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EDITORIAL

Postoperative ileus: Impact of pharmacological treatment, laparoscopic surgery and enhanced recovery pathways

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Abstract

Almost all patients develop postoperative ileus (POI) after abdominal surgery. POI represents the single largest factor influencing length of stay (LOS) after bowel resection, and has great implications for patients and resource utilization in health care. New methods to treat and decrease the length of POI are therefore of great importance. During the past decade, a substantial amount of research has been performed evaluating POI, and great progress has been made in our understanding and treatment of POI. Laparoscopic procedures, enhanced recovery pathways and pharmacologic treatment have been introduced. Each factor has substantially contributed to decreasing the length of POI and thus LOS after bowel resection. This editorial outlines resource utilization of POI, normal physiology of gut motility and pathogenesis of POI. Pharmacological treatment, fast track protocols and laparoscopic surgery can each have significant impact on pathways causing POI. The optimal integration of these treatment options continues to be assessed in prospective studies.

Key words: Postoperative ileus; Pathophysiology; Cost utilization; Pharmacologic treatment; Laparoscopic surgery; Enhanced recovery pathways

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INTRODUCTION

All patients with a bowel resection develop postoperative ileus (POI), an interruption of bowel function after surgery[1-4]. POI is characterized by a transient cessation of bowel function with a variable reduction in motility sufficient to prevent effective transit of intestinal contents[5]. POI is the single most important determinant of length of stay (LOS) after abdominal surgery, and thus has significant implications for individual patients and hospital resource utilization.

POI has been discussed by surgeons for more than two centuries[6,7]. In 1906, Finney divided POI into three subgroups according to pathophysiology: mechanical, septic and adynamic[8]. After a century of debate a conse-

nsus conference in 2006[5] proposed a definition of POI as: "transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents or tolerance of oral intake". Primary POI was defined as such cessation occurring in the absence of any precipitating complication, whereas secondary POI was defined as that occurring in the presence of a precipitating complication (infection, anastomotic leak, *etc*.). Patients undergoing major abdominal surgery are at highest risk for developing POI, which is related to the degree and length of manipulation of the intestines. Other surgical procedures may also be associated with POI, such as cardiac surgery, orthopedic surgery and trauma[9-12]. In addition to surgery and trauma, postoperative opioid analgesics that are necessary to manage postoperative pain contribute significantly to the incidence of POI.

Clinically POI is characterized by the inability to tolerate a solid diet, delayed passage of flatus and formed stool, pain and abdominal distention, nausea, vomiting, and accumulation of gas or fluids in the bowel[9,13]. Several pharmacological substances have been introduced to treat or prevent POI[14-26]. There has however been little if any proven success in pharmacologic limitation of POI until the reports investigating selective antagonism of opioid receptors.

In addition to pharmacological treatment, fast track or enhanced recovery pathways (ERP) and laparoscopic surgery have introduced new dimensions in treatment of POI. ERP shorten the postoperative recovery period[27] and laparoscopic surgery shortens the average length of POI[28]. The objective of the present paper is to highlight POI and its consequences for patients and society, and the impact pharmacological treatment, laparoscopic surgery and ERP have upon the pathogenesis and duration of POI.

COST IMPLICATIONS OF POI

POI as a complication of major abdominal surgery can have a substantial clinical and economic impact. POI is associated with increased postoperative morbidity, reduced patient satisfaction, and increased length of hospital stay. Moreover, POI-related increases in LOS and use of resources translated into increased costs for the health care system[29]. It has been estimated that POI accounts for a significant amount of perioperative health care costs in the US[5], with estimated total hospital costs attributable to POI $1.28 billion[5].

A recently published study by Iyer *et al*[30] identified 17 000 patients undergoing colectomy in the US Premier Perspective database. The mean hospital LOS was significantly longer in patients with POI compared with patients without POI (13.8 d *vs* 8.9 d). POI in colectomy patients is a significant predictor of increased hospital resource utilization.

