REVIEW ARTICLE

Postoperative Gastrointestinal Tract Dysfunction

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Postoperative gastrointestinal (GI) tract dysfunction (PGID) is common and is associated with increased patient suffering and cost of care. The pathogenesis of PGID is complex and multifactorial. Traditional measures intended to reduce the incidence of PGID, such as the use of prokinetic drugs, nasogastric tube drainage, and the avoidance of early fluid and/or food intake, are apparently not beneficial. The administration of larger volumes of IV fluids to achieve predetermined increases in cardiac output has been shown in randomized trials to improve gut perfusion and reduce the incidence of PGID. A multimodal approach that includes limited surgical incision, regional local anesthesia, early mobilization, and enteral feeding has been associated with a dramatic reduction in postoperative complications, PGID, and length of hospital stay. However, none of these approaches has been validated in adequately powered multicenter prospective randomized controlled trials.

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After surgery, postoperative gastrointestinal tract dysfunction (PGID) is common and is associated with increased patient suffering, morbidity, decreased survival, and increased length of hospital stay. The primary functions of the GI system are the digestion and absorption of nutrients and the elimination of waste material (Table 1). The average adult consumes approximately 800–1000 g of food and 1200–1500 mL of water per day. In a functioning system, approximately 50 g of undigested material and 100 mL of water are normally lost in the feces per day.

In general, postoperative complications can be defined by severity (e.g., major versus minor), time of starting (e.g., immediate or delayed), and duration (e.g., moments, days, or weeks). The GI tract has numerous functions (Table 1), but here I will focus on the absorption of adequate nutrients. Table 2 shows a schema for classifying postoperative GI tract complications. Of these, immediate, transient, postoperative nausea and vomiting is very common (up to 80%) and has been reviewed extensively elsewhere (1). For the purpose of this review, I will concentrate on persistent postoperative GI tract dysfunction (PGID)—i.e., dysfunction persisting beyond the first 72 h postsurgery—defined as intolerance of enteral nutrition (2). This covers a broad spectrum from, for example, persistent nausea and vomiting through ileus to multiorgan failure and death from dead bowel. Furthermore, I will concentrate more on discussing pathogenesis than therapeutic strategies, because there is little evidence from adequately powered, prospective, randomized controlled trials (PRCTs) to guide our patient management, and what little there is has been reviewed elsewhere (3–5).

Epidemiology

The term *ileus* is often restricted to, and thought to be, an inevitable consequence of bowel surgery. Much has been written about postoperative ileus in the context of major intraabdominal surgery. It is thought to occur as a result of a nonobstructive delay in coordinated movement of the GI tract, and it results in accumulation of gas and fluid in the GI tract, abdominal distension, pain, nausea, and vomiting. Ileus is relatively ill defined, and the diagnosis covers a spectrum of clinical signs, including abdominal distension, lack of bowel sounds, and delayed passage of feces and/or flatus. Ileus after intraabdominal surgery is common (>90% in many series) and is reviewed extensively elsewhere. Although many regard it as an inevitable consequence of intraabdominal surgery, Kehlet and Holte (5) have reported an incidence as infrequent as 5% for persistent PGID after the adoption of a multimodal approach to postoperative ileus. PGID is far more common than ileus and occurs to varying degrees across the entire range of surgeries.

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Table 1. Major Functions of the Anatomical Structures in the Gastrointestinal Tract

Component	Function
Mouth	Chewing, lubrication, salivary amylase
Pharynx and esophagus	Swallowing
Stomach	Storage and initial digestion
Small intestine	Digestion and absorption
Pancreas	Digestive enzymes, pH adjustment
Liver and gallbladder	Bile salts for emulsifying fats
Large intestine	Storage and concentration of undigested food
Rectum	Defecation

Table 2. Schema for Classification of Postoperative Gastrointestinal Tract Dysfunction

Classification	Definition
Onset	
Immediate	<6 h
Early	7–48 h
Delayed	2–7 d
Duration	
Transient	<72 h
Persistent	>72 h
Severity	
Minor	Tolerant of adequate enteral diet
Moderate	Intolerant of adequate enteral diet
Severe	Systemic manifestation/prolongation of hospital stay/life-threatening

Relatively few studies including patients with nonintraabdominal surgery have reported the incidence of persistent PGID. Bennett-Guerrero et al. (2) studied 443 patients undergoing major noncardiac surgery and found PGID (defined as intolerance of a full enteral diet) to be the most common postoperative morbid event associated with prolongation of hospital stay beyond 7 days (51% of patients). In the same study, it was reported that PGID was independent of the site of surgery. In another study by Bennett-Guerrero et al. (6), of 1056 patients undergoing major noncardiac surgery in a different hospital, persistent PGID was the most common problem associated with delayed discharge beyond 10 days (42% of patients).

