Postoperative Ileus

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Key Points

1. Avoid perioperative fluid overload.
2. Employ a standard enhanced recovery after surgery (ERAS) protocol.
3. Minimise the use of opioids.
4. Utilise minimal access techniques.
5. Prevent blood loss.
6. Don't re-operate for postoperative ileus.

Introduction

In this chapter we will consider the definition and incidence of this condition, explore the burden of prolonged postoperative ileus (PPOI) on both the patient and the health system, describe of the pathophysiology of PPOI and the main risk factors for its occurrence, list interventions that may prevent or reduce the occurrence of PPOI and present the evidence for the treatment of established PPOI. The chapter concludes with a proposed management strategy.

Definition and Incidence of Ileus

Postoperative ileus is an abnormality of the motility of the gastrointestinal tract that prevents the normal ingestion and absorption of food and elimination of waste products. Symptoms depend on the site of dysfunction. Involvement of the stomach and proximal small bowel is characterised by nausea and vomiting while more distal dysfunction results in lack of passage of flatus or stool and abdominal distension from the bowel dilatation. This dilatation of the bowel can be identified on abdominal X-ray or CT scan as bowel distension with air-fluid levels in the absence of a clear transition point to collapsed bowel on CT (Fig. 1). It is generally accepted that there is a period of 'normal' or physiological gut dysfunction following major abdominal surgery that should resolve spontaneously after a day or two. Prolongation of this period or the reoccurrence of it after return of normal function postoperatively have been recognised as Prolonged or Recurrent Postoperative Ileus.

Various definitions of PPOI have been proposed in the past including the necessity to insert a nasogastric tube after surgery, nausea and vomiting, inability to tolerate oral diet and failure to pass stool or flatus.

A novel study from the Netherlands included patients undergoing elective surgery for colonic cancer and compared scintigraphic studies of gastric emptying on day 1 and colonic scintigraphy on days 2 and 3 with specific symptoms associated with return of gut function [1]. They showed that the best measure of return on GI function was the combined measure of tolerance of solid food and defaecation. This also correlated inversely with length of hospital stay. They did not, however, provide a definition of PPOI but rather considered that all patients had postoperative ileus until both defaecation and tolerance of oral food had been achieved.

In an attempt to clarify the definition of PPOI, Vather et al. carried out a systematic review and global survey amongst those who had recently published in this area [2]. This study differentiated between normal physiological bowel dysfunction that follows surgery and when this becomes pathological as PPOI. Based on this survey they defined PPOI as the presence of any 2 of the five cardinal symptoms on or after day 4 post operatively. These are nausea or vomiting, inability to tolerate an oral diet, failure to pass flatus or stool, abdominal distension, and radiological signs of PPOI. Each of these were carefully defined. This definition provides not only the essential elements to be included but also a timeline for the commencement of

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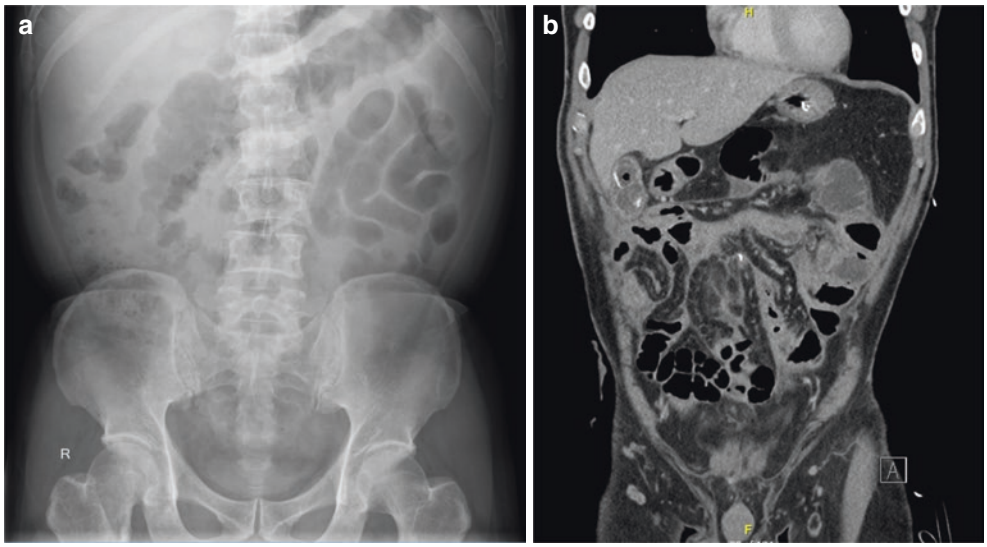

