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Postoperative Ileus

Progress Towards Effective Management

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Contents

Abstract

The pathogenesis of postoperative ileus (PI) is multifactorial, and includes activation of inhibitory reflexes, inflammatory mediators and opioids (endogenous and exogenous). Accordingly, various strategies have been employed to prevent PI. As single-modality treatment, continuous postoperative epidural analgesia including local anaesthetics has been most effective in the prevention of PI. Choice of anaesthetic technique has no major impact on PI. Minimally invasive surgery reduces PI, in accordance with the sustained reduction in the inflammatory responses, while the effects of early institution of oral nutrition on PI *per se* are minor. Several pharmacological agents have been employed to resolve PI

(propranolol, dihydroergotamine, neostigmine, erythromycin, cisapride, metoclopramide, cholecystokinin, ceruletide and vasopressin), most with either limited effect or limited applicability because of adverse effects. The development of new peripheral selective opioid antagonists is promising and has been demonstrated to shorten PI significantly. A multi-modal rehabilitation programme including continuous epidural analgesia with local anaesthetics, enforced nutrition and mobilisation may reduce PI to 1–2 days after colonic surgery.

Recent improvements in anaesthetic and surgical techniques have facilitated substantial reductions in convalescence and hospital stay after major surgical procedures. In this context, development of clinical programmes to facilitate resolution of postoperative ileus (PI) has been a major issue, since PI is a common cause of prolonged hospitalisation after major surgery.[1-3] Recent advances in anaesthetic and surgical management, and the development of selective peripheral opioid antagonists have resulted in substantial reductions of PI.[1,4] Subsequently, a combined approach of anaesthetic and surgical techniques, and pharmacological treatment in a multimodal rehabilitation programme may further reduce or prevent PI.[1,5]

In this paper, we review the pathophysiology and current treatment options for PI, with an emphasis on the pharmacological approaches.

1. Pathophysiology

The pathophysiology of PI is multifactorial (table I). The duration of PI correlates with the degree of surgical trauma and is most extensive after colonic surgery.[1] However, PI may develop after all types of surgery including extraperitoneal surgery as demonstrated in a recent review of 21 589 patients undergoing lower extremity arthroplasty, where 0.32% of patients developed PI.[6]

Activation of inhibitory reflexes with afferent limbs originating from the incision (somatic fibres) as well as from the intestines (visceral fibres) and manipulation of the intestines is a major pathogenic factor in the development of PI.[1,7] These reflexes may be inhibited by epidural local anaesthetics, with subsequent reduction of PI (see section 2).

Release of inflammatory mediators either locally or as part of the stress response to surgery also contributes to the development of PI.[1,8] In an elegant series of experimental studies, Bauer's group has demonstrated that cellular infiltration and gut paralysis to bethanechol stimulation are directly proportional to the intestinal trauma.[8] In further studies, a causative link between the immigration of leucocytes into the intestinal muscularis externa and gut paralysis has been established.[9] The gut paralysis was found to be bi-phasic,[10] with nitric oxide (NO) as an important mediator of the initial paralysis.[11] Furthermore, intestinal manipulation was found to lead to increased mucosal permeability, resulting in the hypothesis that endogenous bacterial products may act synergistically with the inflammatory response in the development of PI.[12] NO and several peptides (vasoactive intestinal peptide [VIP], substance P, calcitonin gene-related peptide [CGRP]) are released locally in the gastrointestinal tract and may contribute to PI.[11,13-15] Finally, new evidence from an experimental study suggests that prostaglandins (via induction of cyclo-oxygenase [COX]-2) is important in the pathogenesis of PI.[16] However, the relative role of these peptides and other inflammatory mediators in the initiation and prolongation of PI remains to be clarified.

Opioids are of major importance in the pathogenesis of PI as a result of their depressing effects on gastrointestinal transit.[17] The gastrointestinal effects of opioids are mediated primarily by receptors within the bowel, whereas spinal or cerebral opioid receptors play a minor role.[18,19] The receptor primarily involved in pain control and delay in gastrointestinal transit is the μ receptor.[17] Administration of the non-selective opioid antagonist naloxone reverses gut paralysis, but systemically ab-

Table I. Pathogenesis of postoperative ileus and treatment modalities

Pathogenic factor	May be modified by
Inhibitory splanchnic reflexes	Epidural blockade (local anaesthetics)
Increased efferent inhibitory sympathetic activity	α– and β–Antagonists
	Parasympathomimetics
	Epidural blockade (local anaesthetics)
Local inflammation/inflammatory stress response	Minimally invasive surgery
	Anti-inflammatory agents
Gastrointestinal peptides (VIP, substance P, CGRP)	Antagonists
Opioids (exogenous)	Opioid-sparing analgesic techniques
	Selective peripheral μ-opioid antagonists
Opioids (endogenous)	Selective opioid receptor antagonists
Starvation	Early postoperative feeding
Fluid excess	Fluid restriction