Clearly, reducing the LOS associated with POI has become a health care priority for the surgical community, with interventions reducing the LOS having great implications both for the individual patient and for hospital cost utilization.

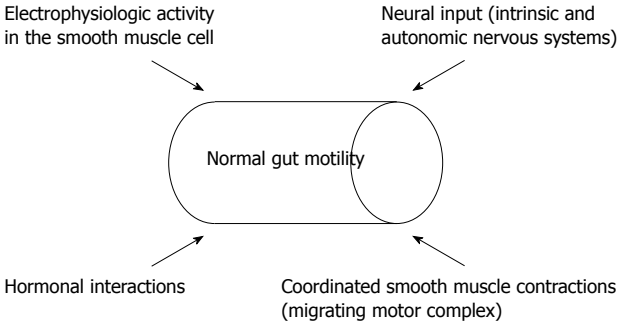

Figure 1 Normal physiology of gut motility.

Bell *et al*[31] recently published a paper, where the economic effect of the use of alvimopan in four randomized controlled trials (RCT) trials was analyzed. This paper used LOS data from the North American alvimopan trials, and calculated cost by extrapolation of cost from the Premier Perspective database, and cost of medication, using mathematical modeling techniques. Compared with placebo, alvimopan was associated with a significantly shorter mean time to gastrointestinal (GI) recovery and a mean hospital LOS of one full day less than placebo. The mean estimated hospital cost was $879-$977 less for patients who received alvimopan compared with placebo. Bell *et al*[31] suggest that use of alvimopan compared with placebo may have a cost-saving effect in the hospital setting. It is however unresolved if alvimopan is more cost effective than optimal use of laparoscopic surgery and ERP protocols, and further research is needed.

PATHOGENESIS OF POI

Normal bowel function is a complex interaction between GI motility, mucosal transport and defecation reflexes. The motility of the intestines is dependent upon the electrophysiological activity in the smooth muscle cells, neural input from the intrinsic and autonomic nervous system, hormonal interactions and coordinated smooth muscle interaction[32] (Figure 1). The migrating motor complex (MMC) has a central position in the normal gut motility[10,33]. The MMC is divided into four phases and regulates the gut motility (contractile pattern) between meals[34] and occurs approximately once every 1-2 h; Phase Ⅰ: Oscillating smooth muscle membrane potentials without actual muscle contractions. Phase Ⅱ: Occurrence of intermittent muscle contractions. Phase Ⅲ: Contractions increase to the maximal contractile frequency (i.e. stomach 3 contractions/min and duodenum 11 contractions/min). Phase Ⅳ: cessation of contractions, and the bowel returns to Phase Ⅰ.

In addition, the nervous system (enteric and central)[35], hormones[36] and smooth muscle activity play roles. Ingestion of food activates these mechanisms and turns off the MMC contractile pattern.