Fig. 1 A 57 year old man seven days following proctectomy and ileoanal pouch. (**a**) A plain abdominal film demonstrating distension of the small bowel and stomach. (**b**) A coronal abdominal CT demonstrating distention of the entire small bowel with a nasogastric tube visible in the stomach

PPOI. Subsequent studies have utilised this definition in their randomised clinical trials [3–5].

The incidence of PPOI varies greatly between studies from 3% to greater than 30% [3, 6]. This variation is likely to be explained by the difference in populations included in the studies, whether the data were collected prospectively and most importantly the definitions used. A recent systematic review that included 54 studies reported a pooled rate of 10% for PPOI. Unfortunately the definition of PPOI differed across the studies with the commonest definition being the reinsertion of a nasogastric tube. They showed that the rates varied depending on the definition used [7]. A snapshot study over six weeks in 10 hospitals in United Kingdom reported that 22.5% of the patients having a left or right-sided colonic resection required nasogastric tube insertion [8]. A very large study out of United States using American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) data for patients undergoing colectomy identified prolonged postoperative ileus as the most common complication, occurring in 10% of the patients [9]. Recent prospective studies using the definition proposed by Vather et al. have identified that more than one patient in four is likely to develop PPOI following a colorectal resection [3, 10].

Burden of Ileus (Effect on Morbidity and Cost of Stay)

Prolonged postoperative ileus has major negative impacts on the patient. The patient may initially appear to be progressing well but then develops nausea and abdominal distension. Vomiting follows and the bowels cease functioning. This often requires insertion of a nasogastric tube and if it does not resolve quickly intravenous feeding is required. For patients it is frightening, unpleasant and extremely disheartening. PPOI is associated with an increase in hospital stay, prolonged intravenous fluid administration and several major complications. The most serious and sometimes fatal complication is aspiration pneumonia but bronchopneumonia, thromboembolic events, electrolyte imbalance and psychological distress are also frequently associated. Recent studies have identified it as the commonest postoperative complication after colorectal surgery [9]. This complication along with anastomotic leak caused the greatest increase in hospital stay and total treatment cost following colectomy [9].

This increased cost associated with PPOI has been estimated by Goldstein et al. to be greater than $1.5 Billion annually in USA alone [11]. A study utilising the Premier Perspective Database in USA assessed nearly 20,000 patients with colectomy. Postoperative ileus was associated with a 29% increase in length of stay and a 15% increase in cost after adjusting for the influence of all other factors [12].

Pathophysiology

The aetiology of PPOI is multifactorial. Its initiation is associated with activation of inflammatory cells, autonomic dysfunction, opioid stimulation of gut opioid receptors, electrolyte abnormalities, direct injury to the intestine and derangement of gastrointestinal hormones. These interactions, triggered by both a somatic and a visceral insult and resulting in the final gut dysmotility of PPOI, are summarised in Fig. 2.