Resource Implications

PGID has a substantial effect on resource utilization (2,7–10). Additional morbidity results in costly investigations and therapeutic interventions, often with associated prolongation of hospital stay. More serious morbidity will result in admission to and/or prolongation of stay in intensive care facilities, which limits other patients' access to these resources and is very costly. In one study of patients undergoing major surgery, it was calculated that the cost of care of the 14% of patients who developed serious morbidity associated with reduced gut perfusion was nearly 50% of the total cost of care of the study population (9).

Pathogenesis of PGID

Successful digestion and absorption of nutrients is dependent on coordinated motor and secretory activities. The GI tract is a single long muscular tube. Peristaltic and segmental movements cause food to move from the oral end to the anal end and facilitate the mixing of ingested nutrients with enzymes and digested fluids.

GI tract motor and secretory activities are controlled by a range of neural and hormonal systems. Many of the activities are controlled by local GI reflexes initiated by a number of luminal stimuli, such as distension, osmolarity, pH, and the concentrations of specific digestive products. These stimuli act on receptors in the wall of the GI tract to trigger reflexes that influence smooth muscles and endocrine and exocrine glands. Neural control can be excitatory or inhibitory, local or central, and parasympathetic (predominantly excitatory) or sympathetic (mainly inhibitory). Similarly, hormonal control of both motor and secretory activities can be either excitatory or inhibitory. Hormones can act locally or can exert their effects remotely via the bloodstream.

The pathogenesis of PGID is multifactorial. Mechanisms can be either direct or indirect and local or systemic. Disruption of the neural reflexes that determine coordinated bowel motility and/or inflammation of the intestinal muscularis are thought to be central to the pathogenesis of manipulation-induced ileus. However, it is clear from the brief review of normal anatomy and physiology above that the possible causes of non-manipulation-induced PGID are far more extensive.

Manipulation-Induced PGID Injury

It is intuitive that GI tract dysfunction after intraabdominal surgery may occur as a direct result of bowel manipulation. In animal models, it has been shown that bowel manipulation induces a local inflammatory reaction (11) that results in postoperative ileus. Bowel manipulation may result in a loss of mucosal integrity, allowing the translocation of gut luminal contents that can act synergistically, either locally or systemically, to compound any inflammatory reaction (12). Bowel manipulation also influences neuronal and neurohumoral signaling via local and central pathways, resulting in abnormal gut motility (13–15).

It seems that almost every conceivable pathway—signal, mediator, and transmitter—has been implicated as a cause of GI tract injury in animal models,

yet corroborative evidence in humans is lacking. Evidence in humans mainly comes from the relative reduction in PGID if handling of the bowel is reduced or avoided (16). It is important to note that in animal models in which the relative effects of the various stages of bowel surgery have been examined (e.g., anesthesia, skin incision, and bowel manipulation) or when open surgery has been compared with laparoscopic surgery in both humans and animals, bowel manipulation compounds inevitable gut dysmotility and/or inflammation but is not the sole cause of them (16–18).

Surgery-Induced PGID

It is now clear from both animal and human studies that virtually any proinflammatory stimulus (trauma, hypoxia, ischemia-reperfusion, infection, and so on) can produce gut injury and/or dysmotility (10). Most of this evidence comes from literature that seeks a relationship between gut mucosal injury and postoperative organ dysfunction. The dominant theory is that gut injury results in gut barrier disruption, leakage of gut luminal contents into the body, and subsequent activation of multiple inflammatory pathways (7). There are numerous human studies that support this general hypothesis, but the exact mechanisms remain uncertain. Most, but not all, human evidence comes from observations that the development of a relative gut luminal hypercarbia over the course of surgery, measured with a gastric tonometer, is a sensitive predictor of poor outcome (2,10,19,20). The poor outcome is often associated with PGID, and this is well described in surgeries that do not involve gut manipulation (e.g., cardiac surgery) (19).