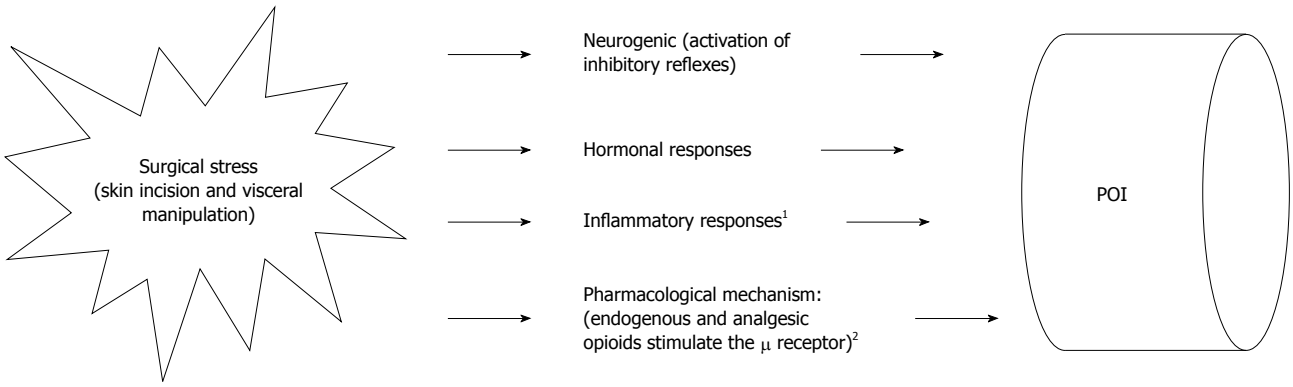

Figure 2 Pathogenesis of postoperative ileus. [1]Laparoscopic surgery decreases the surgical stress and inflammatory response; [2]Primarily exogenous opioids, e.g. morphine, binding to μ-receptors in the GI tract, which results in disorganized and non propulsive motility and, thus, prolongs ileus. In addition, activation of opioid receptors, which occurs following major abdominal surgery, inhibits acetylcholine release, reduces gastrointestinal motility, and has been demonstrated to play a key role in POI regulatory pathways[10,29,36-38]. Alvimopan inhibits this effect by blocking the pheripheral opioid μ receptor.

The interactions between these regulatory components are complex and much is unknown. Contractions in the colon differ from the small intestine, with irregular oscillations and contractile patterns[10,35].

Although multiple factors are thought to contribute to the pathogenesis of POI, four major pathways have been identified (Figure 2): (1) Neurogenic: surgical stress (i.e. skin incision and bowel manipulation) response stimulates inhibitory neural reflexes resulting in decreased bowel motility. This activation of inhibitory reflexes inhibits the normal MMC pattern and is activated as early as at the moment of skin incision (by somatic fibers) and from manipulation of the intestines (by visceral fibers)[37]; (2) Inflammatory: bowel manipulation and resection stimulates normally inactive macrophages and neutrophil recruitment with release of inflammatory mediators that reduce bowel motility; this includes endogenous opioid peptides. Manipulation also causes secretion of proinflammatory cytokines[37]. An increase in the degree of surgical manipulation leads to increased accumulation of neutrophils, macrophages, mast cells, T cells, natural killer cells and dendritic cells which in turn leads to increased inflammation in the intestine and tissue damage[32]. All these factors induce paralysis of the intestine and in turn POI; (3) Hormonal: surgical stress results in elevation of corticotrophin-releasing factor, which stimulates release of inflammatory mediators in the bowel[38]. In addition, a wide variety of local factors, hormones and neurotransmitters may play a role in POI (i.e. Substance P, Nitric Oxide and Calcitonin gene-related peptide CGRP)[10]; and (4) Pharmacologic: primarily exogenous opioids, e.g. morphine, binding to μ-receptors in the GI tract, which results in disorganized and non-propulsive motility and thus prolongs ileus. In addition, activation of opioid receptors, which occurs following major abdominal surgery, inhibits acetylcholine release, reduces GI motility, and has been demonstrated to play a key role in POI regulatory pathways[10,32,39-41].

Opioid-based regimens are the most common treatments to effectively manage post-surgical pain. However, morphine and other μ-opioid receptor agonists can prolong the duration of POI through delayed gastric emptying, reduced GI motility, and disrupted colonic myoelectric activity[42,43]. In addition to exogenous opioids, studies have suggested a role for endogenous opioid peptides in various postoperative responses, including ileus[43-46].

PHARMACOLOGICAL TREATMENT AND POI

Up to the year 2000, several pharmacological agents had been studied in order to prevent POI, however none of these agents was effective enough to become part of routine established practice[14-26].

Chewing sugarless gum following elective intestinal resection is associated with improved outcomes. Gum chewing is thought to promote physiological simulation of the cephalic-vagal axis, thereby increasing bowel motility and GI stimulation[47-49]. There exist two meta-analyses analyzing the effects of chewing gum[50,51], however, all of the included trials in these meta-analyses were small, and only two trials had an adequate sample size calculation.