CGRP = calcitonin gene-related peptide; **VIP** = vasoactive intestinal peptide.

sorbed naloxone enters the central nervous system (CNS) with withdrawal or loss of analgesia.[20] The ratio between analgesic and constipating effect of morphine is approximately 4 to 1, that is, four times more morphine is needed to obtain analgesic effect than to slow gastrointestinal motility.[21] With repeated opioid administration for pain relief, tolerance to the analgesic effect subsequently develops; however, tolerance to the gastrointestinal adverse effects does not develop.[21] In addition to the effects of exogenous opioids on PI, it has recently been demonstrated that plasma concentration of endogenous morphine is increased following surgical injury.[22-24] The exact release mechanisms and subsequent biological effects are unknown, but may include PI.[25]

Gut permeability may be increased following a surgical trauma with enhanced uptake of luminal bacterial products, which may contribute to the development of PI.[12] It has been hypothesised that enteral feeding may maintain the integrity of the gastrointestinal mucosa[26] and, thus, may theoretically reduce PI.

Finally, perioperative fluid excess may contribute to PI possibly by delaying gastrointestinal motility as a result of the presence of excess fluid in the intestinal wall.[27]

In the following sections we review the various strategies in perioperative management to reduce PI.

2. Anaesthesia and Analgesia

2.1 Anaesthesia

Intraoperative analgesic treatment (in the absence of an epidural or spinal block) usually consists of opioids, with half-lives which may influence gastrointestinal motility well into the postoperative period. Therefore, recent anaesthetic advances with light sedation regimens (propofol) combined with newer short acting opioids (remifentanil) may theoretically improve postoperative gastrointestinal motility. However, no data from clinical trials are available. A single-dose neural block (spinal or intraoperative epidural) does not influence PI.[28]

2.2 Analgesia

After major surgery, dynamic pain relief (i.e. pain relief allowing mobilisation) may only be achieved by a continuous infusion including epidural local anaesthetics,[29,30] and opioids may only provide sufficient static pain relief after major surgery. The advantages of postoperative epidural local anaesthetics are many: (i) superior pain relief allowing mobilisation; (ii) opioid-sparing thereby avoiding opioid-related adverse effects; and (iii) the important stress reducing effect of epidural local anaesthetics obtained by blocking of afferent input from the wound.[28]

It is well documented from randomised, clinical studies that continuous thoracic epidural blockade (>24 hours) with local anaesthetics decreases PI compared with systemic opioid administration.[1,2,30-32] From a meta-analysis of five studies with 261 patients, epidural local anaesthetics alone reduced PI (first passage of stool) by 54 hours compared with systemic opioid administration.[30] However, the effect of postoperative epidural local anaesthetics on PI compared with other postoperative non-opioid analgesia is uncertain in relatively minor procedures, as only a reduction in time to flatus and not time to bowel movement was observed in patients with 24-hour postoperative epidural local anaesthetics compared with patients receiving paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative analgesia in a randomised study of 60 patients undergoing abdominal hysterectomy.[33] While addition of opioid to the epidural local anaesthetic improves pain relief,[29] PI may be slightly prolonged than with a continuous epidural blockade with local anaesthetics alone.[1,30,31,34,35] From the same meta-analysis, the reduction in PI was 21 hours when epidural local anaesthetics were compared with epidural opioids and 16 hours when compared with epidural local anaesthetics-opioid mixtures.[30] Duration of PI seems to be similar with epidural opioid administration compared with systemic opioids.[1]

It must be emphasised that the pathogenesis of the reduction of PI by epidural local anaesthetics relies on a blockade of inhibitory sympathetic reflexes, primarily arising from the wound and viscera.[1,28] It is therefore essential that the adequate neural segments are blocked for the epidural analgesia to be effective. Thus, in order to block the afferent input from colonic surgery the epidural has to be thoracic at the level including the incision. A lumbar epidural blockade cannot be expected to modify afferent input in abdominal surgery, which is confirmed by several studies demonstrating little or no ileus-reducing effect of lumbar epidural analgesia after abdominal surgery.[1,2,36]

The importance of taking these physiological aspects into consideration when designing clinical trials aiming to investigate effects of epidural analgesia on PI is demonstrated in a recently published randomised clinical trial in 168 patients undergoing aortic surgery.[37] Postoperative epidural analgesia was predominantly opioid-based, with administration of local anaesthetics in a very low dose, which therefore will not provide a significant afferent or efferent neural blockade. Subsequently, length of PI did not differ between patients randomised to postoperative opioid-based analgesia versus epidural local anaesthetics (90 hours to first bowel movement after intraoperative epidural anaesthesia plus postoperative opioid analgesia, and 117 hours to first bowel movement after intraoperative epidural anaesthesia plus postoperative epidural local anaesthetics/opioid mixture).[37] Similar results were found in another study with 44 patients undergoing small bowel or colonic surgery randomised to thoracic epidural analgesia (T10–12) with local anaesthetic-opioid mixture or systemic opioid-based analgesia, where no difference in PI (time to bowel movement 3.8 in patients receiving epidural analgesia vs 3.7 days in those receiving systemic opioid) was seen.[38] Again, the postoperative epidural analgesia was predominantly opioid-based and thus the results are not surprising.[38]

