Pathophysiologic, translational and clinical aspects of postoperative ileus – A review

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Summary

1. Postoperative ileus (POI) is an abnormal pattern of gastrointestinal motility characterized by nausea, vomiting, abdominal distension and/or delayed passage of flatus or stool which may occur following surgery. POI slows patient recovery, increases the risk of developing postoperative complications, and confers a significant financial load on healthcare institutions.

2. The aim of this review is to provide a succinct overview of the clinical features and pathophysiologic mechanisms of POI, with final comment on selected directions for future research.

3. Terminology used when describing POI is inconsistent, with little differentiation made between the obligatory period of gut dysfunction seen after surgery ('normal POI') and the more clinically and pathologically significant entity of a 'prolonged POI'. This has impaired ability to determine incidence and risk factors of ileus, and has compromised the external validity of clinical trials investigating it. Both normal and prolonged POI represent a fundamentally similar pathophysiologic phenomenon.

4. The aetiology of POI is postulated to be multifactorial with principal mediators being inflammatory cell activation, autonomic dysfunction (both primarily and as part of the surgical stress response), agonism at gut opioid-receptors, modulation of gastrointestinal hormone activity, and electrolyte derangements. A final common pathway for these effectors is impaired contractility and motility, and gut wall oedema.

5. There are many potential directions for future research. In particular, there remains scope to accurately characterize the gastrointestinal dysfunction that underscores an ileus; development of an accurate risk stratification tool will facilitate early implementation of preventive measures; and clinical appraisal of novel therapeutic strategies that target individual pathways in the pathogenesis of ileus warrant further investigation.

Introduction

Postoperative ileus (POI) is an abnormal pattern of gastrointestinal motility distinct from mechanical obstruction that frequently occurs after abdominal surgery. The primary features of POI include nausea and vomiting, inability to tolerate an oral diet, abdominal distension, and delayed passage of flatus and stool. POI may also follow procedures that do not involve breach of the peritoneum, most notably spinal operations.[1]

The occurrence of an ileus has consequences for both patient and hospital. POI has been shown to slow patient recovery, thereby prolonging length of hospital stay,[2] and is associated with an increased rate of complications (especially those infectious or thrombotic in nature) although the retrospective nature of previous studies have made it difficult to establish direction of causality.[3-7] Prolonged hospital stay may have a negative psychological impact on the patient and create a barrier to postoperative recovery.[8] POI also imparts a substantial financial and resource-intensive burden on healthcare institutions, with one study estimating that the cost of its management in the USA alone approaches $US1.5 billion annually.[2]

It has been shown that following major abdominal surgery motility typically returns first in the small bowel (<24 hours), then in the stomach (24-48 hours), and finally in the large bowel (>48 hours).[9] However, recovery of large bowel function occurs much less predictably than in other parts of the gut, and the passage of flatus and stool have therefore traditionally been used as endpoints indicating complete clinical resolution of postoperative gastrointestinal dysfunction.[10] In healthy human controls, colonic transit and defaecation are associated with propagating circular muscle contractions, commonly referred to as propagating sequences or propagating contractions.[11-13] Marked increases in propagating sequence activity have been shown to occur in response to consumption of calorie-rich meals, morning waking and electrical stimulation, suggesting that they are neurogenically mediated.[14,15] It is postulated that an ileus represents an absence or attenuation of neurogenic motor activity, although this has yet to be proven.

It is now well accepted that the pathogenesis of POI is multifactorial with dysmotility being caused by disturbances in immunologic, inflammatory, neurologic, electrolyte and receptor-mediated functioning. Studies investigating such pathways at a physiologic level have tended to focus on individual segments of the gastrointestinal tract. However, it is of importance to appreciate that ileus can be observed in all parts of the digestive tract, from stomach to the colon. Although small and large bowel dysmotility feature prominently, they should not be considered as independent entities but rather an analogous endpoint of the gastrointestinal response to surgery.

The aim of this review is to provide an overview of the clinical features, pathophysiologic mechanisms, and therapeutic implications of postoperative ileus, with a final comment on selected directions for future research.