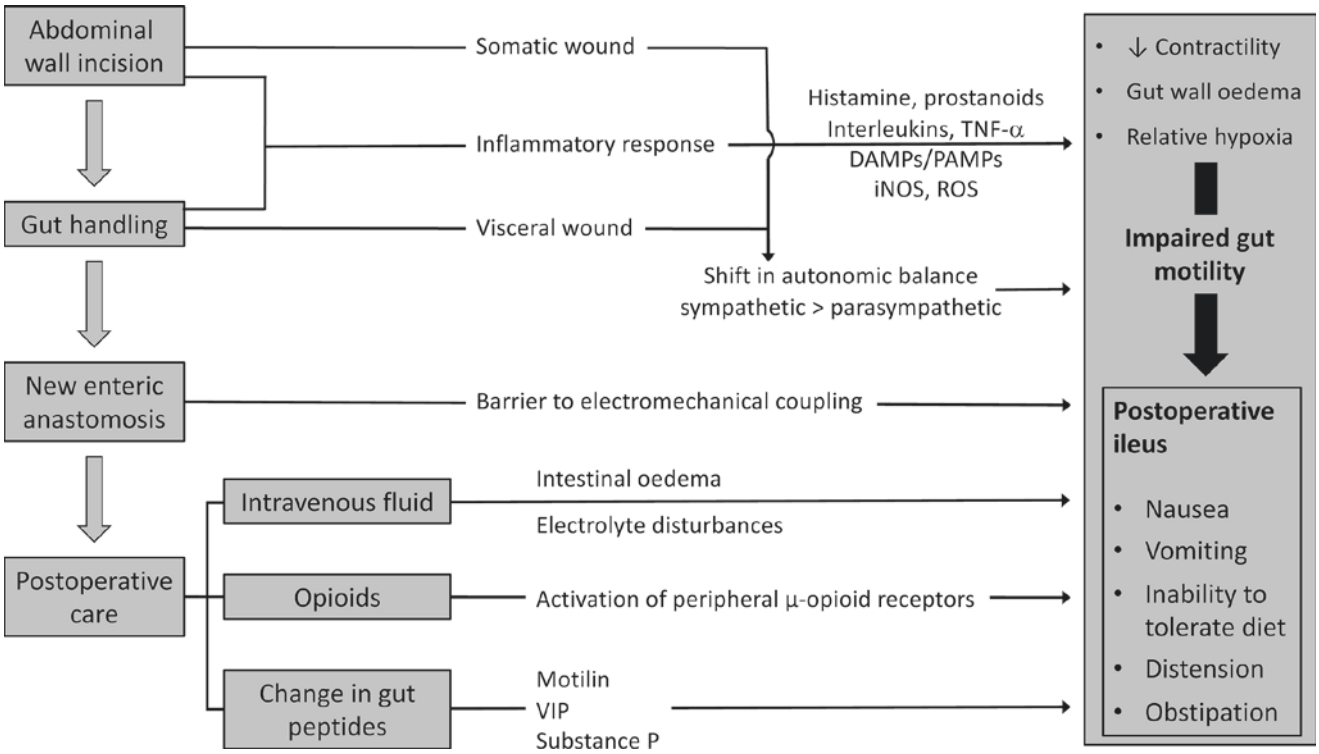

Fig. 2 Pathophysiological basis for the development of a postoperative ileus. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; VIP, vasoactive intestinal peptide, TNF-α, tumour necrosis factor alpha, iNOS, inducible nitric oxide synthetase, ROS, reactive oxygen species [13, 19] with permission [13].

Risk Factors

Multiple risk factors for PPOI have been identified in retrospective analysis of data including; increasing age, male gender, pre-existing chronic airway disease, increasing perioperative opioid consumption, increasing intra-operative blood loss and the formation of an ileostomy [6, 14–16]. These are summarised in Table 1. In a prospective study in colorectal surgery patients using a precise definition of PPOI the factors that were independently identified out of 92 different variables were; male gender, decreasing preoperative albumin, open or converted technique (vs laparoscopic), increasing wound size, operative difficulty, operative bowel handling, red cell transfusion, intravenous crystalloid administration over postoperative day 0–3, and delayed first mobilization. These factors were then combined to create an I-Score that differentiated between those with a low, intermediate and high risk of developing PPOI [17].

Table 1 Risk factors and possible mechanisms for postoperative ileus [6, 14, 16, 18–25]. Adapted from Bragg, et al. [19], with permission

Risk factor	Possible mechanisms
Increasing age [6, 24]	Reduced overall capacity to recover from surgical insult [24]
Male gender [16]	Greater inflammatory response to surgery [21] Increased pain threshold in males, [18] resulting in higher catecholamine release [22]
Low preoperative albumin concentration [16]	Increased oedema and intestinal stretch
Acute and chronic opioid use [6, 14]	μ-opioid receptor stimulation reduces peristalsis [20, 24]
Previous abdominal surgery [6]	Increased need for adhesiolysis, increased bowel handling
Pre-existing airways/ peripheral vascular disease [16]	Reduced physiological reserve
Long duration of surgery [14, 16]	Increased bowel handling [23] and opioid use
Emergency surgery [18, 21]	Increased inflammatory and catecholamine response; secondary causes of POI
Blood loss and need for transfusion [6, 14, 16]	Increased crystalloid administration resulting in oedema [25]
Procedures requiring stomas [21]	Oedema in abdominal wall muscle and cut bowel

