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REVIEW

Postoperative ileus: Pathophysiology, incidence, and prevention

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Summary Postoperative ileus (POI) is a major focus of concern for surgeons because it increases duration of hospitalization, cost of care, and postoperative morbidity. The definition of POI is relatively consensual albeit with a variable definition of interval to resolution ranging from 2 to 7 days for different authors. This variation, however, leads to non-reproducibility of studies and difficulties in interpreting the results. Certain risk factors for POI, such as male gender, advanced age and major blood loss, have been repeatedly described in the literature. Understanding of the pathophysiology of POI has helped combat and prevent its occurrence. But despite preventive and therapeutic efforts arising from such knowledge, 10 to 30% of patients still develop POI after abdominal surgery. In France, pharmacological prevention is limited by the unavailability of effective drugs. Perioperative nutrition is very important, as well as limitation of preoperative fasting to 6 hours for solid food and 2 hours for liquids, and virtually no fasting in the postoperative period. Coffee and chewing gum also play a preventive role for POI. The advent of laparoscopy has led to a significant improvement in the recovery of gastrointestinal function. Enhanced recovery programs, grouping together all measures for prevention or cure of POI by addressing the mechanisms of POI, has reduced the duration of hospitalization, morbidity and interval to resumption of transit.

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Key points
- There is no consensual definition of a normal interval to resumption of transit resulting in non-reproducible results in studies of postoperative ileus.
- Postoperative ileus occurs following 10 to 30% of abdominal surgeries.
- The main risk factors are male gender, advanced age and the volume of blood loss.
- Ileus occurs in three phases: a neurological phase, an inflammatory phase, and a phase of activation of the vagal nervous system.
- In France, pharmacological prevention is limited by the non-availability of effective drugs.
- Enhanced recovery after surgery programs make use of several measures aimed at the different phases of ileus to reduce the interval to ROT.

Introduction

Postoperative ileus (POI) has become a public health problem because of its role in postoperative morbidity and increased hospital stay [1—3]. Its reported rate of incidence varies among different authors and specialties, but is generally between 10 and 30% for abdominal surgery [4—11]. The consequences of POI can be severe since it causes gastrointestinal stasis with a risk of nausea and vomiting, which can be complicated by pulmonary aspiration. Besides this extremely serious complication, POI may also cause dehydration, electrolyte imbalance, or sepsis.

Recent recommendations for perioperative management (initially proposed by the ERAS group [12] and thereafter by the GRACE Association [13]) have enabled a net decrease in hospital stay and morbidity, but also a decrease in the interval to resumption of transit (ROT) [14—17]. ERAS management protocols include preoperative measures (patient information, sweetened oral liquids, no bowel preparation, avoidance of routine anxiolytic premedication, reduction of preoperative fasting period to 2 hours for liquids and 6 hours for solids), intraoperative measures (preference for laparoscopic approach, avoidance of bladder, gastric and abdominal drains, optimal fluid replacement based on suitable monitoring, avoidance of long-acting opioids, active measures to combat hypothermia, nausea and vomiting), and postoperative measures (immediate postoperative removal of the nasogastric tube, feeding on the evening of the intervention, a multimodal analgesic program, mobilization on the evening of surgery, removal of the bladder catheter on day 1 [D1], limitation of postoperative intravenous fluids, thromboprophylaxis, digestive stimulation by gum chewing, and carbohydrate loading [18,19]. The purpose of enhanced recovery programs is to reduce perioperative stress, in hope of facilitating the return of patient autonomy.

The mechanisms that reduce the interval to ROT are beginning to be understood, but much more remains to be determined. It is probably for this reason that no author has managed to propose a consensual cut-off interval for defining POI and that treatment and prevention of POI are only partially effective.

This review is intended to update knowledge with regard to POI, and to describe each measure used to combat POI as it derives from our pathophysiological understanding of the condition. Better understanding of POI provides insight into clinical studies in a context where there is no consensual definition.

Definition and risk factors

POI is a physiological arrest of gastrointestinal transit in response to surgical stress. In 2005, Kelhet et al. underscored the need for a consensual definition of POI, especially regarding what constitutes a normal time interval to ROT [20]. In 2016, several authors have noted the persistent lack of such a definition [17,21].

In the literature, various qualifiers have been applied to POI: ''pathological'' or ''prolonged'' (longer than the presumed normal duration), or ''secondary'' (linked to extrinsic causes such as postoperative peritonitis...).