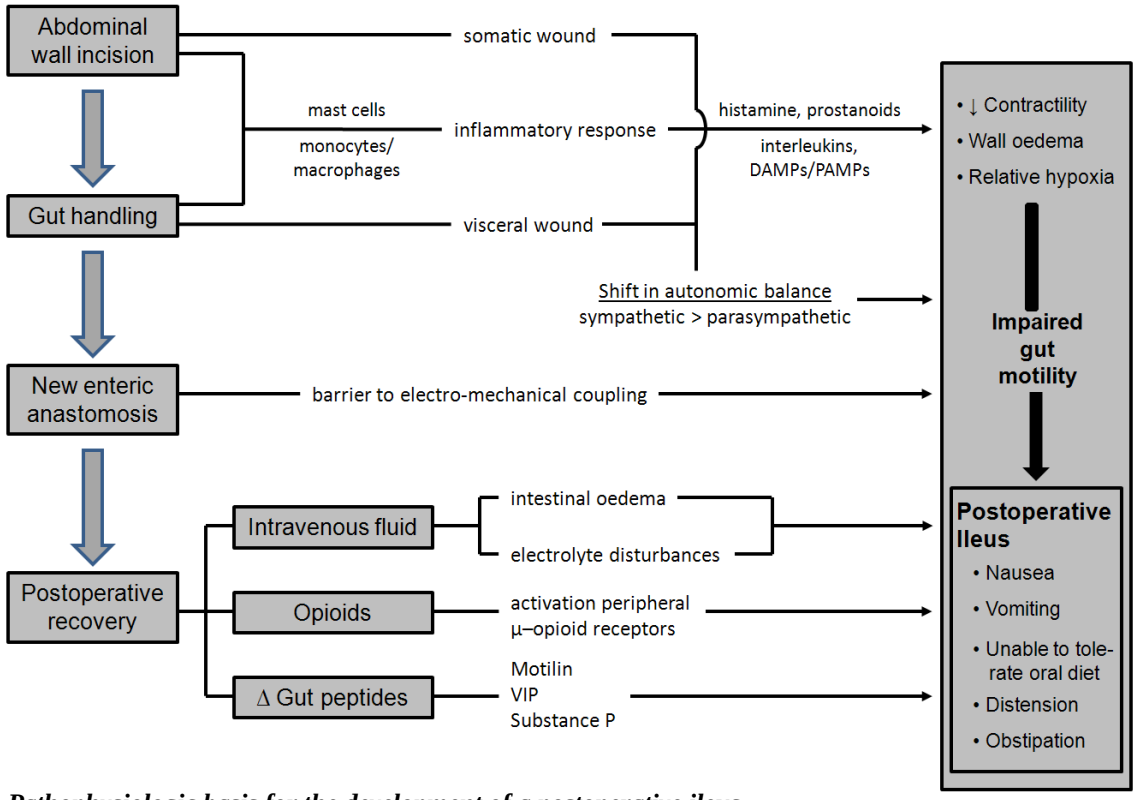

Figure 1. Pathophysiologic basis for the development of a postoperative ileus.

Definition and clinical features

Despite the increasing number of clinical trials investigating potential therapeutic interventions for POI over the last two decades, an internationally accepted, standardized clinical definition is still lacking. This has made it difficult to reliably determine incidence (often quoted as lying between 3-32% after abdominal surgery)[3] and identify risk factors. Furthermore, as the outcome measures are not standardized in these trials comparison of the relative efficacy of competing interventions is difficult.

The terminology used when describing POI is also inconsistent and it is therefore important to clarify that the condition falls into two distinct classifications. These have recently been defined, based on a systematic review and global survey:[10]

i. *POI* is defined as the obligatory period of gut dysfunction occurring immediately after surgery with resolution being signalled by passage of flatus or stool and tolerance of an oral diet.

ii. *Prolonged POI* is defined as two or more of a) nausea/vomiting b) inability to tolerate an oral diet over the preceding 24h period c) absence of flatus over the preceding 24h period d) abdominal distension or e) radiologic evidence of bowel distension without mechanical obstruction – occurring on or after Day 4 postoperatively without prior resolution of POI.

It is apparent from these definitions that an ileus may be characterized by dysfunction affecting stomach, small bowel or large bowel, either individually or in combination. However, it is important to note that while these definitions are designed to facilitate standardization of endpoint reporting, they provide little indication as to the underlying physiology. Although prolonged POI is the more clinically important entity, from a pathophysiologic standpoint it is fundamentally a similar process to a 'normal' POI, representing the more severe end in the spectrum of duration.

Pathophysiologic basis of and risk factors for postoperative ileus

Gastrointestinal dysfunction following abdominal surgery has been recognised for over a century.[16] However, it is only over the last two decades that we have begun to understand some of the mechanisms that underpin it. There is now a general agreement that the aetiology of POI is multifactorial with inflammatory cell activation, autonomic dysfunction (both primarily and as part of the surgical stress response), agonism at gut opioid-receptors by exogenous narcotics, modulation of gastrointestinal hormone activity, and electrolyte derangements all being implicated. A final common pathway for these effectors is impaired contractility and motility, and gut wall oedema (Figure 1).

Inflammatory response

It has been postulated that an early event in the pathogenesis of POI is the release of pro-inflammatory mediators, initially due to peritoneal breach and later due to bowel handling.[17,18] Although the composition of the inflammatory environment is relatively well known (histamine, prostanoids, interleukin-6 and interleukin-8 feature prominently) the cell types triggering the inflammatory response are less well-defined.[19] Mast cells have been found in peritoneum and the *muscularis propria* of the intestinal wall, and there is a growing body of evidence supporting the role these cells play in the genesis of the inflammatory cascade.[20,21] Indeed, a murine model of POI revealed that animals pre-treated with mast cell stabilisers experienced reduced manipulation-induced inflammation and improved gastric emptying; mast-cell deficient animals likewise exhibited a diminished inflammatory response to surgery.[20] Preliminary work in humans has correlated laparoscopic surgery to reduced mast cell activation, and has attributed this finding to a reduced degree of intestinal handling.[18] Circulating monocytes and resident macrophages have also been implicated in the inflammatory response,[22,23] and activation of these cells within the bowel wall is believed to be in part caused by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).[24] The former are macromolecules released in response to mechanical or chemical cellular injury (for example, physical manipulation of the gut); the latter can be found on commensal intestinal flora and are postulated to translocate through the gut wall as a consequence of the increased permeability associated with inflammation.[24]