Prevention of PPOI

An understanding of the pathophysiology of and risk factors for PPOI as described above provides a foundation for the possible interventions that may reduce the risk of developing this condition. Many of the advances in the perioperative management of patients undergoing major elective abdominal surgery potentially impact on the trigger factors for PPOI. The advent of Enhanced Recovery after Surgery (ERAS) protocols has seen a much greater emphasis on optimising the patient's physiology in the perioperative setting. Recent evidence suggests that the ERAS protocol may actually have an anti-inflammatory effect at both the gut wall and mucosal level [26]. Systematic reviews of ERAS have consistently demonstrated reduced complications and earlier discharge from hospital [27, 28]. Increased volume of crystalloids in the perioperative setting was an independent risk factor for development of PPOI in Vather's study and those of VandeHei et al. and Lobo et al., [17, 29, 30] but this finding has not been confirmed in other randomised studies [31–33]. A possible mechanism relating the association of fluid overload with PPOI is summarised in Fig. 3 [25].

A recent systematic review of preventive measures for PPOI has summarised the different interventions [34]. These include early feeding, chewing gum, epidural anaesthetic, laparoscopy, peripheral μ-opioid receptor antagonists, prokinetic agents, non-steroidal anti-inflammatories, and coffee.

Early Enteral Feeding

Early feeding has become a central plank of the ERAS pathway, RCT evidence of its efficacy in reducing PPOI is inconsistent. In the eleven RCTs that were reviewed by Chapman et al. six showed a significant reduction in time to flatus, stool or oral tolerance, two of which also showed a reduction in length of hospital stay [34]. Early enteral feeding is widely accepted as beneficial and safe in postoperative management