In 2013, Vather et al., in their conclusions to a meta-analysis, proposed a clinical definition of POI [10] defined by the combination of at least two of the following five signs on or after the fourth postoperative day, with no improvement since surgery:
- nausea and vomiting;
- an inability to tolerate solid or semi-liquid diet during the preceding 24 hours;
- no gas or stool for the preceding 24 hours;
- abdominal distension;
- radiological evidence of ileus.

These data were confirmed in the works of van Bree et al. [22] who considered the best endpoint to define ROT to be the combination of passage of stool and tolerance of solid food.

However, there is still no real consensus for a ''normal'' interval that would distinguish between pathological POI and physiological POI. The cut-off limit used by various authors to describe pathological POI varies from 1 to 7 days (Table 1) and this variable limit leads to non-reproducibility of studies dealing with POI because their rates vary from one to threefold for different teams. For example, in the same patient population and depending on the cut-off interval selected, we found enormous variation in the rate of POI ranging from 2% for a cut-off of 7 days and 60% for a cut-off of 1 day [17].

A physiological study, published in 1990, concluded that gastric motility recovered within 24—48 hours, small intestinal motility within 12—24 hours, and colonic motility in 3—5 days [23]. Advances in management have probably reduced these physiological durations since several teams have reported a median ROT (using the endpoint of Van Bree et al. [22]) of 24—48 hours.

Risk factors

Several risk factors have been identified in the literature but the studies are not reproducible for the reasons cited above. In fact, the low reliability of the data does not allow this problem to be effectively addressed. Table 1 reports the various reported risk factors, and the definition of ''normal'' interval to ROT used for data analysis. Despite this lack of reproducibility, various authors have repeatedly identified several risk factors, such as male gender, advanced age or significant blood loss [4,5,7,9,10].

Similarly, ROT is affected by the surgical approach, i.e., decreased for laparoscopy compared to laparotomy [24,25]. However, ''hand-assisted'' laparoscopy and robotic surgery do not appear to provide similar benefit compared

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Table 1 Risk factors in relation to various definitions of POI.

Authors	Year	Type of surgery	Study design (# of patients)	Cut off time for POI (days); definition	Risk factors (OR or *P*-value)
Artinyan et al. [8]	2008	Abdominal surgery	Retrospective ($n=88$)	6 days Intolerance to feeding	Blood loss ($P=0.021$), opioid dosage ($P=0.031$)
Svatek et al. [6]	2010	Radical cystectomy	Retrospective ($n=283$)	6 days Absence of intestinal function Vomiting after a period of dietary tolerance	Advanced age (1.09), elevated BMI (1.09)
Kronberg et al. [86]	2011	Laparoscopic colectomy	Retrospective ($n=413$)	5 days Absence of intestinal function or need for NG tube for abdominal distention, nausea, or vomiting	Narcotic use (3.17), previous abdominal surgery (2.41)
Kim et al. [11]	2011	Urologic surgery by laparoscopy	Retrospective ($n=249$)	6 days Intolerance to solid feeding ± Abdominal distention ± Radiologic signs of ileus by abdominal plain X-ray	Dindo/Clavien score (5.3)
Millan et al. [9]	2012	Colorectal cancer surgery	Retrospective ($n=773$)	6 days Absence of flatus with or without intolerance to feeding	Male sex (1.6), COPD (1.9) Stoma creation (1.9)
Vather et al. [10]	2013	Colorectal surgery	Retrospective ($n=255$)	4 days POI definition of Vather et al. [10]	Advanced age (1.032), blood loss (1.943)
Chapuis et al. [4]	2013	Colon surgery	Retrospective ($n=2400$)	3 days Abdominal distention + Absence of bowel sounds + Nausea and vomiting + No passage of flatus or stool	Male sex (1.7) PAOD (1.8) Respiratory comorbidity (1.6), emergency surgery (2.2) Perioperative transfusion (1.6), stoma formation (1.4), operative time exceeding 3 hours (1.6)
Vather et al. [7]	2015	Colorectal surgery	Prospective ($n=327$)	4 days POI as defined by Vather et al. [10]	Male sex (3.1), low preoperative albumin level (1.11) Laparotomy approach (6.37) Increased size of incision Blood transfusion (1.84), volume of IV crystalloid infusion (1.55)
Moghadamyeghaneh et al. [5]	2015	Colon surgery	Retrospective ($n=27{,}560$)	7 days No return of intestinal function	Ileocolic anastomosis (1.25), intra-abdominal infection (2.56), anastomotic leak (1.25), preoperative sepsis (1.63), carcinomatosis (1.24), COPD (1.27)

POI: postoperative ileus; COPD: chronic obstructive pulmonary disease; PAOD: peripheral arterial occlusive disease; BMI: body mass index.

to standard laparoscopic surgery. In addition, the retroperitoneal approach also helps to reduce POI; for abdominal aortic surgery, the risk of POI is decreased fivefold (odds ratio = 0.17; $P<0.0001$) for the retroperitoneal approach compared to laparotomy [26].