Anesthesia- and Analgesia-Induced PGID

All anesthetic and analgesic drugs have the potential to contribute to PGID. Although, for example, nitrous oxide accumulates in body cavities and thus contributes to bowel distension, opioid analgesics are the prime suspects (3). Opioids have direct and indirect effects on bowel function, causing decreased motility and constipation. Most balanced anesthetic techniques rely on opioids for pain relief. Opioids remain the mainstay of systemic postoperative analgesia for moderate to severe pain and are often added to epidural infusions of local anesthetics (21,22). It should be noted that pain may also contribute to PGID, either directly, through noxious stimuli affecting gut perfusion (23), or indirectly, by gut pain contributing to delayed mobilization, delayed eating, or difficulty breathing (23–25).

The effects of opioids on the GI tract are multifactorial. The receptor primarily responsible for both analgesia and the GI effects of opioids is the μ receptor (26). Opioids have a central effect, causing nausea and vomiting (27). There are some central and spinal effects on gut tone, but these dystonic effects are now thought to be primarily via gut opioid receptors (26,28–30). When opioid receptors in the presynaptic nerve terminals of the myenteric plexus are activated, they send signals that result in increased resting tone and decreased propulsive peristaltic waves. As a result of the delayed transit time, water absorption may be increased from the gut lumen, resulting in drier and harder lower bowel contents. Numerous other drugs have potential for compounding GI tract dysfunction, either directly or indirectly (e.g., clonidine or adrenergic agonists) (31,32).

Neurogenic PGID

Modified neural reflexes are thought to be central to the pathogenesis of PGID. There are both afferent links to the spinal cord and efferent innervation from the sympathetic nervous system. For example, one theory suggests that gut stimulation (e.g., handling) results in the release of corticotrophin-releasing factor in the paraventricular nucleus of the hypothalamus and the dorsal vagal complex (15). This is then thought to activate efferent adrenergic and nonadrenergic noncholinergic inhibitory motor neurons via both vagal and splanchnic routes. Another theory suggests that mucosal injury secondary to hypoxia or hypoperfusion, for example, results in the local release of 5-hydroxytryptamine-3 and caudal transmission and activation of the central vomiting center via vagal efferents (33). In a model of cisplatin-induced gut mucosal injury, it was demonstrated that radiolabeled 5-hydroxytryptamine-3 released in the injured gut mucosa moved caudally to appear in the vomiting center (34). Other locally released nonadrenergic noncholinergic inhibitory neurotransmitters that are thought to play a role include nitric oxide, vasoactive intestinal peptide, substance P, calcitonin gene-related peptide, and prostanoids (35).

Inflammation-Induced PGID

The gut is a hotbed of inflammatory mediators (36–38). This is most likely the result of its unique interface with the external world, and in particular with the luminal contents of the GI tract. The GI tract has the complex task of digesting and absorbing nutrients while defending against invading organisms or other toxic luminal chemicals and disposing waste. The concentration of innate immune defenses in and around the GI tract makes good sense. The gut mucosa, and, in particular, the microvillus tips, is exquisitely sensitive to injury that will trigger a brisk local, then systemic, inflammatory response (36,39). Similarly, the muscularis externa is packed with leukocytes and, in particular, resident macrophages (35,40). These macrophages are the foot soldiers of the defending army

and, once triggered by any proinflammatory stimulus (e.g., bowel manipulation, hypoxia, or endotoxin), will release, or cause to be released, an array of substances such as cytokines, prostanoids, defensins, nitric oxide, and reactive oxygen intermediates (11–13,35,41–51). Multiple inflammatory and antiinflammatory pathways are triggered, the endothelium is activated to adhesion molecules, and other cells, particularly mast cells, are recruited via chemical signaling. Numerous local inflammatory pathways have been shown to play an important mechanistic role in animal models of ileus (35). Similarly, the sepsis literature demonstrates that any systemic inflammatory stimulus (e.g., hemorrhage, trauma, burns, or infection) results in GI tract dysfunction and loss of gut barrier function (36–39,52). As noted above, surgery is a major proinflammatory stimulus associated with activation of multiple pathways (9,10,53,54). In both animal models and human studies, endotoxin has repeatedly been demonstrated to cause both gut motor dysfunction and loss of mucosal integrity (39,46). Endotoxemia is extremely common during major surgery, and low levels of antibodies to endotoxin are associated with poor outcome, including a frequent incidence of PGID (6,55).