The mechanisms by which bowel wall inflammation may causes dysmotility are three-fold. Firstly, several molecules involved in the inflammatory cascade are potent smooth muscle relaxants (especially the COX-2 dependent prostaglandin E2 and nitric oxide), and therefore have a direct effect on contractility.[19,24,25] Secondly, bowel wall oedema is believed to add to the existing dysmotility by mechanically impairing the efficacy of myotonic contraction.[24,26] Oedema is thought to be primarily mediated by the local inflammatory response, although it has been shown that overzealous peri-operative fluid administration may also contribute.[27] Finally, there is preliminary evidence to suggest that relative intestinal ischaemia may play a role in an ileus and this occurs either as a by-product of the inflammatory state or *via* direct reduction in arterial blood flow. A murine study found that a reduction in oxidative stress (effected by CO-releasing molecules) was associated with reduced development of POI.[28] The role of relative intestinal ischaemia in POI is also supported by clinical studies from two separate groups, who have found a potential benefit for hyperbaric oxygen therapy in POI.[29-31]

Neural derangement

Disturbances in neural activity play an integral role in the pathophysiological gut response to surgery, and extend to the somatic, autonomic and enteric nervous systems.[24] Changes in neural function are also thought to be closely coupled to the immunologic/inflammatory response outlined above, and these factors have collectively been termed the "surgical stress response".[32] Neural derangements impact upon both afferent and efferent pathways.

Afferent pathways

Two types of wounds are caused by surgery – a) 'somatic wound' created by incision at the abdominal wall; and b) 'visceral wound' created by incision of peritoneum and handling of viscera,[33] further detailed as follows:

a. *Somatic wound* – the abdominal wall receives sensory innervation from the anterior and lateral branches of the ventral rami of the lower intercostal and upper lumbar nerves.[34] Nociceptive stimuli associated with the creation of a somatic wound are carried *via* sensory neurons (with cell bodies in dorsal root ganglia) to synapse in the posterior column of the spinal cord.[24] Release of the excitatory neurotransmitter glutamate at this site activates spinothalamic projections that invoke the perception and localization of pain, and incites a local autonomic response mediated by sympathetic efferents with cell bodies in the lateral horn.[33,35]

b. *Visceral wound* – the peritoneum is a metabolically active tissue lining the abdomen and enveloping intestinal viscera. Injury to peritoneum leads to the activation of inflammatory and immunologic cascades as described above.[36] By contrast, contained within intestinal viscera are a dense interconnected network of enteric neurones that derive information from a variety of mechanoreceptors and chemoreceptors. "Silent nociceptors" which are located within the extrinsic sensory innervation of the gastrointestinal tract and remain quiescent in the absence of intestinal injury or inflammation may also be activated with gut handling.[37] Sensory information from viscera and peritoneum are conveyed primarily by the vagus nerve, which has been shown histologically at the sub-diaphragmatic level to be over 80% afferent.[38] In addition to receiving input from nociceptors, paraganglia cells within the parasympathetic ganglia of the vagus nerve express interleukin-1 receptors, thus making the nerve sensitive to the early humoral changes associated with inflammation.[39,40] Vagal afferents travel to the *nucleus tractus solitarius* (NTS) of the brain stem, which is considered a major 'relay centre' of the neuro-immuno-humoral response to injury.[39] The importance of the vagus nerve in transmitting visceral afferents has been demonstrated in animal models which have shown blunting of a supraspinal response to intra-abdominal manipulation following vagotomy, but not after sectioning of the spinal cord.[40-42]

Efferent pathways

Neurogenically-mediated gastrointestinal dysmotility following surgery is brought about by an autonomic shift favouring sympathetic over parasympathetic outflow. This is postulated to occur initially as part of a local reflex response and may be perpetuated by activation of supraspinal centres. Specifically, both the hypothalamus and NTS have been implicated in central inhibition of gut motility, with activation occurring *via* neural afferents and circulating inflammatory metabolites.[43-45]

Parasympathetic efferents originate in neural circuits connecting the NTS to the vagal motor nucleus and *nucleus ambiguous* within the brainstem.[39] Outflow to the gastrointestinal tract travels *via* the vagus nerve and pelvic splanchnic nerves, which meet at the splenic flexure.[34] Postganglionic neurons release acetylcholine which, *via* agonism at M_2 and M_3 muscarinic receptors, serve to increase smooth muscle excitability and contractility.[39,46]

Thoracolumbar sympathetic efferents originate from the lateral horn of the spinal cord.[47] Their activation occurs as part of a reflex adrenergic response to nociception as well as supraspinal excitation.[48-50] Release of catecholamines within the gut leads to activation of α-2 adrenoceptors which act on presynaptic parasympathetic cholinergic nerves to inhibit release of acetylcholine and directly on myocytes to stimulate production of nitric oxide. These pathways serve to reduce myocyte tonicity and contractility.[51-54] Additionally, evidence has emerged for a non-adrenergic noncholinergic vagally-mediated pathway that impairs motility *via* local release of nitric oxide and vasoactive intestinal peptide.[55,56]

It is important to note the significant visceral sensory and motor contribution of the vagus nerve in this context, and to appreciate that it is a direct extension of the central nervous system with its passage to the abdomen occurring sequentially through neck, thorax and diaphragm. Therefore, while epidural blockade may attenuate the initial somatically-mediated gastrointestinal response to nociceptive stimuli, the blockade does little to obliterate the more prolonged vagally-mediated inhibition associated with visceral handling.[24] High epidural local anaesthetic blockade nevertheless still accelerates gastrointestinal recovery after surgery by interrupting contributing spinal afferent and efferent signals.[57-60]