Similarly, the risk of ileus depends on the type of surgery: the rate of POI for colorectal surgery is 10—30% [4—11] versus 8—13% after pancreatic and gastric surgery [27].

Other risk factors such as high-grade complications (on the Dindo-Clavien scale), intra-abdominal infection, or

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anastomotic fistula are often reported [5,11], but should probably be classified as secondary POI.

Because most of the studies are retrospective and do not specifically focus on the role of morphine, opioids have not been commonly reported as risk factors for POI. However, prospective or retrospective studies that specifically evaluate morphine have highlighted its role in aggravating the risk of POI (OR = 12.1) [28]; opioids have a dose-dependent inhibitory effect on intestinal motility [28—30]. In addition, morphine aggravates the consequences of POI and increases the duration of hospitalization [29].

Risk factors that have been more anecdotally identified include a history of prior laparotomy, the length of the abdominal incision [29—32], and emergency surgery (with associated major intestinal edema) [33].

Pathophysiology

While the lack of consensus regarding the normal duration of POI causes confusion and non-reproducibility of studies, progress in basic science could help to advance understanding of the pathophysiology of POI, thereby helping to prevent and cure this complication.

POI arises from autonomic nervous and hormonal mechanisms. Its origin is multifactorial since intestinal manipulation, administration of opioid or anxiolytic medications, and postoperative stress all seem to be involved in the initiation of POI.

However, most experimental studies on the mechanism of POI have dealt with murine models, which are only partially superimposable to man.

POI develops in three phases. The initial phase involves neurological processes (via the sympathetic nervous system), while a second phase involves hormonal and inflammatory mechanisms. Finally, a third phase involves parasympathetic nervous activation, which plays a major role in the resolution of ileus (anti-inflammatory role).

Neurological phase

The first phase of ileus involves sympathetic nervous system pathways. Anesthesia and the surgical incision induce the activation of presynaptic noradrenergic B receptors (AF I think these are called ''presynaptic beta-adrenoceptors'' they are beta even in French!), however, manipulation of the intestine does not appear to involve this pathway [34].

These fibers act on the enteric nervous system (ENS) and the sympathetic nerves. The connections between these two entities are not yet identified. Furthermore, within the ENS, glial cell dysfunction could lead to dysequilibrium of the intestinal mucosal barrier [35].

Stimulation of alpha-2 adrenergic receptors in the inflamed muscularis mucosae could play a role in aggravating ileus by increasing the synthesis of messenger RNA of the inducible nitric oxide synthetase (iNOS mRNA) with release of nitrogen monoxide (NO) [36]. An increase in NO causes activation of CycloOxygenase-2 (COX2). This has raised the question of whether NSAID drugs could be useful to improve ROT (but there is a corresponding possibility that they also impair wound healing, leading to an increased rate of anastomotic leaks) [37—41].

Inflammatory phase and intestinal manipulation

As the neurological phase fades, increased inflammation is noted in the walls of the intestine, involving monocytes, macrophages and mast cells that secrete pro-inflammatory molecules and autoregulate themselves.

Manipulation of the intestines induces an inflammatory response in the 3rd hour of a laparotomy intervention. This inflammation is not observed with the laparoscopic approach [42], which may explain some of the beneficial effect of this surgical approach in preventing POI. Manipulation activates dendritic cells that produce interleukin 12 (IL) [43]. IL adheres to T1 helper lymphocytes (T1H) that then migrate to non-manipulated sites and induce inflammation in these remote areas by secreting alpha interferon (IFN alpha), which, in turn, recruits macrophages. This is called the ''field effect'' [43]. This dissemination of inflammation could explain how a drain that creates localized inflammation in the pouch of Douglas may result in prolongation of POI in the entire digestive tract.

During this second phase, the permeability of the intestinal epithelial barrier is increased, resulting in bacterial translocation, which could also increase inflammation and POI [42].

Furthermore, variations in potassium concentration may play a role in POI by opening calcium channels [44]. These last two items explain the role of fluid and electrolyte over-replacement in the pathogenesis of POI and thus, the potential benefits of reducing crystalloid replacement to maintain optimal ''natural'' homeostasis.

Phase of resolution of ileus and vagal activation

Increased vagal tone reduces the inflammation induced by intestinal manipulation. This is mediated through nicotinic alpha 7 acetylcholine receptors (alpha7-nAChR) and 5-hydroxytryptamine 4 receptors (5-HT4R). Activation of 5-HT4R results in increased acetylcholine release by the myenteric cholinergic neurons. This allows activation of alpha7-nAChR on monocytes and macrophages and thereby reduces the inflammatory response [45].