Hypoperfusion-Induced PGID

Reduced perfusion to the GI tract during major surgery has repeatedly been described in both animal and human models. There is a strong association between relative gut luminal hypercarbia, suggesting gut hypoperfusion, and postoperative organ dysfunction, including PGID (2,19,56). The GI tract is particularly sensitive to a reduction in circulating blood volume. Hamilton-Davies et al. (57) showed that healthy subjects could tolerate a 25%–30% hemorrhage without changes in commonly measured hemodynamic variables such as heart rate and arterial blood pressure, yet gastric perfusion, as judged by tonometry, was compromised after a 10%–15% hemorrhage. It has been demonstrated in PRCTs that the preemptive administration of larger volumes of fluid improves gut perfusion and outcome (8,58).

Systemic Hypoxemia and Hypercarbia

There is no clear link between hypoxemia and persistent PGID in humans. In one animal model, if blood volume and splanchnic blood flow were maintained, the gut mucosa did not become acidotic in response to hypoxemic hypoxia (59,60). In another animal model, hypoxemic hypoxia induced gut mucosal acidosis despite the maintenance of mucosal blood flow, and the gut became leaky (76). Whether higher supplementary oxygen therapy affects immediate postoperative nausea and vomiting remains controversial, with reasonably powered PRCTs giving conflicting results (61–64). It has been demonstrated in animal models that respiratory acidosis impairs gastropyloric motility (65). The relationship between systemic hypercarbia and persistent PGID is unknown.

Acid-Base, Glucose, and Electrolyte Imbalance

Any disturbance of acid-base, glucose, or electrolyte balance has the potential to cause PGID. Hypokalemia, hyponatremia, and hypomagnesemia are often implicated in the surgical literature on ileus. It is clear from the diabetic literature that relatively mild hyperglycemia delays gastric emptying, and the reverse is true of hypoglycemia (66,67). In animal models, both metabolic and respiratory acidosis have been shown to delay gastric emptying (65). In human studies, the relationship between PGID and iatrogenic hyperchloremic acidosis caused by the infusion of 0.9% sodium chloride-based solutions remains uncertain (68,69).

Temperature

Both hypothermia and hyperthermia are associated with reduced perfusion of the GI tract (70–72). Similarly, rapid changes in temperature can result in redistribution of blood flow away from the GI tract (71,72). The exact relevance of temperature changes to PGID remains unclear. However, it is clear that cardiopulmonary bypass is often associated with acute temperature changes, gut hypoperfusion, and PGID (19,20,70,73,74). The influence of the temperature changes *per se* relative to the other effects of cardiopulmonary bypass remains controversial (70,74).

Fluid Balance

Positive postoperative fluid balance can result in clinically significant interstitial edema. Gut edema is a likely contribution to PGID (75,76), but much of the evidence supporting this in humans is circumstantial. Lobo et al. (77) demonstrated a significant reduction in the duration of PGID with restrictive postoperative fluid management (water and sodium intake) in a randomized trial of 20 patients undergoing elective colonic surgery. In a larger randomized study of 102 patients undergoing major surgery, Cook et al. (78) found that regulating postoperative water intake had no effect on postoperative ileus. Woods and Kelley (79), in a study of 69 patients undergoing vascular surgery, found that randomizing patients to receive postoperative albumin supplementation increased their oncotic pressure but had no effect on bowel dysfunction. Moretti et al. (76) randomized 90 patients undergoing major noncardiac surgery to receive 1 of 2 colloids ($n = 60$) or crystalloid ($n = 30$) for intraoperative fluid replacement. They found that patients treated with colloids received smaller volumes of fluids to achieve similar cardiovascular goals. They also

found significantly fewer edema-related complications, in particular PGID, in patients treated with colloids. It is important to note that dehydration and/or hypovolemia may be associated with PGID and that increased perioperative fluid administration has been associated with improved indices of gut perfusion and reduced PGID (8,58).