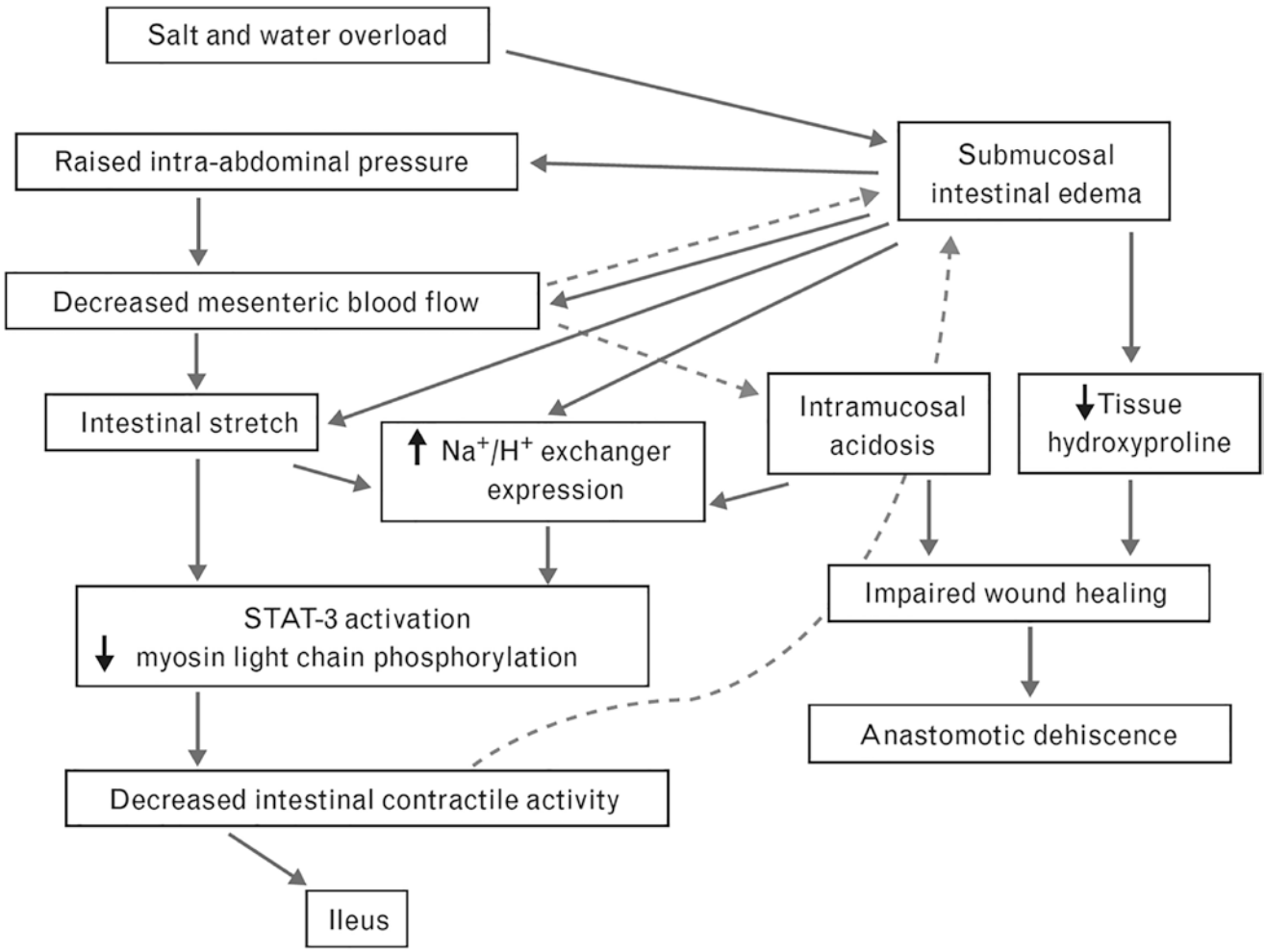

Fig. 3 Mechanisms for adverse effects of salt and water overload on gastrointestinal function, summarising data from human and animal studies. (From Chowdhury and Lobo [25], with permission)

of elective abdominal surgery with a likely benefit in hastening the return of normal intestinal function.

Chewing Gum

Chewing gum in the immediate postoperative period has the potential to stimulate salivation, swallowing and gastrointestinal hormones. A systematic review of eleven randomised studies has assessed this intervention in promoting intestinal recovery after surgery. There was no significant reduction in time to normal oral intake or time to flatus or stool in the high-quality studies but five other studies that were prone to bias did have significant reductions in time to pass flatus and/or stool. A Cochrane review that included 81 randomised studies and 9702 participants did demonstrate a reduction in time to flatus and stool but no other benefit in terms of tolerating food or shortening length of stay [35]. The reviewers state that most of the included studies had a high risk of bias. Chewing gum has little risk of causing harm and may be beneficial in reducing the time to return of normal intestinal function.

Epidural Anaesthetic

There is robust evidence provided in a Cochrane review including more than 20 studies and over 100 patients that epidural anaesthesia leads to a decrease of time to passage of stool and flatus in patients undergoing open surgery, but that there is no decrease in nausea and vomiting in the first postoperative day [36]. The evidence for a benefit in laparoscopic surgery is however much less clear. A large retrospective case matched study of US data found that in laparoscopic colorectal surgery epidural is associated with longer hospital stays, higher expense and a greater risk of urinary tract infections [37]. The benefits of epidural anaesthesia are probably limited to those undergoing open surgery.

Laparoscopy

The laparoscopic approach to surgery has repeatedly been demonstrated to result in a more rapid return of gastrointestinal function and reduction of PPOI [17, 38]. Randomised studies that have specifically addressed this issue, using gastrointestinal transit studies as the outcome, have shown laparoscopy was associated with improved gastrointestinal motility [39–41].

Alvimopan

Alvimopan is a peripheral μ-opioid receptor antagonist without central effects. It has been compared with placebo in 5 randomised clinical trials, four of which demonstrated an improvement in gastrointestinal function using a combined upper and lower GI function measure [42–45]. At present it is only available in USA in restricted centres but it has the potential to mitigate the opioid-related gut dysmotility that so often impairs postoperative recovery.

Prokinetic Agents

Multiple prokinetic agents, although theoretically promising, in practice have mostly been disappointing. However, the serotonin 4 receptor agonists, cisapride and mosapride have demonstrated enhanced gastrointestinal recovery [46, 47]. Cisapride has been withdrawn because of its significant cardiac side-effects, but other Serotonin 4 receptor antagonists, such as prucalopride are under investigation.

