Postoperative ileus—an update on preventive techniques

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INTRODUCTION

Postoperative ileus (POI) is a mandatory stress response to major abdominal surgery and includes clinical symptoms such as abdominal pain, postoperative nausea and vomiting (PONV), distension, delayed passage of stool and the inability to take in sufficient fluids and solids.\(^1\) The definition of POI is the time from surgery until passage of flatus or stool together with the time to adequate oral intake maintained during 24 h.\(^1\) Secondary POI is defined by the same symptoms, but is precipitated by a complication of surgery (e.g. anastomotic leak, abscess, peritonitis, etc.).

During the past 5–8 years, there has been an increased focus on the pathogenesis of POI and the preventive techniques available to reduce the duration of or avoid POI, with a concomitant reduction of morbidity, length of stay, readmissions and overall costs. The mechanisms and treatment modalities of POI have been extensively reviewed between 2000 and 2007;\(^1\)\textsuperscript{−}\textsuperscript{7} this article provides an update on the evidence, and outlines how all the data can be used together to create the concept of multimodal postoperative rehabilitation (fast-track surgery).\(^8\)\textsuperscript{,}\textsuperscript{9}

PATHOGENESIS

Three major mechanisms are thought to contribute to POI: neural sympathetic inhibitory reflexes, opioids, and intestinal inflammatory responses.\(^1\)\textsuperscript{−}6,\textsuperscript{10−13} In addition, it has been demonstrated that a perioperative fluid excess prolongs POI.\(^14\) The pathogenesis of POI is not discussed further here as it is beyond the scope of the article. Instead, the article reviews evidence from clinical studies in which interventional strategies have been applied on the basis of current evidence on pathogenic mechanisms. Factors thought to contribute to enhanced or delayed recovery from POI are summarized in Table 1.

PREVENTIVE TECHNIQUES

Epidural local anesthetic

It is well established from several randomized studies and systematic reviews\(^15,16\) that a
continuous thoracic epidural local anesthetic infusion reduces the duration of POI, allowing early postoperative oral nutrition. The optimal duration for which to give the epidural local anesthetic seems to be for the first 2–3 days after the operation.\textsuperscript{15,16} It is mandatory that the epidural catheter is inserted in the mid-thoracic region to reduce inhibitory neural reflexes and provide optimal pain relief with reduced opioid requirements.\textsuperscript{15,16} Postoperative analgesia by epidural opioids has no positive effects on POI.\textsuperscript{15,16} The need for epidural analgesia to reduce the duration of POI in patients undergoing laparoscopic colonic surgery is unclear since the three randomized trials that have investigated its use in this setting had flaws in their design.\textsuperscript{17–19} Nevertheless, the results of these studies combined with other clinical experience in laparoscopic colonic surgery suggest that epidural analgesia might not be as important for early resolution of POI in laparoscopic colonic surgery as in open surgery.\textsuperscript{9}

### Prokinetic drugs and laxatives

There are no effective prokinetics available for the treatment of POI\textsuperscript{3,20} since cisapride was withdrawn because of potential cardiac adverse effects.\textsuperscript{3,20} It should be emphasized that metoclopramide, although widely used, has no effect on the duration of POI.\textsuperscript{3,20} Neostigmine might increase colonic motility, but further data on safety and efficacy are required before general recommendations concerning its use in the setting of POI can be made.\textsuperscript{20,21} The possible effect of laxatives such as bisacodyl or magnesium oxide on the duration of POI is interesting since they are cheap and probably effective,\textsuperscript{3,22} but their potential use requires further study. In patients undergoing major gynecological surgery, magnesium oxide combined with disodium phosphate has been demonstrated to reduce the duration of POI.\textsuperscript{23} Use of laxatives, therefore, requires study in relation to other major abdominal surgeries.

### Table 1 Factors contributing to enhanced or delayed recovery from postoperative ileus.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence for the effect on recovery</th>
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<tbody>
<tr>
<td><strong>Enhances recovery</strong></td>
<td></td>
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<tr>
<td>Thoracic epidural local anesthetics</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Intravenous or wound local anesthetics</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Laxatives</td>
<td>Preliminary studies positive; further studies required before general recommendations are made</td>
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<tr>
<td>Peripheral opioid antagonists</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Goal-directed fluid therapy and avoiding fluid excess</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Early oral feeding</td>
<td>Preliminary studies positive; further studies required before general recommendations are made (although early feeding is indicated for other reasons (anabolism/morbidity))</td>
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<tr>
<td>Laparoscopic surgery</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Chewing gum</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Mobilization</td>
<td>Limited, inconclusive data</td>
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<tr>
<td>Length and/or type of incision</td>
<td>Limited, inconclusive data</td>
</tr>
<tr>
<td>PONV anti-emetic agents</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<td><strong>Delays recovery</strong></td>
<td></td>
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<tr>
<td>Nasogastric tubes</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
</tr>
<tr>
<td>Restrictions for oral intake</td>
<td>Preliminary studies positive; further studies required before general recommendations are made</td>
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<tr>
<td>Fluid excess</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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<tr>
<td>Opioids</td>
<td>Two or more randomized, controlled trials or meta-analyses</td>
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**Abbreviations:** POI, postoperative ileus; PONV, postoperative nausea and vomiting.
Nasogastric tubes
A main component of classic perioperative care after major abdominal surgery has traditionally been the insertion of a prophylactic nasogastric tube to reduce gastric retention, nausea, vomiting and POI. However, several randomized trials and systematic reviews have clearly demonstrated the ineffectiveness of a nasogastric tube to reduce the duration of POI, and contrarily it might contribute to pulmonary morbidity.

