



Prolonged postoperative ileus after colorectal surgery: still an unresolved problem

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Prolonged postoperative ileus (PPOI) is often an unavoidable event after surgery, and is associated with important financial consequences such as increased complications and mortality, resource utilization and healthcare costs (1,2). An estimated 2.7 million procedures are performed annually in the US that develops PPOI leading to a readmission rate of 10% in abdominal surgeries (3). PPOI is estimated to add \$8,000–9,000 to hospital costs per patient (3). Total PPOI costs to the US healthcare system were estimated to be \$1.46 billion annually (1).

Data from the literature (3–13) reveal that the incidence of PPOI after colorectal surgery ranges from 2% to 54% (Table 1). Pooled data from a wide variety of settings show that the median incidence of PPOI is 10.3% (Table 1).

According to some recent studies, length of stay doubles in patients with PPOI when compared to that of patients without (3,4,8). In our previous study, the mean hospital stay was 11 days in patients without PPOI and 20 days for patients with PPOI ($P<0.001$) (10).

There is considerable heterogeneity with respect to the definition of PPOI and there remains a need for uniformity (14). To some (7,15), postoperative ileus is the occurrence of three episodes of vomiting over 24 h, the need for re-insertion of a nasogastric tube, or the cessation of progression of oral diet. Moreover, it can be further stratified into primary (e.g., within 5 days), or PPOI (e.g., after 5 days or requiring readmission). Indeed, PPOI lasts longer, and the symptoms are uniformly recognized: abdominal pain and distention, nausea, vomiting, lack of

flatus and intolerance to diet.

In our previous study (10), patients with a postoperative anastomotic leak, pelvic abscess, peritonitis, or evidence of dehiscence at relaparotomy were excluded from analysis. We defined PPOI as no flatus by postoperative day (POD) 6, with or without intolerance to oral intake by POD 6. This definition held, regardless of whether there was intolerance to oral intake by POD 6 due to abdominal distension, nausea, and emesis after starting a liquid diet and in the absence of mechanical obstruction. Finally, in some studies PPOI was defined as no return of bowel function within 7 days of operation (8).

Many surgeons have suggested that postoperative ileus after a bowel resection should last 3 days following a laparoscopic surgery and 5 days in an open approach (16). In some studies, however, the duration of PPOI is still reported to be as long as 4 days in the laparoscopic approach, which is just about 1 day earlier than that in the open approach (17).

The cause of PPOI is thought to be multifactorial and impaired contractility, dysmotility, and gut wall oedema constitute a common final pathway. Physical (e.g., manipulation of the bowel or peritoneal irritation), neural (e.g., postoperative sympathetic hypersensitivity), inflammatory (e.g., inflammatory cell activation), and humoral factors (e.g., increased circulating catecholamines, changes in gastrointestinal hormones released to the circulation or acting locally at the intestinal wall) or electrolyte disturbances seem to be involved in the

Table 1 Incidence of PPOI after colorectal surgery

Author	Year	Laparotomy	Laparoscopy	Elective	Organ	Type of study	Patients (n)	PPOI (%)	
								Overall	Laparoscopy
Hain <i>et al.</i> (4)	2018	–	x	x	Rectum	Single Institution	428	15	15
Lee <i>et al.</i> (5)	2016	–	x	x	Colorectal	Single Institution	3,188	5.5 (previous surgery) vs. 2.0	5.5
Wolthuis <i>et al.</i> (6)	2016	x	x	x	Colorectal	Meta-analysis	18,983	10.3	6.4
Gan <i>et al.</i> (3)	2015	x	x	x	Colon, gallbladder	Premier research database	138,068	10.3	–
Vather <i>et al.</i> (7)	2015	–	–	x	Colorectal	Single institution	327	26.9	–
Moghadamyeghane <i>et al.</i> (8)	2016	–	–	–	Colorectal	NSQIP database	27,560	12.7	–
Boelens <i>et al.</i> (9)	2014	–	–	–	Rectum	Single institution	123	54 (enteral) vs. 68 (parenteral)	–
Millán <i>et al.</i> (10)	2012	x	x	x	Colorectal	Single institution	773	15.9 (patients without anastomotic leak)	–
Poon <i>et al.</i> (11)	2011	–	x	–	Colorectal	Single institution	180	6	–
Kronberg <i>et al.</i> (12)	2011	–	x	–	Colorectal	Single institution	413	10.2	10.2
Delaney <i>et al.</i> (13)	2010	–	x	–	Colorectal	Multicenter	148	10.1	10.1

x, indicates type of surgery where available. PPOI, prolonged postoperative ileus.

mechanism (2,10,14,18,19).

Several studies have identified numerous risk factors that are associated with the occurrence of PPOI after colorectal surgery (Table 2).

Chronic preoperative use of narcotics is independently associated with PPOI in patients undergoing laparoscopic colectomy (3,12). Administration of opioids to patients who develop ileus following abdominal surgeries is associated with prolonged hospitalization, greater costs, and increased readmission rate. Furthermore, higher doses of opioids are associated with higher incidence of PPOI (3).

Open or converted operative technique is an independent predictor for the development of PPOI after colorectal surgery (4,7). In some studies, the incidence of PPOI is higher after open colorectal resection when compared to the laparoscopic approach (6). Moreover, male gender has been observed to be associated with a higher risk for the development of PPOI (4,7,10). Age (>70 years old in one study) is an independent predictor of PPOI (4,12).

