Facilitating Return of Bowel Function after Colorectal Surgery: Alvimopan and Gum Chewing

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Abstract

Keywords

- postoperative ileus
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- chewing gum
- health care utilization
- enhanced recovery pathways

Postoperative ileus is common after colorectal surgery, and has a huge impact on hospital LOS. With the impending cost crisis in the United States, safely reducing length of stay is essential. Chewing gum and pharmacological treatment with alvimopan are safe, simple tools to reduce postoperative ileus and its associated costs. Future research will determine if integrating these tools with laparoscopic procedures and enhanced recovery pathways is a best practice in colorectal surgery.

Objectives: On completion of this article, the reader should be able to summarize the etiology and costs of postoperative ileus, and the evidence for the use of alvimopan and chewing gum for postoperative ileus.

One of the major impediments in recovery from colorectal surgery is the return of bowel function. Approximately 25% of patients experience postoperative ileus (POI) following colorectal surgery.¹ In addition to patient discomfort and dissatisfaction, delay in bowel motility is a major factor in prolonging length of stay (LOS) and health care costs.² The development of POI is associated with a 29% increase in hospital days with costs exceeding \$1.75 billion in the United States.³

The development of standardized fast-track protocols or enhanced recovery pathways has optimized the return of bowel function. Minimizing the use of systemic narcotics, early refeeding, and the elimination of standard nasogastric tubes each play a role in facilitating patient care, and are covered elsewhere within this issue of *Clinics in Colon and Rectal Surgery*. Treatment and prevention of ileus also includes the use of pharmacological and gastric-stimulating agents; this will be reviewed within this article.

Postoperative Ileus: Definition and Etiology

Postoperative ileus is defined as the cessation of coordinated bowel motility preventing tolerance of oral intake. In general, a delay lasting greater than 3 days after laparoscopic surgery or greater than 5 days after open surgery is considered a delayed POI.³ The pathophysiology of ileus has been well studied, but remains incompletely understood. The gastrointestinal (GI) tract is controlled by a combination of neurologic, hormonal, inflammatory, and extrinsic factors that determine timing of return of bowel function.^{4–6} Many of these factors are listed in **Table 1**.

The parasympathetic nervous system has a stimulatory effect on the intestinal tract, and is generally balanced by inhibitory signals from the sympathetic nervous system. The stress of surgery and direct bowel manipulation cause a surge in sympathetic stimulation, overriding parasympathetic stimulation and slowing bowel function.⁷ The effects of this are most pronounced in the colon, where it may take 2 to 3 days for normal peristalsis to return in the postoperative period.⁸ The small intestines are heavily innervated by intrinsic enteric stimulation, also known as migrating motor complexes (MMC).^{4,6} Because sympathetic stimulation does not inhibit MMC's, small bowel function

Table 1 Neurologic, hormonal, inflammatory, and extrinsic factors contributing to postoperative ileus

Neurologic factors
Sympathetic innervation: Inhibitory Parasympathetic innervation: Stimulatory Intrinsic neurologic factors: Migrating motor complexes return function to the small bowel after surgery
Local inflammatory mediators
Macrophage and neutrophil infiltration release inflammatory mediators that contribute to ileus: Vasoactive intestinal peptide Nitric oxide Substance P Calcitonin gene-related peptide Corticotropin-releasing factor Cyclooxygenase 2 (COX-2)
Anesthesia
Inhaled anesthetics often decrease gastric emptying. Epidurals: May block afferent and efferent inhibitory reflexes Narcotics: Increase nonpropulsive waves in colon
Surgical factors
<ul style="list-style-type: none"> • Longer surgery, increased bowel manipulation and open surgeries may increase intestinal edema and negative effects of ileus • Blood loss: Inhibits intestinal recovery • Edema: Inhibits intestinal recovery

returns more rapidly, in 1 to 2 days after surgery.^{4,9} Interestingly, abdominal cases are not the only type of surgery prone to cause ileus—orthopedic and extremity surgery also cause sympathetic stimulation and delay in bowel motility without direct intestinal manipulation.¹⁰

Hormonal and local inflammatory factors both play a vital role in ileus. Bowel manipulation, edema, and blood loss cause migration of neutrophils, damage to tight junctions, and release of inflammatory and paracrine mediators. These local factors modify the local inflammatory milieu and cause inhibitory input to the cholinergic neurons, decreasing gastric activity.^{11,12} Antagonistic activity to vasoactive peptide and substance P has been shown to improve postoperative bowel recovery.^{13,14} Corticotropin-releasing factor and calcitonin gene-related peptide have each been shown to induce delays in gastric emptying and GI ileus.^{12,15} Nitric oxide is released from local cells postoperatively causing inhibition of GI motility; experiments have demonstrated improved intestinal motility when production of nitric oxide is blocked.¹⁶