Early Ingestion of Fluids and/or Food

There is no clear evidence to suggest that early ingestion of fluids and/or food increases the incidence of PGID (80–83). There is also no evidence that the routine drainage of gastric contents reduces the incidence of PGID (84).

Treating and/or Avoiding PGID

Possible treatments and management of PGID have been recently and extensively reviewed elsewhere (3–5). Therefore, for the purpose of this review, I will provide only a brief overview of most of the proposed interventions and refer readers to the other texts for more detailed discussions and citations (4,5,35,85).

Reduced Manipulation of the Bowel

It is generally accepted that less and more careful manipulation of the GI tract is associated with less PGID. Most of the evidence for this comes from studies that have compared laparoscopic versus open surgery (17). However, it is difficult to determine whether the GI benefits of laparoscopic surgery result directly from reduced bowel handling. Avoiding open surgery modifies many of the factors that are thought to contribute to PGID, including the magnitude of tissue trauma, painful stimuli, the need for opioid analgesics, and more substantial fluid shifts. Furthermore, laparoscopic surgery with a carbon dioxide insufflation pneumoperitoneum may cause PGID in its own right, either as a result of reduced splanchnic blood flow or as a direct result of local hypercarbia. Thus, laparoscopic surgery is associated with less PGID, but it is by no means a panacea.

Nasogastric Tube Decompression

Placement of a nasogastric (NG) tube as a preventative measure to avoid or reduce the incidence of PGID is not routinely indicated. Routine rather than selective placement of NG tubes is associated with an overall increase in morbidity (84). Although patients undergoing abdominal surgery who are treated without an NG tube may have an increased incidence of early abdominal bloating and vomiting, one meta-analysis concluded that for every patient receiving an elective NG tube, 20 patients would not have required one (84).

Anesthesia and Analgesia

Overall, it seems that the use of effective local and/or regional anesthetic techniques with the avoidance of general anesthesia (particularly opioid analgesia) is associated with a reduced incidence of PGID. Numerous studies demonstrate a reduced duration of ileus with epidural local anesthesia and analgesia compared with systemic opioid analgesia (3,5). It has also been demonstrated that ileus during intraabdominal surgery is shorter if epidural local anesthetics are used for analgesia without the addition of epidural opioids (3,5).

The use of a balanced analgesic technique combining epidural analgesia with local anesthetics and a non-opioid analgesic such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) should reduce the incidence of PGID, but evidence from large clinical trials is lacking. The wider use of newer NSAIDs, particularly cyclooxygenase-2 inhibitors, may allow a reduction in the use of postoperative opioid analgesia and may have a direct effect on the incidence of PGID (86,87). The risk/benefit ratio for NSAIDs in terms of clinically significant GI tract morbidity is yet to be fully elucidated (3,87).

Because most of the deleterious affects of opioids on the GI tract are thought to be mediated peripherally via gut μ-opioid receptors, research has focused on developing selective peripheral opioid receptor antagonists (88). Early clinical trials of selective opioid antagonists have demonstrated earlier resolution of ileus after intraabdominal surgery without effects on the quality of postoperative analgesia (88).

Pharmacological Strategies Aimed at Improving Gut Motility

Numerous pharmacological strategies have been used in the treatment of PGID (Table 3) (3). The use of drugs to stimulate the bowel in the postoperative period has been disappointing (3). A review of the probable pathogeneses of PGID is consistent with the results of clinical trials. Most of the therapeutic strategies have focused on modifying the neurogenic reduction in gut motility, which is usually a secondary manifestation of the underlying cause. It is interesting that the more global approaches used to avoid tissue hypoperfusion are sometimes associated with the administration of adrenergic agonists, which may have the combined affect of improving splanchnic blood flow and being antiinflammatory (89). It can be clearly demonstrated in humans undergoing major surgery that different adrenergic agonists and phosphodiesterase inhibitors have varying and often unpredictable effects on splanchnic blood flow (90–92). The relationship

Table 3. Pharmacologic Strategies in the Treatment of Postoperative Ileus from Randomized Controlled Trials