This last so-called ''resolution'' phase is mediated by the vagal system, and could explain the positive effect of gum chewing or early mobilization (prehabilitation) that stimulate the vagal system and thereby reduce POI [46].

Treatments

With knowledge of the different risk factors and progressive understanding of the pathophysiology of POI, ERAS protocols have grouped together a variety of therapeutic measures, with the aim, among other goals, of preventing POI.

These measures target the different phases of ileus and upcoming subchapters connect each preventive measure to the pathophysiology.

Alvimopan

Alvimopan is an antagonist of the μ opioid receptor; its efficacy has been evaluated several times including in randomized studies. Alvimopan is not currently available in France. It acts essentially on phase 1 of ileus, opposing the

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muscle relaxant effects of opioids. Recent literature suggests that use of alvimopan shortens the interval to ROT [47]. The effectiveness is more marked when patients are receiving analgesic doses of morphine [48]. A 2012 meta-analysis confirmed that alvimopan is beneficial in decreasing POI but noted that the beneficial effect has not yet been confirmed for laparoscopic surgery [49].

Lidocaine

Intravenous infusion of lidocaine works on phase 1 of POI by reducing pain and therefore sympathetic stimulation. Some ERAS protocols have recently introduced intravenous lidocaine as a therapeutic measure. Its effect on improving ROT has recently been demonstrated (decrease in risk of POI with an OR = 0.38), but current ERAS protocols are not consensual and two recent meta-analyzes have pointed out the inadequate documentation of side effects and that there is no consensus for the protocols for lidocaine infusion [50,51].

Propranolol

Propranolol, a beta-blocker agent that acts on beta-adrenergic fibers, was evaluated in a randomized controlled trial that was unable to show any effect on intestinal myoelectric activity [52].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs act on phase 2 of ileus and are intended to reduce postoperative inflammation by their action on COX2 (as well as COX1 for non-specific NSAIDs). While NSAIDs have a promising theoretical mode of action on the pathophysiology of POI, some authors have decried their use after colorectal resection, particularly because they attribute an increased risk of postoperative anastomotic leak (AL) to them [37,38]. However, NSAIDs have a clear beneficial effect on ROT [39] while the increased risk of AL remains debated [41]. A recent review of the literature concluded that short (48 h) treatment with NSAIDs after colorectal surgery could be recommended [40].

Pro-kinetic agents: magnesium-gastrografin

Many prokinetic have been evaluated in literature.

Intravenous magnesium

Intravenous magnesium was studied in a randomized controlled trial that demonstrated a decrease in the interval to ROT without any side effects [53]. Magnesium sulfate was administered as a bolus of 40 mg/kg, followed by an infusion of 10 mg/kg during the operative period.

Metoclopramide

Metoclopramide has been little studied with regard to its effect on ROT. While an initial study showed no effect on gastrointestinal function [54], a more recent study showed more rapid ROT following gastrectomy and intraperitoneal chemotherapy [55].

Choline citrate

A single randomized controlled trial concerning choline citrate found no effect on ROT [56].

Mosapride citrate

Mosapride citrate may have a beneficial effect on the rate of ileus by increasing gastric and duodenal muscular contraction and reducing the interval to ROT. However, only one study with a small number of patients has investigated this effect [57].

Erythromycin

Two randomized controlled trials have studied oral erythromycin after colonic and gastric surgery and were unable to show any beneficial effect on ROT [58,59].

Gastrografin

Gastrografin has been studied in two recent randomized controlled trials and, although it did not significantly reduce the duration of POI [60,61], it may have reduced the duration of nasogastric suction [60]. Moreover, gastrografin has clinical benefits by shortening the interval to passage of flatus and stool and by reducing abdominal bloating [61].

In 2008, a Cochrane meta-analysis studied many prokinetic agents and could not identify any beneficial effect on ROT [62]. Magnesium was not evaluated in this meta-analysis. Alvimopan was evaluated but the authors concluded that despite the existence of several studies reporting a beneficial effect, there were too many methodological biases and that alvimopan must still be considered experimental.

Prevention

Epidural analgesia

Although highly recommended to improve pain control after laparotomy, the role of epidural analgesia in the era of laparoscopic surgery is debatable. Recent studies have not been able to show any benefit associated with the use of epidural analgesia after laparoscopic colorectal surgery [63,64]. These results, however, are open to debate since the definition of POI was variable for each author.