Disruption of intestinal continuity

A consideration specific to procedures involving resection of viscera is the impact of anastomoses on enteric neural continuity. Work in animal models has shown that tissue healing and longitudinal nerve trunk regeneration occur at sites of bowel wall anastomosis,[61] but there is limited literature investigating electrical or pressure wave propagation across these joins in the immediate postoperative period. It is feasible that the disruption of neural continuity caused by visceral resection directly impairs downstream intestinal motility by creating a physical barrier to electro-mechanical coupling. Indeed, this theory has been examined in a murine model of small bowel resection, which described acute disruptions to interstitial cell of Cajal (ICC) networks, slow waves and phasic contractions.[62] Preliminary observations to a similar effect have also been made in animals,[63] and a single human study which investigated distal colonic motility post resection.[64]

Essential to gut motility are the inter-related functions of the ICC and enteric nervous system (ENS) within the gut wall. ICC form a continuous cellular network through the gut wall and their function includes generating and propagating slow waves that pattern myocyte depolarization.[65] In the small bowel, ICC pattern contractility, but the integrated motility response is also strongly modulated by the ENS. This co-regulation is exemplified by the myenteric stretch response which underpins peristalsis.[66,67] Conversely, although colon and rectum possess networks of ICC, their coordinated function appears to depend more on extrinsic regulatory neural stimulation.[50,68-70] The comparative independence and resilience of myenteric motility mechanisms of the upper gut may in part explain why procedures involving colorectal resection have a longer duration of POI and higher incidence of prolonged POI when compared to more proximal surgery.[3,10,71]

Disturbances of gastrointestinal hormones and neuropeptides

Both the surgical insult and lack of early oral intake after surgery modulate the levels of gastrointestinal hormones and neuropeptides. Those of greatest interest are motilin, substance P (SP) and vasoactive intestinal peptide (VIP) – all of which play a role in normal gut motility.[72] Cyclical increases in the hormone motilin are central to the genesis of the migrating motor complex and were found to be absent in a canine model of POI.[72] Conversely, antagonism at receptor sites or prevention of release of the enteric neurotransmitters SP and VIP in animal models has been shown to accelerate recovery of postoperative gut function.[73-75] These findings are somewhat contradictory when considering SP is a potent tachykinin known to stimulate gastrointestinal motility *via* direct action on smooth muscle and excitation of neurons within the ENS.[76] However, SP is also involved in excitatory neurotransmission of visceral afferents and is believed to play a key role in mediating the neuro-immuno-humoral inflammatory response to tissue injury.[76-78] It is therefore feasible that blockade of these mechanisms in the peri-operative setting underlie the efficacy of SP antagonists. VIP is thought to have several different effects on gut motility, although precise mechanisms and overall action have not yet been clearly defined.[79] VIP is a smooth muscle relaxant, possibly explaining the efficacy of VIP antagonists in accelerating post-operative gut recovery.[73,75] However, VIP also acts as a major anti-inflammatory agent[79] and there is a growing body of evidence supporting its role as an excitatory secretomotor neurotransmitter within the ENS (most notably in the context of intraluminal enterotoxins).[80-83] The role of each of VIP's mechanisms of

action and their degree of involvement in the pathogenesis of an ileus is therefore unclear.

Accurate profiling of serum hormone and neuropeptide levels in humans is needed in the first instance in order to define this further.

Electrolyte derangement

Peri-operative electrolyte disturbances may play a central role in the aetiology of an ileus.[84] This hypothesis is supported by the well-described effects of electrolyte variations on gut motility[69] and the observation that such disturbances often occur during an episode of prolonged POI.[84,85] An editorial published in 1971 identified hypokalaemia as a probable contributing cause for prolonged ileus in a small series of postoperative patients, with correction being associated with resumption of gut functioning.[86] Recent retrospective reviews have implicated postoperative electrolyte disturbances as a risk factor for developing prolonged POI.[3,6] Kronberg *et al.* noted a significant association between ileus and postoperative hypokalaemia and hypocalcaemia; hypermagnesemia was also associated but not significantly.[3] Our research group has found hyponatremia to be a significant correlate of prolonged ileus.[6] Importantly, the retrospective nature of these studies has made it difficult to determine direction of causality – although it is plausible that electrolyte disturbances cause myenteric dysfunction, it is also possible that gastrointestinal fluid shifts during POI contribute to electrolyte derangements.[18,85]

Iatrogenic mechanisms: intravenous fluid, antiemetics and opioid analgesia

Exogenous substances administered within the peri-operative period may impact significantly on gastrointestinal function. While correlations have been observed between intravenous fluid[87] and various antiemetics or prokinetics,[88] there is no consistent evidence to support a definite role. Conversely, the negative impact of narcotic analgesia on gastrointestinal motility has now been well defined. This mechanism was initially evaluated in nonsurgical populations,[89] but has since been examined in the postoperative setting where opiate administration is now widely considered to be a key contributor to both the development and maintenance of ileus.[3,6,90] The surgical insult induces a spike in endogenous opioids, while exogenous opioids are administered to reduce postoperative pain.[91] The analgesic properties of opioids are caused by direct action on the CNS, while their gastrointestinal side effects result from agonism at the peripheral μ–opioid receptor.[92] Activation of these receptors at the myenteric plexus inhibits release of acetylcholine from nerve endings, thereby increasing smooth muscle tone and impairing gut motility.[93] This mechanism of action of narcotic-related dysmotility is confirmed by the demonstrated success of Alvimopan – a peripherally-acting μ-opioid receptor antagonist – in enhancing postoperative gastrointestinal recovery.[94]

Mechanisms of panenteric dysfunction

While a number of different causes of POI have been detailed above, further discussion is required to understand how these factors combine to result in gastrointestinal dysfunction. Despite the differing recovery times for stomach, small bowel and large bowel,[24] all gastrointestinal segments are affected together, and it is therefore important to consider ileus as a generalised gut dysfunction.