Anesthetic agents may also affect the return of bowel function. Some inhalational anesthetics such as halothane slow gastric motility, while nitrous has promotility properties.¹⁷ Exogenous narcotics bind to receptors within the GI tract and slow motility.¹⁸ Perioperative epidural anesthesia is believed to create a sympathetic blockade that may decrease the effects of stress on POI.¹⁹

Surgical factors also contribute to ileus in the postoperative period. Laparoscopy, with smaller incision size, magnitude of sympathetic activation, and decreased bowel manipulation may lessen the duration and prevalence of ileus.⁴ Others have found that metabolic disarray, blood loss, or hypoalbuminemia may correlate with higher frequency of ileus.²⁰

Pharmacologic Agents

Multiple pharmacologic agents have been trialed in attempts to reduce or eliminate the incidence of POI. Trials of β blockade of adrenergic receptors aimed at reducing sympathetic stimulation were performed as early as 1983.²¹ Neostigmine, an acetylcholine inhibitor, and cisapride, a serotonin receptor antagonist, were also trialed. Results were mixed and side-effect profiles, including abdominal cramping and significant cardiovascular events, limited their utility and clinical use.^{22,23} Metoclopramide has also been used. Although it reduces the risks of nausea and vomiting, it has not been found to reduce duration or frequency of POI.²⁴

Alvimopan is the most promising of selective mu opioid receptors to reach the market. The size and composition of alvimopan (Entereg®, Adolor and GlaxoSmithKline, Exton, PA) prevents the molecule from crossing the blood-brain barrier and therefore provides opioid antagonism within the GI tract, while allowing for continued central nervous system effects of the pain medication.²⁵ Studies have demonstrated that side effects are similar to placebo with nausea and vomiting the most common side effects.²⁶

The first double-blind prospective results on postoperative use of alvimopan were published by Taguchi in 2001.²⁷ Seventy-eight patients underwent total abdominal hysterectomy (TAH) or open colon resection and were randomized to receive alvimopan or placebo. The treatment group experienced a significant decrease in time to passage of first flatus, first bowel movement, and discharge. A multicenter, randomized double-blind trial validated results with reduced time to solid food, flatus, or bowel movement: 86.2 hours in the alvimopan group versus 100.3 in placebo.²⁸ Alvimopan was also noted to accelerate time to discharge order.²⁹ A

comprehensive meta-analysis encompassing five studies and over 1,500 patients found alvimopan accelerated time to return of bowel function and reduced the postoperative LOS by 2 to 15 hours (4/5 studies).³⁰

Data from Ludwig et al demonstrated that the number needed to treat (NNT) to realize clinical benefits is small. In a pooled analysis, only seven patients required treatment to achieve significantly accelerated bowel recovery and discharge order.³¹ There has been a single report that demonstrated a nonsignificant reduction in mean time to tolerate solid food, first flatus, or bowel movements; benefits were noted only for patients who received postoperative patient-controlled analgesia.³²

The benefits of alvimopan on patients undergoing laparoscopic surgery are less clear. Patients who undergo laparoscopic colectomy have been noted to have less pain, lower opioid requirements, and a shorter recovery time at baseline.³³ One multiarm study demonstrated a significant decrease in LOS for the open/hand assisted laparoscopic surgery patients treated with alvimopan (5.6 ± 2.5 vs. 6.8 ± 3.3 d, $p = .009$), but no difference in POI ($p = 1.00$) or LOS ($p = .305$) in the laparoscopic group.³⁴ A more recent case series noted benefits of alvimopan in elective uncomplicated laparoscopic colectomy.³⁵ In this case series, the addition of alvimopan to an enhanced recovery protocol significantly decreased LOS (1.55 d, $p < .0001$) and incidence of POI (2% vs. 20%; $p < .0001$).

Alvimopan may have a significant cost impact through reduction in LOS. A cost analysis of alvimopan in the North American studies found the mean hospital LOS to be one full day shorter with a mean savings of \$879 to \$977 per patient when patients received an average of 8.9 doses.³⁶ Further analysis of prospective and retrospective data demonstrated a reduction in postoperative LOS of 1.2 days in the alvimopan group ($p = 0.01$), with an even larger difference (3.2 d) observed in elderly patients.³⁷ In this trial, a mean cost savings of \$531 per laparoscopic patient and \$997 per open patient was noted. Using a mathematical formula, Gaines found that a reduction of 24 hours was needed for costs savings if patient receive six or fewer doses of alvimopan, and for patients receiving more than six doses the LOS needs to be 2 days to decrease total hospital costs.³⁸

Based on the GI recovery benefits of alvimopan, its use can be recommended in patients undergoing open surgery, with a slight reduction in overall hospital costs, but a significant reduction in LOS. For laparoscopic surgery, both cost and clinical benefits require further evaluation and study to determine benefits.