The meta analysis showed an improvement in first time to bowel movement of 23 h and a reduction in LOS of 1.1 d, and is similar to the effect shown by alvimopan. An adequately powered, methodologically rigorous trial of gum chewing is however required to confirm if there are any benefits[52].

After five RCT, alvimopan represented a novel breakthrough in pharmacological treatment of POI. Alvimopan is a selective peripherally acting μ-opioid antagonist administered orally, blocking the μ-opioid receptor and minimizing the paralytic effect opiates have upon the intestines. The medication blocks the peripheral μ-receptor with high affinity, therefore minimizing the paralytic effect opiates have upon the intestines (Figure 2). This molecule is large and polar and therefore does not cross the blood brain barrier and therefore does not impair analgesia. During the last 5 years five RCTs have been conducted upon alvimopan and its effect upon POI[53-58]. In all these trials

Table 1 Overview of RCT trials 2004-2008 of alvimopan

Author	Number of patients	Primary end point	GI[2] improvement (h)	GI[3] improvement (h)	Hazard ratio	DCO improvement (h)
Wolff *et al*[57]	510	GI[3]	20.0[1]	15.0[1]	1.28[1]	13.0[1]
			28.0[2]	22.0[2]	1.54[2]	20.0[2]
Viscusi *et al*[56]	666	GI[3]	16.4[1]	7.5[1]	1.20[1]	14.2[1]
			13.7[2]	9.9[2]	1.24[2]	15.2[2]
Delaney *et al*[55]	451	GI[3]	15.2[1]	14.1[1]	1.45[1]	14.0[1]
			10.5[2]	7.5[2]	1.28[2]	7.2[2]
Ludwig *et al*[53]	654	GI[2]	20.0[2]	16.0[2]	1.50[2]	17.0[2]
Buchler *et al*[58]	911	GI[3]	14.3[1]	8.5[1]	1.18[1]	8.1[1]
			10.7[2]	4.8[2]	1.37[2]	5.9[2]

[1]6 mg alvimopan; [2]12 mg alvimopan. Hazard ratio: The ratio of two hazard rates. Hazard rate is defined as the probability to failure given survival to date. DCO: Discharge order; GI[2]: The time to recovery of GI function, a composite end points that represent full upper and lower recovery. i.e. time that the patient first tolerated solid food and time that the patient first passed a bowel movement; GI[3]: The time to recovery of GI function, a composite end points that represents full upper and lower recovery. i.e. time that the patient first tolerates solid food, or time that the patient first passes flatus or a bowel movement.

recovery of bowel function was enhanced, except one from Europe when lower opioid doses were used. The primary endpoints in these trials were time to recovery of GI function, measured as either GI[2] or GI[3], composite measures that were developed to track recovery of upper and lower GI function. In these trials GI[2] was defined as "the time that the patient first tolerated solid food and had passed a bowel movement". GI[3] was defined as "the time that the patient first tolerates solid food, and the patient first passes flatus or a bowel movement".

The results from these trials lead to Food and Drug Administration approval in May 2008. A summary of the trial results is shown in Table 1.

The definition of lower GI recovery has been controversial and debated, and up to date there exists no consensus upon this definition. All of the RCTs chose GI[3] as their primary endpoint for GI recovery, except the study by Ludwig *et al*[53], as GI[2] had been noted to be a more robust endpoint by the collaborative study group. GI[3] uses documentation of passage of flatus which can be subject to considerable variability[59], since the patient has to be conscious and willing to report it. In this way it was advocated that GI[2] is a more objective endpoint[53], i.e. a composite end point that was represented by the time the patient first tolerated solid food and time that the patient first passed a bowel movement. In the trial by Ludwig *et al*[53], GI[2] recovery was primarily driven by time to first bowel movement, as this was the later occurring of the two components of GI[2] recovery. In the RCTs there are no obvious dose response curves for alvimopan, and a dose of 12 mg does not give an increased GI recovery, although data were slightly more consistent through the trials (Table 1). This phenomenon is common for new drugs, particularly biologic agents, where effects on a receptor are not directly related to the concentration of the agent. These discrepancies may also be attributed to differing patient populations. However, a pooled analysis has shown that a 12 mg dose provided more consistent benefits across both sexes and all ages[54].