Non-steroidal Anti-Inflammatory Drugs

A systematic review that identified 10 RCTs comparing non-steroidal anti-inflammatory drugs (NSAIDs) with placebo in the perioperative setting found that those receiving NSAID passed both flatus and stool earlier, and tolerated a diet sooner than those receiving placebo [48]. The possible role of NSAIDs in anastomotic leak needs to be considered when deciding on the use of these agents. The studies addressing this are conflicting, but to date the selective COX-2 inhibitors have not been implicated in increasing the risk of this complication [49].

Coffee

Coffee has been proposed as an agent to reduce postoperative gut dysmotility. A randomised clinical trial comparing decaffeinated coffee, caffeinated coffee and water in the postoperative period demonstrated accelerated passage of stool and tolerance of solid diet in the decaffeinated group compared with both of the other groups. This suggests that some component of coffee rather than caffeine may stimulate earlier return of normal GI function [50].

Treatment of Prolonged Postoperative Ileus

Although the interventions above have been associated with prevention of PPOI, the treatment of an established PPOI is more problematic. At the outset a precipitating intra-abdominal complication such as anastomotic leak, intra-abdominal abscess or mechanical obstruction should be sought (usually with a contrast enhanced CT scan) and

Fig. 4 A coronal CT of a 77 Year old male following right hemicolectomy demonstrating distended small bowel with the distension bowel distension also involving the anastomosis.

treated appropriately if identified (Fig. 4). The foundation of treatment of PPOI, however, is conservative and involves optimising the patient's physiology. The main features of this are: correction of fluid and electrolyte balance, reduction of opioid administration, decompression of a distended gastrointestinal tract and ensuring ongoing nutritional requirements are met.

The specific electrolytes associated with PPOI that have been reported are hypokalaemia, hyponatraemia, and hypocalcaemia [51]. Regular monitoring of these electrolytes with appropriate correction of abnormalities is required. Often patients will also have a burden of extra fluid leading to oedema of multiple tissues including the intestinal wall. Overzealous replacement of fluids must be avoided and this can be achieved by providing maintenance as isotonic dextrose-saline at a rate of 1–1.25 ml/kg/h and replacing gastric losses with an equivalent volume of balanced isotonic crystalloid solution including supplemental potassium.

Patients in the postoperative setting with PPOI may have both postoperative wound pain and discomfort associated with intestinal distension. The management of this requires a careful balance to ensure that the analgesia is adequate to control the pain without producing opioid-induced intestinal dysmotility. This can often be achieved using regular paracetamol, NSAID medication and tramadol while keeping the amount of opioid analgesia to a minimum. Alvimopan may also be used if it is available and opioids cannot be avoided.

Most patients with PPOI will require a nasogastric tube and this should be inserted if there is recurrent vomiting even if this is low volume as it may represent an overflow of a very distended stomach. Distressing abdominal distension may also be markedly relieved by insertion of a nasogastric tube. Aspiration with subsequent pneumonitis is perhaps the commonest cause of death in those with PPOI and adequate emptying of the stomach is likely to reduce the chance of this serious complication.

A combined analysis of two placebo controlled, randomised clinical trials of the use of Gastrografin in an established postoperative ileus has demonstrated an earlier onset of oral intake in those receiving Gastrografin [52]. However, the study of only 108 patients was not able to demonstrate either a shorter hospital stay or duration of the composite PPOI definition used in the studies. A potential risk associated with Gastrografin is the severe, often fatal, pneumonitis associated with its aspiration and therefore it should only be used when the stomach is known to be empty.

Patients' nutritional requirements need to be considered as oral intake is not feasible in the context of PPOI. Parenteral feeding should be initiated by 7 days postoperatively and earlier for those presenting with malnutrition to ensure that the patient does not suffer serious nutritional decline during management of PPOI [53]. Prolonged under-nutrition in the postoperative setting is associated with increased complications and mortality [54]. Provision of 25 kcal/kg and1.5 g/kg protein (based on ideal body weight) in the administered PN is likely to lead to an improvement in nitrogen balance [53]. The patient should be transitioned back to enteral nutrition as soon as tolerated.