A history of chronic obstructive pulmonary disease (8,10), or finding of disseminated cancer at laparotomy (8) are disease predictors of PPOI. It is of interest to note that

oral antibiotic bowel preparation seems to act as a protector against the development of PPOI (8).

Finally, delayed first mobilization (8), parenteral nutrition (9), ileostomy (10), and emergency surgery (2) are associated with an increased risk for the development of PPOI.

In a recent issue of the *Journal of Gastrointestinal Surgery*, Sugawara *et al.* (20) published the results of the analysis of 841 patients operated on for major abdominal surgery that were managed following an enhanced recovery after surgery (ERAS) program. Patients who underwent less-invasive surgery (such as laparoscopic cholecystectomy, appendectomy, stoma construction or closure, and gastrointestinal bypass), ileus-related surgery, and emergency surgery were excluded from the analysis. A total of 73 patients (8.8%) developed prolonged PPOI. The authors identified smoking history, colorectal surgery, and an open approach as independent predictive factors for PPOI. Further, they elegantly devised a nomogram based on these three predictive factors that aided in identifying patients with a high probability of developing PPOI.

According to their findings, the authors (20) suggest

Table 2 Risk factors associated with PPOI after colorectal surgery

Variables	Hain <i>et al.</i> , 2018 (4)	Vather <i>et al.</i> , 2015 (7)	Moghadamyeghaneh <i>et al.</i> , 2016 [§] (8)	Gan <i>et al.</i> , 2015 (3)	Millán <i>et al.</i> , 2012 (10)	Kronberg <i>et al.</i> , 2011 (12)	Other
Opioid use	–	–	–	1.99	–	3.17	–
Open surgery	–	6.37 ^Φ	–	–	–	–	x
Male gender	2.3	3.01	–	–	1.61	–	–
Age	2.0*	–	–	–	–	1.89	–
Conversion to open approach	4.9	–	–	–	–	–	–
Intraabdominal surgical infection	3.8	–	2.56	–	–	–	–
Duration of surgery	–	–	–	–	–	–	x
Previous major abdominal surgery	–	–	–	–	–	2.41	x
Anastomotic leakage	–	–	2.5	–	–	–	–
Preoperative sepsis	–	–	1.63	–	–	–	–
Disseminated cancer	–	–	1.24	–	–	–	–
Chronic obstructive pulmonary disease	–	–	1.27	–	1.99	–	–
Ileo-colonic anastomosis	–	–	1.25	–	–	–	–
Oral antibiotic preparation	–	–	0.77	–	–	–	–
Laparoscopic surgery	–	–	0.51	–	–	–	–
Decreasing preoperative albumin	–	1.11	–	–	–	–	–
Increasing wound size	–	1.09	–	–	–	–	–
Operative severity	–	1.28	–	–	–	–	–
Operative bowel handling	–	1.38	–	–	–	–	–
Red cell transfusion	–	1.84	–	–	–	–	–
Intravenous crystalloid administration	–	1.55	–	–	–	–	–
Delayed first mobilization	–	1.39	–	–	–	–	–
Parenteral nutrition	–	–	–	–	–	–	x
Ileostomy	–	–	–	–	1.95	–	–
Emergency surgery	–	–	–	–	–	–	x

Data are expressed as odds ratio (OR). x, indicates association where no OR data is available; *, >70 years old; ^Φ, vs. laparoscopic approach; [§], adjusted OR. PPOI, prolonged postoperative ileus.

that patients with a high probability of PPOI should have a different perioperative management compared to those with a low probability of PPOI. The recommendations of the ERAS protocols, namely preoperative counseling, a non-fasting period, optimal fluid management, decreased use of tubes, enforced early mobilization, gum chewing, and opioid-sparing analgesia, should be enforced in these patients.

It is believed that multimodal postoperative rehabilitation (fast-track care, ERAS), and minimally invasive surgery can reduce PPOI without shortening its duration (11,21). Minimalization of surgical manipulation may help in this regard (22).

Sugawara *et al.* (20) further explain that numerous studies have shown a lower incidence of PPOI in laparoscopic

colorectal surgery compared with the open approach. However, a brief review of several studies shows that the median incidence of PPOI using the laparoscopic approach for colorectal surgery is 10% (Table 1), a figure similar to the overall data obtained from patients in different settings.

In terms of treatment, it has been suggested that medications such as alvimopan, ghrelin agonists, and intravenous lidocaine can prevent PPOI (16). Alvimopan is an oral, peripheral μ -opioid receptor antagonist, and currently the only US FDA-approved medication to accelerate the return of gastrointestinal function postoperatively (1). The beneficial effect of alvimopan has been validated, although it augments risk of myocardial infarction and its costs are high (22).

Recently, Gastrografin[®] has been examined in two randomized clinical studies comparing patients with PPOI after colorectal surgery treated with gastrografin *vs.* patients treated by placebo (23,24). Both studies did not observe benefit in shortening length of stay. However, in one trial (23), Gastrografin accelerated significantly time to flatus or stool, and time to resolution, or improved abdominal distension. Further studies are needed with larger series including a wider range of colorectal procedures to determine which groups of patients could benefit from its use.

In conclusion, PPOI still represents a clinical problem that increases postoperative length of stay with an important impact on the economic burden. To study and demonstrate the mechanisms responsible of PPOI, to develop a clinical risk stratification tool, as well as to analyze the response to specific treatments on a larger series, will provide benefit to patients and health systems.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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