The panenteric effects of narcotic use or electrolyte imbalance are self evident. Likewise, it is feasible that local neural afferents initiate reflex arcs in the CNS with efferents acting on other parts of the gastrointestinal tract. Indeed, it has been shown in a murine model that isolated handling of the small bowel generates inhibitory neural efferents that delayed gastric emptying.[95] Panenteric inflammation has been postulated as a mechanism for generalised dysmotility, and may be the consequence of three major pathways – i) intra-peritoneal dissemination of mast cell mediators upon peritoneal injury;[20,21,24] ii) intramural production and haematogenous circulation of T helper type 1 memory cells;[96] or iii) translocation of intraluminal commensal endotoxins to the *muscularis propria* with generation of a local and systemic inflammatory response.[97]

Future directions for research

Given the broad pathophysiologic basis of an ileus, there are many directions for future research which may prove useful. We have chosen here to limit discussion to three areas where we believe there is scope for enhancing understanding of POI and improving clinical management.

1. Improving pathophysiologic understanding

High resolution manometry

It is important to appreciate that our understanding of how pathophysiologic disturbances impact actual intestinal contractility is limited. Clinical symptoms such as nausea, vomiting and absence of flatus and stool may be readily explained when presented in the context of radiologically proven gut dilation and fluid accumulation. However, it is unclear if this dysfunction results from intestinal dysmotility, hypomotility or the complete absence of motility. Better understanding of the changes in gut contractility associated with POI is needed.

Techniques currently used to define normal or abnormal gut motility are largely confined to transit studies and manometry. Transit studies involve radiologic, fluoroscopic or scintigraphic tracking of radio-opaque markers as they move through the gastrointestinal tract,[98] and have more recently used the ‘SmartPill’ (WMC: SmartPill Corporation, Buffalo, USA). This ingestable capsule includes an in-built pH sensor, and changes in pH readings allow investigators to determine segmental transit times through stomach, small bowel or colon.[99] However, while these transit techniques allow information to be collated on gross movement *between* anatomical segments of the gut, they do not qualify spatiotemporal pressure

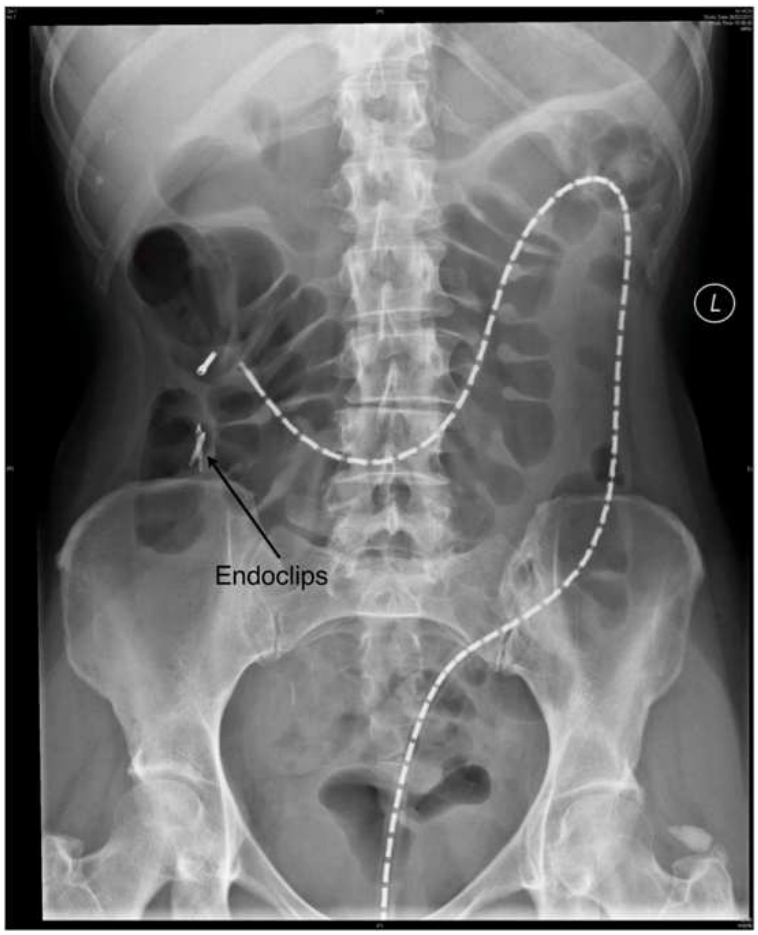

Figure 2. Plain abdominal radiograph showing* in situ *placement of a high-resolution manometry catheter.

characteriztics *within* these segments and are therefore of little use in defining local intraluminal motility changes occurring in ileus.

Manometric devices are able to quantify, in real-time, intraluminal pressures generated by contractions of the gut wall across multiple isolated points. Data from adjacent sensors allow investigators to determine when and where propagating contractions occur, therefore making it a potentially valuable tool for characterizing POI. Past work in this area has been critically limited by the lack of suitable and accurate clinical manometry technology, but recent developments in fibre-optic manometry have seen the emergence of catheters capable of recording pressure at up to 120 locations (spaced at 1cm intervals) along any section of the gut (Figure 2).[14,100] Information gained from these 'high resolution' devices far surpass those retrieved from traditional low resolution manometry catheters, with the latter being shown to miss up to 90% of propagating activity (Figure 3).[101]

It is proposed that peri-operative *in vivo* high resolution manometry may serve as a practical and valuable method for establishing the basic pattern of gut dysmotility that occurs in an ileus. The colorectum is an appropriate target site for such investigations, given its accessibility to endoscopic placement and the potential to correlate manometric activity to clinical markers heralding resolution of ileus (such as passage of flatus or stool).