Summary

Prolonged postoperative ileus is the commonest postoperative complication following colorectal surgery and is associated with a large burden of expense. Perioperative measures to reduce its incidence include careful avoidance of fluid overload, minimally invasive surgical approaches, adherence with ERAS principles, avoidance of postoperative opioids, early feeding and mobilisation postoperatively, non-steroidal anti-inflammatories and possibly gum chewing and coffee. Interventions once PPOI is established are primarily conservative aimed at optimising nutrition and physiology. See Table 2 prevention and Table 3 treatment below.

Table 2 Prevention

Intervention	Strength of evidence	Summary of evidence	Patient group
Early feeding	++ SR	Early feeding is safe and may reduce time to postoperative gut recovery	All
Early mobilisation	+ OS	Delayed mobilisation is a risk factor for prolonged postoperative ileus. No consensus regarding optimal mobilisation interventions	All
Avoidance of opioids	+ Large OS	Increased use of postoperative opioid analgesia impairs recovery of gut motility and prolongs length of stay. Minimise opioid analgesia postoperatively	All
Minimally invasive surgery	++ SR	Laparoscopic surgery leads to clinically significant reductions in time to gut recovery and reduces postoperative ileus compared to open surgery	All
Avoidance of fluid overload	+ RCTs, large OS	Perioperative fluid overload may impair gut motility postoperatively. Restrict IV fluid where possible, using a chloride-restricted crystalloid	All
NSAIDs	+ SR	Use of perioperative NSAIDs reduces time to passage of flatus, stool and tolerance of diet in patients undergoing open bowel resection. Role in laparoscopic resection is unclear	All
Alvimopan	++ SR	Alvimopan improves time to gut recovery and reduces ileus after open surgery. It may reduce ileus after laparoscopic surgery. The cost effectiveness of Alvimopan in an enhanced recovery setting is unclear	Open surgery
Thoracic Epidural	++ SR	Thoracic epidural reduces time to passage of flatus and stool after abdominal surgery. Unproven benefit in laparoscopic surgery	Open surgery
Prokinetics	++ SR	Currently used prokinetics (erythromycin, metoclopramide) are unlikely to improve postoperative gut recovery and to reduce postoperative ileus	NR
Chewing gum	+/– SR	Chewing gum is safe postoperatively and leads to small improvements in time to gut recovery. Clinical relevance is unclear	NR
Coffee	+/– Small RCTs	Coffee may improve postoperative gut recovery but the evidence is of low quality	NR
Novel agents (Prucalopride)	+/– RCTs	Serotonin-4 receptor agonists, such as Prucalopride, may reduce postoperative ileus and improve time to pass flatus and stool after colorectal surgery	Await further studies

SR Systematic Review, *RCT* Randomised Clinical Trial, *OS* Observational Studies, *NR* Not recommended

Table 3 Treatment

Correct electrolytes	+ OS	Electrolyte disturbances (sodium, potassium, calcium and magnesium) impair gut motility and may prolong postoperative ileus	All
Balance IV fluids with losses	+ OS	Maintenance fluid with a balanced crystalloid solution, instead of 0.9% saline, based on patient hydration status. Replacement of gastric losses with an equivalent volume of potassium-rich crystalloid	All
NG placement if required	+ OS	Selective use of nasogastric tube for patients with postoperative nausea and vomiting for symptomatic relief. Not all patients with prolonged postoperative ileus require NGT insertion	Selective use as required
Optimize analgesia	++ OS	Opioid analgesia should be used sparingly during postoperative ileus. Use of paracetamol, non-steroidal anti-inflammatories and tramadol may be effective	All
Provide PN if prolonged	+ OS	Commence parenteral nutrition if patient is unable to tolerate adequate oral intake for 7 days postoperatively. Can commence earlier if evidence of preoperative malnutrition	Selective use as required
Alvimopan	+/–	Alvimopan reduces the incidence of postoperative ileus after colorectal surgery. Not yet proven to reduce the duration of an established ileus	Await further studies
Hyperosmolar radiocontrast media (Gastrografin)	+ RCTs	Gastrografin given at the onset of prolonged postoperative ileus may improve time to tolerance of diet and passage of flatus/stool. Further studies are required	Await further studies

SR Systematic review, *RCT* Randomised Clinical Trial, *OS* Observational Studies, *NG* Nasogastric

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