Alvimopan has had fewer side effects than placebo. Treatment adverse events reported in the published RCTs were most commonly nausea and vomiting, but these were less common in the alvimopan treated groups[60]. All studies on alvimopan have been conducted for open abdominal surgery.

Alvimopan will increase pharmacy expenditures; the cost of acquiring gum is substantially lower but more research is needed upon the effect of gum. Whether there is an additive effect upon GI recovery of pharmacological treatment (i.e. alvimopan and/or chewing gum) in combination with laparoscopic surgery and ERP protocols is unresolved.

LAPAROSCOPIC SURGERY AND POI

The greatest advance in limiting POI to date has probably resulted from the expanded use of laparoscopic surgery and the advantage of limiting tissue trauma. Recent studies suggest that laparoscopic surgery causes a lesser degree of mast cell activation and inflammation, and thus prolonged POI[61] (Figure 2). Laparoscopic surgery has many potential advantages over conventional open surgery, including smaller incisions, earlier GI recovery, shorter hospital stay and less pain[62].

Studies of large national databases suggest a higher rate for all commonly identified complications for open compared to laparoscopic colectomy. In a recent published study by Senagore *et al*[63], 4419 cases of open laparotomy were compared to 2728 cases of laparoscopy. All perioperative complications were more frequent in the open laparotomy group. Other database studies, identifying more than 30 000 cases of colectomies, shows superior results of laparoscopic colectomies compared to open cases[64]. Similarly, most other trials have demonstrated significant reductions in time to recovery of GI function after laparoscopic colectomy compared with open techniques, which translate into decreased hospital LOS. In a recent published study[28], mean GI recovery and LOS after laparoscopic colectomy were accelerated compared with those for patients in open laparotomy bowel resection.

Table 2 Effect of interventions to improve gastrointestinal recovery and reduce LOS

Trials	Type of study	Intervention	Improvement passage flatus	Improvement first bowel movement	Decrease in LOS
Noble *et al*[52]	Meta analysis	Chewing gum	14 h	23 h	1.1 d
Delaney *et al*[54]	Pooled analysis	Alvimopan	12 h[1] (6 mg) 15 h[1] (12 mg)	15 h[2] (6 mg) 18 h[2] (12 mg)	18.4 h[3]
Delaney *et al*[28]	Observational multicenter study	Laparoscopic surgery	NA	0.7 d[2]	1.7 d[3]
Walter *et al*[69]	Meta analysis	ERP	NA	NA	3.64 d

[1]Defined as GI[3]; [2]Defined as GI[2]; [3]Discharge order written. Standard elective open colorectal resection is usually associated with LOS of 8-12 d. Pharmacological treatment, laparoscopic surgery and ERP have substantially decreased LOS after surgery. LOS: Length of stay; ERP: Enhanced recovery pathways; NA: Not available.

The primary end points were time to upper and lower GI recovery (GI[2]: toleration of solid food and bowel movement) and postoperative LOS.

Overall POI-related morbidity (postoperative nasogastric tube insertion or investigator-assessed POI resulting in prolonged hospital stay or readmission) was similar between the open bowel resection and laparoscopic colectomy populations, suggesting that POI continues to cause significant morbidity regardless of the surgical approach[28].

Overall, there is substantial evidence that laparoscopic surgery helps accelerate GI recovery after surgery. Although the results in a study by Basse *et al*[65] did not show a benefit with laparoscopy, in our opinion the burden of evidence supports laparoscopic surgery as the standard approach when appropriate.