Gum Chewing

Chewing gum following elective intestinal resection was first proposed in the literature in 2002 as a mechanism for sham feeding and gastric stimulation.³⁹ Sham feedings have been noted to promote the cephalic phase of digestion through vagal cholinergic stimulation and the release of GI hormones in the upper GI tract.^{40,41} Gum chewing provides an inexpensive, convenient, and physiological method to stimulate these pathways,⁴² while avoiding complications

of food intolerance associated with food intake.⁴³ Chewing gum preoperatively and in the direct postoperative phase may ameliorate POI and enhance postoperative recovery.⁴⁴

Asao et al first described an earlier return of flatus (1.1 d, $p < 0.01$), time to defecation (2.7 d, $p < 0.01$) and time to discharge (1 d, not significant) in 19 patients randomized to chew gum after laparoscopic colectomy.³⁹ Although this study was poorly powered, a larger, randomized multicenter trial supported the data; patients who chewed gum four times daily after laparoscopic surgery had shorter duration of ileus (2.6 vs. 3.3 d, $p = 0.0047$), and hospital stay (4.0 vs. 5.3 d, $p = 0.029$) compared with controls (45). A trial of open sigmoid colectomy noted statistically decreased time to flatus (65.4 vs. 80.2 h, $p = 0.05$), defecation (63.2 vs. 89.4 h, $p = 0.04$), and LOS (4.3 vs. 6.8 d, $p = 0.01$) in 34 patients randomized to gum chewing.⁴⁵

Data from other studies is less compelling. Matros found no significant decrease in passage of flatus or reduction of ileus in 66 patients randomized to gum chewing after open colectomy.⁴⁶ A second randomized trial of 38 patients undergoing open surgery and found nonsignificant reductions in time to flatus ($p = 0.56$), first bowel movement ($p = 0.38$), and LOS ($p = 0.75$).⁴⁷ Bahena-Aponte also found that although oral tolerance and the time to first defecation occurred significantly faster in the gum-chewing group ($p = 0.05$), the duration of hospital stay was not significantly different among treated and nontreated patients.⁴⁸ Most recently, a randomized trial by Zaghyan et al demonstrated no difference in time to tolerating diet, flatus, bowel movement, or LOS in 114 patients who were placed on early enteric feeding and randomized to gum chewing or control. In addition, patients who chewed gum were noted to have more bloating, indigestion, and eructation.⁴⁹

A systematic review by Chan et al found with combined standard postoperative care and gum chewing, patients had significantly earlier time to pass flatus (24.3% earlier, $p = 0.0006$), time to bowel movement (32.7% earlier, $p = 0.0002$), and time to discharge (17.6% earlier, $p < 0.00001$) than controls.⁵⁰ A later systematic review found chewing gum consistently reduced time to passage of flatus and stool, but results were mixed in reduced hospital LOS (one of three trials).⁵¹ Later meta-analyses on gum chewing confirmed these results,^{52–57} demonstrating a statistically significant reduction in time to flatus and defecation, but only two studies demonstrated a significant effect on the hospital stay.^{54,58}

Difficulties in these studies include small sample sizes, nonblinded trials, and variation in techniques. Some studies include use of open and laparoscopic surgery, use of epidurals, and enhanced recovery protocols, complicating data analysis. In general, studies of laparoscopic surgery, without use of epidurals have demonstrated the greatest effect in reducing POI.^{39,45,59} In addition, although most studies used sugar-free gum, the most recent study by Zaghyan et al may be complicated by the use of sugared chewing gum and the loss of the cathartic effects of sorbitol or sugar-free additives.⁶⁰

Although the evidence may not be overwhelming, the risks and costs of gum chewing are minimal. The financial costs of gum chewing are estimated to be minimal: Schuster's 2006 analysis demonstrated costs of \$.04 per stick of gum three times daily for 5 days⁴⁵ in comparison to the estimated \$1,500 daily cost of a hospital room. Although theoretical complications such as aspiration may exist, only one study demonstrated increased GI distress in patients randomized to chewing gum. There is no physiological evidence that gum chewing increases the volume or acidity of gastric secretions or that swallowing gum increases the risk of aspiration; on the contrary, there is evidence that gum chewing promotes GI motility and physiological gastric emptying.⁶¹

In conclusion, chewing sugarless gum preoperatively and in the direct postoperative phase is a simple, inexpensive tool to stimulate bowel motility and reduce ileus after colorectal surgery. Further, it has the potential impact to reduce health care expenditures with routine implementation. With the potential for substantial cost savings, larger-scale, blinded, randomized controlled trials are warranted.

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