Avoiding routine use of nasogastric tubes has, in fact, been shown to lead to earlier recovery of POI without increased risk of anastomotic leakage. Nasogastric tubes should, therefore, not be used routinely in patients undergoing elective major abdominal surgery, although they can be considered for use in patients undergoing gastrointestinal procedures.

Laparoscopic surgery
The laparoscopic approach to major abdominal surgery has important beneficial physiological effects by reducing pain, inflammatory responses and catabolism, and is, therefore, also expected to reduce the duration of POI. Indeed, several randomized trials and systematic reviews have shown a reduction in the duration of POI by laparoscopy versus open colonic resection from about 4–5 days to about 3 days. However, the clinical significance of these findings is unclear as none of the randomized studies performed provided sufficient information on the perioperative care principles employed, especially concerning the use of nasogastric tubes, early feeding, opioid-sparing analgesic techniques, epidural analgesia, and laxatives, all of which influence the duration of POI.

In the only double-blind, randomized study to revise perioperative care towards multimodal rehabilitation (fast-track surgery), no difference in duration of POI could be demonstrated between open and laparoscopic colonic resection, including a detailed examination of whole gut transit with the 111Indium transit technique. However, in these studies both the open and laparoscopic groups received continuous epidural analgesia and it is possible that laparoscopy per se combined with other fast-track techniques might have benefits by reducing the duration of POI.

Fluids
Liberal intraoperative fluid administration can lead to intestinal edema, which might prolong the duration of POI. In the past 5 years, there has been an increased focus on perioperative fluid management and several randomized studies have shown that perioperative fluid excess prolongs POI, especially if the fluid excess involves large volumes of saline. However, in the only blinded, randomized study performed, no difference in the duration of POI (as measured by gastrointestinal transit of radiopaque markers) could be demonstrated between 1,600 ml and 5,000 ml of Ringer lactate given intraoperatively to patients undergoing fast-track colonic surgery. The specific effect of colloid versus crystalloid solutions on POI has not been assessed. At the same time, the concept of goal-directed fluid management, which includes intraoperative optimization of cardiac stroke volume by small amounts of colloids, has been demonstrated to reduce the duration of POI in a couple of randomized studies. In summary, anesthesiologists and surgeons should pay increased attention to perioperative fluid management to avoid a postoperative fluid excess. Such principles have been included in most fast-track colonic studies, which might also contribute to the success of these enhanced rehabilitation programs.

Chewing gum
The effect of chewing gum on the duration of POI after colorectal surgery has been addressed in five randomized, controlled trials, and a systematic review concluded that there was a clinically and statistically significant reduction in the duration of POI by about 20–30 h. The mechanism of action by which chewing gum exerts its effect is probably stimulation of oral and gastrointestinal major reflexes. Use of chewing gum did not increase complications or readmissions and, in my opinion, owing to its simplicity, efficacy, safety and low cost, it should be considered for use in routine practice for patients undergoing any abdominal procedure. Interestingly, the use of chewing gum has not been addressed in fast-track, laparoscopic, epidural, peripheral opioid antagonist or oral feeding studies, and its relative role compared with or combined with these techniques is unknown and requires further study.

Postoperative nausea and vomiting prophylaxis
Several randomized studies and systematic reviews have confirmed the efficacy of serotonin 5-HT receptor antagonists, droperidol and glucocorticoids for PONV prophylaxis; these
agents are, therefore, recommended on a routine basis. Interestingly, because PONV is included in the definition of POI, the relative role of PONV prophylaxis to reduce the duration of POI should be explored; however, the potential for PONV prophylaxis has not been addressed or included as part of other preventive POI techniques. 

**Opioid-sparing analgesia**

On the basis of the well-established undesirable effect of perioperative opioid pain management on prolonging the duration of POI, multimodal nonopioid analgesic strategies have emerged. Most evidence comes from the use of NSAIDs, which have been demonstrated to reduce opioid requirements and PONV. Consequently, other well-established techniques to reduce opioid requirements (e.g. gabapentanoids, ketamine, neural blockade techniques, glucocorticoids, etc.) could also have potentially beneficial effects to hasten recovery of POI, but confirmation of this requires further study.