Influence of visceral anastomoses

POI is a significant problem following abdominal procedures involving gut resection.[3,4] It has been shown that creation of an end-to-end anastomosis significantly impairs downstream intestinal motility in the postoperative period when compared to non-anastomotic surgery of similar severity.[64] While it is postulated that this effect is related to disruption of neuromuscular continuity, return of gut function even in the presence of an anastomosis generally occurs within 3-4 days postoperatively.[71] Gut recovery at this point is therefore less likely to be due to neural regeneration and more likely due to establishment of a propagating sequence distal to the anastomosis after delivery of intestinal contents and intraluminal bolus distension. This hypothesis could perhaps be best investigated in an animal model, with simultaneous recording of serosal electrical activity and intraluminal manometry across new joins, thereby providing baseline information on degree and importance of neuromechanical coupling in ileus following gut resection. This may also be further qualified at differing sites of anastomosis (*i.e.* small

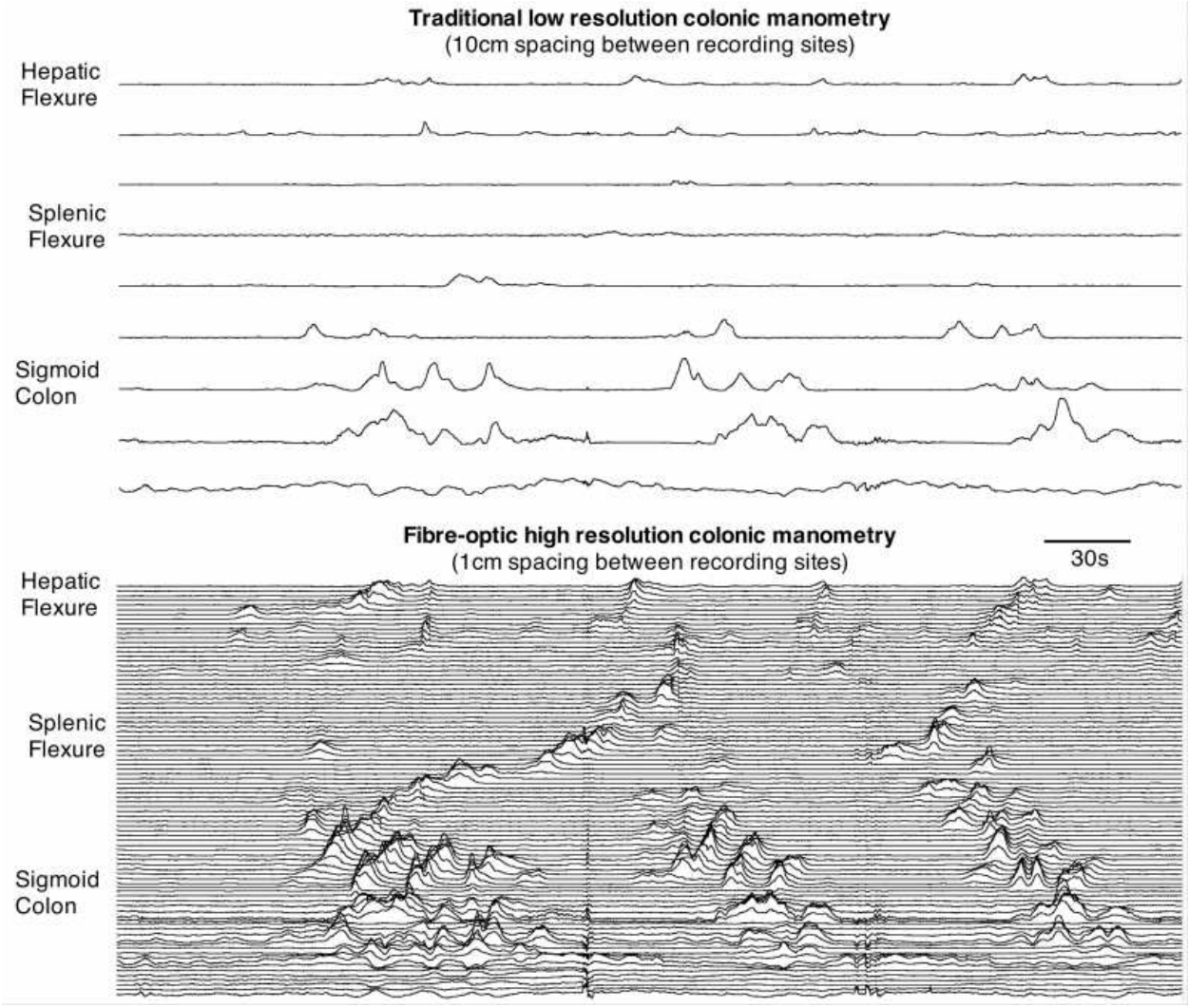

Figure 3. Manometric recordings illustrating the difference between low resolution (upper trace) and high resolution (lower trace) devices in the same patient over the same time period.

bowel *vs.* right-sided colectomy *vs.* left-sided colectomy).

