive measure as avoidance of prolonged fasting, deep anaesthesia, disturbance of sleep-wake cycle or delirogenic medications like benzodiazepines, atropine should be implemented. Systematic delirium screening and symptom-	Strong

Table 4 (Continued)

Perioperative element	Summary and recommendation	Recommendation grade
	oriented treatment should be performed and potential underlying medical causes should be ruled out.	
Attenuation and treatment of postoperative ileus	Primary POI is an inevitable consequence after gastrointestinal surgery and its pathogenesis is multifactorial. Multimodal preventing strategies should be adopted to facilitate the recovery of gastrointestinal function.	Moderate
Early mobilization	Achievement of mobilization goals requires a multidisciplinary approach. Patients should be given written information setting daily targets for ambulation in hospital. Patients should be encouraged to increase their physical activity in the preoperative period. Patients should use a diary or pedometer to record their daily physical activity.	Weak.

Recommendation grade: weak.

Comment

The practice of surgery and anaesthesia is continuously evolving and there is a need to offer the knowledge base for continuous training of those involved in the treatment of surgical patients. The ERAS Society (www.erassociety.org) was initiated by the former ERAS Study Group and was formed in 2010 to support these processes. The multidisciplinary Society participates in the improvement of perioperative care by developing new knowledge through research, education and also by being involved in the implementation of best practice.

The current manuscript presents a consensus review from the ERAS Society, discuss clinical considerations, and provide recommendations, for optimal anaesthesia care within the ERAS programme for patients undergoing gastrointestinal surgery. The quality of evidence supporting each ERAS element has been already evaluated according to the GRADE system and previously published[15–19]. The evidence-based recommendations present the ERAS protocol interventions separately and overall, and are intended to be used by units undertaking to implement and upgrade to what the current literature shows to be best practice: the ERAS protocol. It must be acknowledged that, not being a systematic review, all articles quoted in the manuscript have been selected by the expert in each area, resulting in potential bias. Clinical considerations and recommendations for each of the ERAS elements are listed in Table 4.

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