ERP AND POI

ERP have become part of the standardized postoperative recovery pathway at most hospitals. These protocols include many different elements and interventions, up to 20 elements in a recent published consensus review[66]. The main ERP elements are: avoidance of bowel preparation, preoperative fasting and carbohydrate loading, opioid sparing analgesia and mid thoracic epidural, antibiotic prophylaxis, laparoscopic surgery, small surgical incisions, no nasogastric tubes, normothermia, operative and postoperative fluid restrictions, no abdominal drains, suprapubic urinary drainage, oral diet at will, and early mobilization.

The benefits of fast track protocols (improved recovery, shortening of hospital stay, and earlier recovery of GI function) have been established in several RCTs[67]. Two systematic reviews of controlled and RCT supports the use of fast-track colorectal surgery[68,69]. ERP appear to be safe and shorten hospital stay 1-4 d after elective open colorectal surgery.

During the recent years, old dogmas have been challenged, such as keeping patients fasting after surgery. Allowing patients to eat normal food at will from the first day after major GI surgery does not increase morbidity, including the frequency of POI, when compared with traditional care with nil-by-mouth and enteral feeding[70]. LOS was reduced by approximately 3 d in the group allowed normal food at will. Similarly the use of a nasogastric tube after surgery has been debated. In fact routine nasogastric decompression does not accomplish any of its intended goals (including increased GI recovery) and so should be abandoned in favor of selective use of the nasogastric tube[71].

The best postoperative analgesic regime after surgery has been addressed in several trials, and is still debated. A recent published study advocates the use of thoracic epidural analgesia[72], however this conclusion is contested in a systematic review by Levy *et al*[73]. According to this review there is a paucity of data assessing the benefits of postoperative analgesic regimes following laparoscopic colorectal surgery and none of the protocols were shown to be clearly superior. Low *et al*[74] outlines the concerns of hypotension (increased risk of cardiovascular complications) and splanchnic hypoperfusion (increased risk of anastomotic leak) that are observed in connection with epidural analgesia. The best postoperative analgesic regime is therefore still unresolved; however epidural analgesic regime is included in most published ERP protocols, including a recent published consensus review[66]. Interestingly, while several randomized studies have suggested earlier recovery of GI function with epidurals, this has only been shown for opioid free epidurals, and has never translated into shorter hospital stay.

Over the last decade it has been increasingly realized that the pathophysiology of POI is multifactorial. Thus ideally ERP, and the care provided to colectomy patients should beneficially influence all four pathophysiologic pathways in the pathogenesis of POI (neurogenic, pharmacologic, hormonal, inflammatory, Figure 2)[75]. Although it is not yet clear which pathway is ideal, there is good consensus that fast track, ERP should be used at all modern hospitals, and included in all postoperative care.

FUTURE PERSPECTIVES

Standard elective colorectal resection is usually associated with a complication rate of 20%-30% and a postoperative stay of 8-12 d[67]. The introduction of pharmacological treatment, fast track protocols and laparoscopic surgery has changed this perspective (Table 2).

The introduction of laparoscopy in colorectal surgery improves early postoperative outcome, and randomized

trials have shown promising short term benefits with reduction of LOS by 3-4 d.

Despite rigorous research and several RCT trials during the past decade, the use of alvimopan is still debated, and for unclear reasons its incorporation into practice has been less than might be expected[76,77]. Several important questions remains unresolved, particularly the effect of alvimopan after laparoscopic surgery. After laparoscopic surgery, patients have less pain, lower opioid requirements and a shorter recovery time. It is unclear if alvimopan will have an additive effect upon the duration of POI and consequently LOS for this patient group.

Similarly, all of the alvimopan RCT studies were performed upon patients using a simple and standardized ERP protocol in the treatment and placebo groups. While ERP protocols may include up to 20 different elements, it is unclear which of these elements have the greatest impact upon POI and LOS. Similarly it is unclear what additive effect alvimopan may have upon POI and LOS for patients using ERP protocols. Recent studies[28,78,79] have however included fast track protocols in combination with laparoscopic surgery with promising results upon POI. Future POI research should address fast track protocols, laparoscopic surgery and pharmacological treatment, and the optimal combination of these interventions.

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