Two randomized studies have now demonstrated that intravenous lidocaine can provide improved analgesia, opioid-sparing and reduction of the duration of POI after colonic surgery. Similar findings have been reported for continuous incisional local anesthetic infusion in open colonic surgery. As these techniques are simple, apparently safe, effective and associated with low costs, they should receive further attention and study as part of multimodal rehabilitation programs. Potentially, these effective opioid-sparing techniques could reduce the need for continuous epidural analgesia in patients undergoing major open abdominal procedures, when combined with nonopioid multimodal analgesic strategies.

**Peripheral opioid antagonists**

The common use of postoperative opioid analgesia and the well-known delaying effect of opioids on the duration of POI, means that efforts have been made to synthesize peripherally acting mu-opioid receptor antagonists, either as the oral drug alvimopan or methylnaltrexone for systemic administration. The findings of six placebo-controlled studies, including large phase III studies, have been published and summarized in publications on the effect of alvimopan on POI, while the findings of the ongoing phase II and phase III methylnaltrexone studies have not yet been published. All the alvimopan phase III studies were performed as part of a multicenter setup, with well-defined protocols, early removal (within 24 h) of nasogastric tubes or no nasogastric tubes, and oral liquid given from 24 h postoperatively and oral solids from 48 h postoperatively, using intravenous patient-controlled morphine as the only analgesia. These trials have provided further insight not only into the effect of peripheral opioid antagonists but also into the clinical consequences of a prolonged duration of POI.

On the basis of the findings from the four phase III trials of alvimopan, it is well established that alvimopan 12 mg reduces the duration of POI by about 16–18 h from a mean of about 120 h for placebo after colonic resection. Importantly, the clinical consequences of the achieved reduction in the duration of POI have been a lower incidence of postoperative nasogastric tube re-insertion (from 11.5% to 6.6%). There is also a reduction of POI-related postoperative morbidity (from 8.8% to 2.9%), with a number needed to treat of 12 to prevent 1 patient from experiencing an event of POI-related postoperative morbidity. In addition, readmissions were reduced from 8.3% to 4.9% (P < 0.01). Consequently, total hospital stay was reduced and discharge criteria written almost 1 day earlier than for patients who received placebo. Importantly, alvimopan significantly reduces the incidence of prolonged hospital stay (>7 days) from 6.8% to 2.1% (P < 0.01) as a result of the reduction of POI-related morbidity. The advantageous effects of alvimopan on POI were achieved without an increased incidence of anastomotic leakage (about 1% in all groups) and without any adverse effects on opioid PCA consumption or postoperative pain scores. The effects were more pronounced after intestinal resection than total abdominal hysterectomy, for which POI last for about 2 days only compared with 4–5 days after colonic resection based on findings for the placebo groups. Consequently, the effect of alvimopan on duration of POI after total abdominal hysterectomy is only minimal and not clinically relevant compared with that achieved by a fast-track setup including laxatives.

In summary, the peripheral opioid antagonist data have so far been positive and of clinical relevance and use of peripheral opioid antagonists was approved by the FDA in May 2008. At present, these agents are the only available pharmacological approach to enhance resolution of POI and related morbidity, except for laxatives for which less information is available. However,
although the peripheral opioid antagonist studies have had a well-defined design and have involved more evidence-based perioperative care than previous studies, data from fast-track colonic surgery with avoidance of postoperative nasogastric tubes, with earlier initiation of oral feeding and with epidural analgesia have uniformly shown a faster resolution of POI than the alvimopan trials. Nevertheless, these practices have so far not been widely adopted and peripheral opioid antagonists might, therefore, have a role in the prevention of POI whenever opioid analgesia is provided.

**Early postoperative feeding**

On the assumption that food intake might stimulate a reflex to initiate gastrointestinal motility, early feeding within the first 48 h after surgery could have a potentially advantageous effect and hasten recovery of POI. In addition, it is well established that early oral feeding can attenuate catabolism and potentially decrease infectious complications. However, the findings of available studies on early oral feeding and resolution of POI are inconclusive and interpretation is hindered by inadequate study design, with a lack of specific information about the type of analgesia used, use of nasogastric tubes and lack of early initiation of oral feeding. Nevertheless, early oral feeding should be included as routine in perioperative care after major abdominal surgery, as it is safe and provides benefits for catabolism and infectious morbidity.

**Other techniques**

*Length and type of surgical incision*

The length and type of surgical incision has not been demonstrated to influence the duration of POI per se, but as horizontal or curved abdominal incisions can reduce postoperative pain (and opioid requirements), a secondary benefit on POI resolution might be achieved as a result of the reduced requirement for postoperative opioid use.