2. Prospective risk factor assessment with creation of risk stratification tool

Clinical elements that predict prolonged ileus are poorly defined. Peri-operative and patient factors that appear to be emerging as consistent associations of prolonged POI following abdominal surgery include: increasing age, male gender, pre-existing airway disease, increasing peri-operative opiate consumption, intra-operative blood loss and formation of ileostomy (Table 1).[3-7] However, the retrospective design of current studies, small sample sizes of most, and differing definitions of POI have limited our ability to confidently qualify and quantify the significance of potential risk factors.

A useful step in the further investigation of clinical predictors of prolonged ileus would be through the design and population of a prospective database. All factors relating to patient, operation, and peri-operative care should be recorded. An important consideration is for assessment to occur with a uniform definition for prolonged POI.

Prospective appraisal following major colorectal resection may provide an optimal setting for this work, by allowing evaluation of a relatively homogenous cohort of surgical patients with a significant rate of prolonged POI.

3. Novel therapeutic strategies

The substantial clinical and economic burden conferred by ileus appears to have been acknowledged by the surgical community, with the recent emergence of many clinical trials examining therapeutic strategies. However, a majority of these have yielded disappointing or conflicting results. A recent Cochrane review investigated 15 prokinetic agents across 39 trials and found only one (Alvimopan – a selective μ-opioid receptor antagonist) showed a reproducible therapeutic benefit. The remaining drugs were not recommended due to lack of evidence or absence of effect.[88] Moreover, it is important to note that

Table 1. *Incidence of and independent predictors for the occurrence of prolonged POI following colorectal surgery in five recent retrospective reviews.*

	Year	Incidence of prolonged POI	Independent predictors for prolonged POI
Artinyan	2008	22 / 88 (25%)	-Estimated blood loss across surgery -Postoperative opiate dose
Kronberg	2011	42 / 413 (10.2%)	-Increasing patient age -Chronic pre-operative opiate use -Previous abdominal surgery
Millan	2011	123 / 773 (15.9%)	-Male gender -Procedures requiring formation of stoma -Pre-existing airways disease
Chapuis	2013	336 / 2400 (14%)	-Male gender -Procedures requiring formation of stoma -Pre-existing airways disease -Pre-existing peripheral vascular disease -Acute procedures -Increasing procedure duration -Need for transfusion during surgery
Vather	2013	50 / 255 (19.6%)	-Increasing patient age -Increasing haemoglobin drop across surgery

the clinical outcome evaluated in almost all these studies was time to return of gastrointestinal function post-surgery (*i.e.* a shortened duration of 'normal' postoperative ileus) with no reference to incidence or shortened duration of prolonged ileus.

The following discussion considers selected novel treatment strategies that may prove useful in the management of an ileus. It is only recently that concise evidence-based recommendations for the management of a prolonged ileus have been formulated,[102] and it is recommended that the strategies outlined below are considered in the context of similar best-practice guidelines.

Neural blockade with local anaesthetic or antagonists

The peri-operative administration of local anaesthetic (LA) is mostly administered in the form of epidural anaesthesia and lessens the effects of postoperative gut dysfunction *via* three principal mechanisms: i) reduced need for narcotic analgesia; ii) blockade of somatosensory afferents; and iii) transient chemical sympathectomy.[103] The former two mechanisms may be sufficiently achieved by epidural placement at either thoracic or lumbar location, but it is important to note that sympathetic blockade is only achieved by placement at mid-high thoracic level. Epidural analgesia sited here diminishes sympathetic thoracic outflow to the gut while having no effect on parasympathetic vagal efferents, thereby allowing a shift in autonomic balance conducive to gut motility.[104,105]

Alternate therapeutic strategies utilising local anaesthetic involve systemic intravenous administration (IVLA) or local intra-peritoneal administration (IPLA). Peri-operative administration of IVLA has been shown to have analgesic[106] and anti-inflammatory properties,[107] and it is postulated that these mechanisms account for the accelerated return of normal gastrointestinal function.[108,109] Precedent studies have demonstrated considerable heterogeneity in the type of surgery investigated and outcomes assessed, and although further research is needed to validate findings, it appears IVLA may eventually provide a valuable clinical tool in the management of an ileus.[110]

IPLA has likewise been investigated as a therapeutic measure following abdominal surgery and it has been hypothesized that the local administration of local anaesthetic may blunt the autonomically-mediated visceral nociceptive response to gut handling.[33] Indeed, a recent systematic review found that IPLA appeared to expedite return of gut function following surgery but recommended further research given the difficulty collating data from acute *vs.* elective, laparoscopic *vs.* open, and upper gastrointestinal *vs.* lower gastrointestinal *vs.* gynaecologic procedures.[111]

Transient sympathectomy in the post-operative period may also be achieved by adrenergic blocking agents. Propranolol is a non-selective β-blocker which to date has been investigated in four clinical trials (two examining propranolol alone, and two examining propranolol in conjunction with the parasympathomimetic neostigmine). All studies exhibited methodologic or reporting deficiencies, with a Cochrane review concluding inconsistent and insufficient evidence to support a role in enhancing gut recovery following surgery.[88] As described previously, the effect of sympathetic outflow to the gut is primarily mediated by activation of α-2 adrenoceptors and a potential explanation for propranolol's absence of effect relates to its exclusive antagonism at the β-1 and β-2 adrenoceptors. This hypothesis was recently validated by a

rodent model of POI that showed that both the non-selective adrenergic antagonist guanethidine and the α-2 adrenoceptor antagonist yohimbine improved colonic transit after surgery, while propranolol had no discernible effect when compared to placebo.[112] The clinical value of selective adrenergic antagonism in mitigating gut dysfunction following surgery therefore merits investigation.