Agent	Mechanism of action	Effect on duration of postoperative ileus
Propranalol	β-Receptor antagonist	Decreased or none[a]
Dihydroergotamine	α-Receptor antagonist	Decreased or none[a]
Neostigmine	Acetylcholinesterase inhibitor	Decreased or none[a]
Erythromycin	Motilin agonist	None
Cisapride	Acetylcholine agonist Serotonin receptor agonist	Decreased or none[a]
Metoclopramide	Cholinergic stimulant Peripheral dopamine antagonist	None
Cholecystokinin	Prokinetic peptide	None
Ceruletide	Cholecystokinin	Decreased
Vasopressin	Stimulation of defecation	None

Adapted from Holte and Kehlet (3).
[a] Some randomized studies show a decreased duration and some no effect (see Ref. 3 for details).

between these findings and PGID has not been elucidated. The bottom line is that no single drug is the magic bullet for treating or avoiding PGID.

Early Enteral Nutrition

Most, but not all, studies of early enteral nutrition suggest that it is associated with a more rapid return of GI tract function, regardless of the site of surgery. Early nutrition is also associated with improved outcome in terms of reduced morbidity and length of hospital stay (4,5,80–82,93). The eclectic mix of the trials in terms of types of surgery and perioperative management techniques makes it difficult to say that early enteral feeding is always a good thing, but it is reasonable to suggest that there is no justification for avoiding early attempts at enteral nutrition.

Administration of Additional Fluids With or Without Vasoactive Drugs to Achieve Predetermined Increases in Oxygen Delivery

At least 15 PRCTs of patients undergoing major surgery have explored the effects of treating patients to reach predetermined targets of cardiac output and/or oxygen delivery (94,95). Most conclude that overall outcome can be improved with such a therapeutic regimen. Some studies have focused specifically on the effects of the administration of larger volumes of fluid on GI perfusion and/or the rate of PGID (8,58). It seems that patients who receive larger volumes of fluid in an attempt to maximize intravascular volume and cardiac performance have improved GI tract perfusion and reduced PGID. The exact mechanism leading to any benefits is difficult to determine from these studies, because numerous factors in the pathogenesis of PGID may be affected. Increased fluid administration may improve end-organ perfusion. Furthermore, the fluids used for plasma volume expansion may be antiinflammatory in their own right. For example, hydroxyethyl starch may modify ischemia/reperfusion injury and reduce the rolling and sticking of white cells to vascular endothelium (96).

Multimodal Approaches for the Prevention of Postoperative Ileus

Kehlet and Holte (5) report remarkable results from an evidence-based multimodal approach to improving postoperative GI tract function. The regimen includes a plan for discharge from the hospital at 48 h after surgery, optimal pain relief with regional local (thoracic epidural) anesthesia, limited surgical incision, early postoperative enteral nutrition, and early postoperative mobilization. In a nonrandomized study of 60 consecutive patients with a median age of 74 yr undergoing colonic resection, such an approach was associated with a median length of postoperative stay of 2 days, with 32 patients discharged on Day 2. The overall complication rate—particularly the cardiorespiratory complication rate—was very small; the readmission rate was 15%, with two anastomotic disruptions (5,97). It is highly likely that this approach, which combines many of the successful techniques that have been tested individually in PRCTs, does indeed work. However, such a multimodal approach has not been validated in an independent PRCT. The ethics of conducting such a trial make for interesting debate.

Conclusions

PGID is common and is associated with increased patient suffering and cost of care. The pathogenesis of PGID is complex and multifactorial. Numerous therapeutic interventions are logical and appear beneficial in small randomized and nonrandomized human studies. The administration of prokinetic drugs, the use of NG tubes, and the avoidance of early fluid and/or food intake are not beneficial. The administration of larger volumes of IV fluids to achieve predetermined increases in cardiac output has been shown

in human PRCTs to improve gut perfusion and reduce the incidence of PGID. A multimodal approach that includes limited surgical incision, regional local anesthesia, early mobilization, and early enteral feeding has been associated with a dramatic reduction in postoperative complications, PGID, and length of hospital stay. None of these approaches has been validated in adequately powered multicenter PRCTs.

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