Surgical approach

The main mechanism of POI involves phase 2, particularly the inflammatory response to bowel manipulation. We have previously reported that laparoscopy did not induce inflammation related to intestinal manipulation. The clinical literature has also reported improvement in gastrointestinal motility related to the use of the laparoscopic approach, particularly for colorectal and gallbladder surgery [65,66]. A recent prospective randomized controlled study showed that a laparoscopic approach was associated with a 30% decrease in POI after colectomy for diverticulitis [66].

Nicotine gum and chewing gum

Mastication of chewing gum mimics dietary intake. Chewing stimulates vagal tone, which has an anti-inflammatory effect (phase 3 of ileus). Use of chewing gum has been discussed in the literature with regard to all surgical specialties.

The most significant studies report an improvement in the interval to ROT [67,68]. Its efficacy in pancreatic surgery has not been proven statistically although there was a decreasing interval to ROT [69]. While most studies agree

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that gum chewing improves gastrointestinal function, a consensual protocol has not been defined. In most studies, patients were instructed to chew gum 3—4 times daily for 5 to 45 minutes [68].

Nicotine chewing gum could have a favorable effect on ROT because of its anti-inflammatory effect (anti-TNF, fewer macrophages...) [70].

Finally, it seems that the beneficial effect is greater if gum chewing is started preoperatively. A recent randomized controlled study highlighted improved ROT in this group, along with a decrease in inflammation (reduction of IL 8 and TNF alpha) [71].

Early resumption of diet

Early feeding decreases the risk of infectious complications, protein wasting, and leaky intestinal mucosa [72]. It also reduces the need for IV hydration and potential electrolyte imbalance [72]. Reducing the volume of IV fluids reduces the incidence of POI [73].

Early resumption of diet significantly reduces the duration of ileus after major rectal surgery [74] and is feasible, even after emergency surgery [75].

Coffee

The mechanism of coffee's effect is not currently known. The first randomized controlled trial noted an improvement in gastrointestinal function when patients drank coffee without worsening of postoperative morbidity [76]. In a more recent study, decaffeinated coffee was shown to have the same efficacy [77].

Dai-Kenchu-To (DKT)

DKT is a Japanese herbal remedy that is widely used in traditional medicine. Its anti-inflammatory effect is mediated by the alpha-7nACh receptor (phase 3). Several studies have shown an improvement in the interval to ROT with the use of this herb [78,79].

Experimental agents

Parenteral administration of polyunsaturated fats may have a positive effect on ROT [80].

Enhanced recovery programs

The principles of enhanced recovery programs are now well known. It was reintroduced by Scandinavian teams, including the ERAS Society, which first published recommendations particularly for colorectal surgery [18,19], with the intent of decreasing perioperative stress. Enhanced recovery programs now include most of the above-mentioned measures in order to optimize perioperative management.

Enhanced recovery programs have successfully reduced the duration of hospital stay and recovery time after surgery, while reducing (or at least not increasing) perioperative morbidity [81,82]. Some enhanced recovery programs have also demonstrated improvement in the interval to ROT [17,83—85] and reduced the rate of POI [81]. Thus, compliance with at least 85% of the measures in an enhanced recovery program has been shown to reduce the risk of prolonged (> 4 days) POI (OR = 0.35) [17].

Regarding the resumption of global transit, a meta-analysis by Zhao et al. showed that enhanced recovery programs reduced the interval for passage of flatus by 0.4 days [81] and, in a second meta-analysis, that the laparoscopic approach was of major interest for ROT in enhanced recovery protocols since it decreased the interval to the first bowel movement by 1.1 days ($P < 0.001$) [82].

Most of the work on these programs has been made in the context of colorectal surgery but protocols are available for other surgical specialties on the web sites of the ERAS Society and GRACE Association [12,13]. The effect of enhanced recovery protocols on gastrointestinal recovery in other specialties has not yet been demonstrated.

Conclusion

POI is a complex phenomenon that occurs very commonly and impacts on several surgical specialties. Its mechanism is only partially understood, but several measures have already been proposed that have enabled a significant reduction in the duration and frequency of POI [86]. Most of these measures have been effectively incorporated into enhanced recovery programs.

One of the obstacles to improving the fight against POI is the lack of consensus on its definition, making the literature non comparable. While the majority of measures aim more at the prevention of POI than its treatment, it is logical to think that, just as with gum chewing, patient ''prehabilitation'' could improve the effectiveness of prevention.

Much progress has been made in the fight against POI, but much more remains to be done, especially in the introduction of the concept of ''prehabilitation'' in enhanced recovery protocols.

Disclosure of interest

The authors declare that they have no competing interest.

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