*Early mobilization*

Early mobilization has been included in multimodal rehabilitation programs and assumed to hasten recovery of POI, but the only available study does not support this assumption. However, interpretation of the findings of this study is hindered owing to a lack of specific information on all other factors known to influence POI. Furthermore, an enhanced mobilization program as used in recent fast-track programs was not performed. Nevertheless, early ambulation is recommended because of the benefits for pulmonary function and morbidity, catabolism and muscle function.

**Multimodal postoperative rehabilitation (fast-track surgery)**

An increased understanding of the various components of the pathophysiological responses to surgery and techniques available for their modification, means that the concept of multimodal postoperative rehabilitation, or fast-track surgery, has emerged as an important approach to improving early postoperative recovery and decreasing morbidity, hospital stay, and convalescence time. The concept has proven valid across all surgical specialities, but most physiological data are available for colonic surgery. Fast-track surgery has been shown to enhance POI recovery, with more than 90% of patients having a normal oral intake and defecating within 48 h, and having a hospital stay of 2–4 days (reduced from 5–10 days) after open colonic surgery ($P < 0.01$). These benefits are associated with an improved cardiovascular response to exercise, improved pulmonary function and muscle function, and shorter convalescence time when compared with the findings after surgery undertaken in the absence of a multimodal postoperative rehabilitation program.

As mentioned above, aggressive postoperative multimodal rehabilitation programs have shown similar results, in terms of POI duration, for both open and laparoscopic colonic resection in double-blind randomized studies. This finding emphasizes the importance of the overall perioperative care program compared with a single-modality intervention (i.e. surgical approach). The same could apply to the effects of peripheral opioid antagonists, but no study is available of alvimopan versus placebo when combined with such aggressive rehabilitation programs; the alvimopan studies used nasogastric tubes for between 0–24 h postoperatively, oral solid intake was initiated from 48 h postoperatively and there was no use of epidural analgesia or multimodal nonopioid analgesia.

**LACK OF TRANSLATION OF EVIDENCE INTO CLINICAL PRACTICE**

Despite the evidence made available during the past 5–8 years, several multinational surveys have shown that implementation of advances within perioperative care, including techniques...
to reduce the duration of POI (avoidance of nasogastric tubes, nonopioid analgesia, early feeding, mobilization, etc.) has been slow. As POI is one of the main factors that delays recovery after abdominal surgery, every effort should be made to educate anesthesiologists, surgeons and surgical nurses about POI preventive techniques to ensure their implementation and the elimination of old-fashioned, non-evidence-based care principles that can prolong the duration of POI and have not been shown to have any beneficial effect.8,25

CONCLUSIONS
Evidence from clinical randomized studies has demonstrated the effectiveness of several techniques to reduce the duration of POI (Table 1). When combined as part of aggressive multimodal rehabilitation programs that place emphasis on opioid-sparing analgesia, early oral feeding and ambulation, and implementation of well-defined discharge criteria, studies have shown POI to be a short-lived problem that usually resolves within 48 h in most patients compared with a previous mean duration of 4.5 days with conventional care programs.41,49

Importantly, it seems reasonable to adopt the positive effects of chewing gum31 more widely because of its low cost, effectiveness and safety; however, chewing gum has not been included in previous studies on POI. Obviously, further studies are required to evaluate the optimal combination of techniques with regards to cost, effectiveness and safety (Table 1), and also to include other types of major abdominal (upper gastrointestinal tract) procedures. Importantly, no studies of POI intervention are available for gastrointestinal tract (e.g. avoidance of nasogastric tubes, nonopioid analgesia, early feeding, mobilization, etc.), has been slow

KEY POINTS
- Postoperative ileus (POI) is considered an undesirable stress response to major abdominal surgery that leads to discomfort, morbidity and prolonged hospital stay
- Neural sympathetic inhibitory reflexes, opioids and intestinal inflammatory responses are thought to contribute to POI, and perioperative fluid excess is known to prolong POI
- Several techniques have been shown to reduce the occurrence and/or duration of POI: thoracic epidural analgesia with local anesthetics, peripheral opioid antagonists, laxatives, chewing gum, intravenous and incisional local anesthetics, and avoidance of routine nasogastric intubation and fluid excess
- Early institution of oral feeding and laparoscopic surgery might also be effective, but there is less clear evidence available to support their use
- The duration of POI after open or laparoscopic abdominal surgery can be reduced to 24–48 h in most patients by aggressive, multimodal postoperative rehabilitation (fast-track surgery)
- Implementation of advances within perioperative care, including techniques to reduce the duration of POI (e.g. avoidance of nasogastric tubes, nonopioid analgesia, early feeding, mobilization, etc.), has been slow

References


Kaba A et al. (2007) Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anaesthesiology 106: 11–18