Suppression of inflammatory cascade

Inflammation is thought to be an important component in the genesis of POI and therefore reducing inflammation may prove therapeutically valuable. This may be achieved by a 'blanket' approach with immunosuppresion being effected by systemic administration of corticosteroids, or by a focused approach whereby specific pathways in the response to the surgical insult may be targeted.

There is limited literature investigating the effect of short-course corticosteroids on postoperative gut dysfunction. Indeed, while a recent review found a single pre-operative dose of glucocorticoid reduced complications in major abdominal surgery *via* blunting of the post-surgical inflammatory response, no specific comment was made on return of bowel function.[113] Moreover, although delivery of steroid in the pre-operative setting is likely to prevent initiation of an inflammatory cascade,[17] its selective use following surgery in confirmed cases of prolonged POI theoretically stands to deliver a therapeutic benefit and warrants prospective clinical appraisal.

It has also been proposed that treatment could target specific components of the inflammatory response. As outlined above, mast cells play a central role in this process with prevention of degranulation significantly improving POI in a murine model.[95,114] This subsequently led to a pilot study in human patients investigating the therapeutic value of the mast cell stabiliser ketotifen. While there was a shortened duration to scintigraphically-assessed gastric emptying, no similar findings were observed in colonic transit.[115] Resident macrophages likewise play a key role in the innate immunologic response, and depletion of these cells in a rodent model by chlodronate liposomes has yielded promising results.[116] Similarly, electrical stimulation of the vagus nerve in a murine model reduced inflammation by impairing macrophage activation.[117] These outcomes have yet to be translated to humans, but a recent review has suggested all stages of the activation process from chemoattraction to inducible hypoxic enzymes to intracellular signalling may be viable therapeutic targets.[24]

Mechanical reduction of oedema

The above discussion largely addresses strategies in attenuating the initial stages of an ileus. However, it is of far greater clinical significance to consider therapies which may be useful in established cases of prolonged POI. Dysmotility at this point is likely to be in part due to bowel wall oedema, and administration of agents able to counteract this oedema in a site-specific manner merit investigation. Oral water-soluble hyperosmotic contrast media such as gastrografin have been shown to be of therapeutic benefit in adhesive bowel obstruction,[118] and are believed to exert their effect by drawing fluid out of the bowel wall into the gut lumen thereby reducing dysfunction and promoting peristalsis.[119] The clinical value of gastrografin in POI is however less clear with previous studies being limited to small patient numbers, heterogeneous inclusion criteria and outcome measures, and conflicting results.[120-122] Appropriately powered, randomised and blinded prospective appraisal is required to adequately assess the efficacy of this potential intervention in ileus.

Manipulation of gastrointestinal neuropeptides

Octreotide is a somatostatin analogue believed to inhibit the release of many gastrointestinal hormones *via* direct action on neurons in the ENS.[123-125] Octreotide has been shown in a canine model to accelerate postoperative gastrointestinal transit at low doses, although at higher doses paradoxically inhibited gastric emptying.[123] A subsequent study investigating administration of octreotide in healthy human volunteers found accelerated gastric emptying but delayed mouth-to-caecum transit time.[124] It has been postulated that suppression of postprandial hormones (notably cholecystokinin) may be partly responsible.[124,126]

An important initial step when considering the therapeutic potential of octreotide in ileus would therefore involve a detailed assessment of its effects on individual gut hormones. Four trials have investigated the effect of the cholecystokinin-like drugs cerulean and ceruletide, with a systematic review concluding that there is inconsistent evidence for a reduction in postoperative gut recovery times.[88] VIP and SP receptor antagonists have been shown to improve postoperative intestinal transit in a rat model,[73,75] but they have not been tested in humans.

A blinded trial of intravenously infused motilin *vs.* normal saline in patients following open cholecystectomy revealed no improvement in gut function.[127] Erythromycin is a motilin agonist and its prokinetic side effects when administered as an antibiotic are well known.[128] However, four trials investigating its use in the postoperative period were consistent in their findings of having no treatment effect.[88]

More recently, considerable attention has been given to ghrelin – an endogenous ligand at the growth hormone secretagogue receptor, released from gastric and pancreatic epithelium with structural similarity to motilin.[129] The ghrelin agonist 'TZP-101' has been shown in recent Phase II trials to safely and effectively reduce upper and lower gastrointestinal dysfunction in patients following partial colectomy.[130,131] It has been hypothesized that these findings are primarily attributable to the potent prokinetic effect of TZP-101,[132] although the relative significance and transferability of ghrelin's ability to down-regulate pro-inflammatory cytokines in a sepsis model is unclear.[133,134] Results of Phase III testing are awaited.

Conclusion

POI is a clinically and economically important consequence of major abdominal surgery. There is considerable heterogeneity with respect to its definition, and there remains a need for uniformity in endpoint reporting. The pathophysiologic basis of an ileus is multifactorial, and key contributing factors include generation of an inflammatory response, administration of opioids, autonomic dysfunction, disturbances in gastrointestinal hormone activity, and electrolyte fluctuations. Future research directions offer hope for progress. In particular, there remains much scope to more clearly characterize the gastrointestinal dysfunction that underscores ileus, and an accurate risk stratification tool to facilitate early institution of preventive measures warrants investigation. Clinical appraisal of novel therapeutic strategies that target individual pathways in the pathogenesis of ileus will continue to inform management.

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