The role of pain *per se* for the duration of PI is not known. Preliminary results from a multimodal intervention programme after elective colonic surgery with continuous thoracic epidural analgesia with local anaesthetics, early oral feeding and mobilisation demonstrated that the level of pain did not relate to the duration of PI,[39] thus suggesting that the reduction of PI from epidural local anaesthetics does not primarily depend on pain relief *per se*, but on the intestinal neural blockade achieved by epidural local anaesthetics or other factors. It has been speculated that the increase in intestinal motility by thoracic epidural local anaesthetics may pose a threat to an anastomosis; however, evidence from randomised, clinical trials do not allow final conclusions.[40]

Other opioid sparing techniques includes the use of balanced analgesia.[29] The concept of balanced analgesia consists of combining various analgesics in order to achieve an optimal analgesic effect with reduced adverse effects.[29] This is most commonly achieved after major surgery by combining epidural analgesia with paracetamol (acetaminophen) or NSAIDs, thus minimising overall adverse effects and the need for rescue opioid analgesics.[29] The opioid-sparing effect of NSAID and paracetamol is 20–30%,[41] and may therefore lead to a reduction in opioid-related adverse effects including PI. Furthermore, NSAIDs may increase gastrointestinal motility *per se* as demonstrated in experimental studies, probably as a result of decreased synthesis of inhibitory prostaglandins.[42,43] However, so far the ileus-reducing effects of opioid-sparing by NSAIDs, paracetamol or the new selective COX-2 inhibitory agents have not been defined in abdominal procedures.

2.3 Opioids and Opioid-Antagonists

Since the duration of PI is directly proportional to the amount of administered opioid perioperatively,[44] it makes sense to try to avoid or reduce perioperative opioid administration as discussed in section 2.2. Therefore, research has focused on developing selective opioid-antagonists, that is, drugs that act on peripheral opioid receptors (thus potentially reducing gastrointestinal adverse effects) without entering the CNS (and so not affecting analgesia).Two novel selective opioid antagonists have recently been developed: ADL 8-2698[4] and methylnaltrexone.[45]

ADL 8-2698 is a peripherally restricted opioid antagonist. After oral administration, it specifically acts on receptors within the gastrointestinal tract with high affinity for μ-receptors and the systemic absorption is low.[4] As yet, ADL 8-2698 is the only selective opioid antagonist which has specifically been evaluated in a randomised, clinical trial with PI as primary end-point. Seventy-nine patients undergoing partial colectomy or abdominal hysterectomy were randomised to receive one capsule of 1 or 6mg ADL 8-2698 or placebo 2 hours before surgery, and subsequently twice daily until first bowel movement.[46] Patients receiving ADL 8-2698 6mg had earlier resolution of PI, indicated by decreased time to first flatus (49 vs 70 hours) and bowel movement (70 vs 111 hours). Analgesia was not affected by administration of ADL 8-2698, as evaluated by patient controlled analgesia (PCA)-opioid consumption and visual analogue scale (VAS).[46]

Even though these results are extremely promising, it must be noted that PI was not eliminated by ADL 8-2698, with a time to first bowel movement of approximately 3 days. The results from this study have been used to argue that thoracic epidural infusions may not be needed,[47] but so far, as a single intervention, continuous thoracic epidural analgesia is more effective in reducing PI than the results from ADL 8-2698.[1,2] Furthermore, the stress reducing effects of epidural analgesia may contribute to improved outcome especially if integrated into a multimodal rehabilitation programme.[48,49] Nevertheless, the approach to selectively inhibit peripheral opioid-receptors is fascinating, and should be further explored in a multimodal rehabilitation programme.

Another promising approach to reduce PI is the development of peripheral κ-agonists, which have been found to reduce PI in experimental studies.[1] However, data from clinical trials in post-surgical patients are not yet available.

3. Prokinetic Pharmacological Approaches

3.1 Sympathetic Antagonists

Activation of the sympathetic nervous system is known to depress gastrointestinal motility and surgery-induced excess sympathetic activity is an important pathogenic factor for PI.[1,7] Therefore, treatment with sympathetic blockers may modify duration of PI.

3.2 Propranolol

Propranolol is a non-selective β-blocker and has been investigated in several clinical trials (ta-

ble II). In one randomised, clinical study, twice-daily administration of propranolol 4 or 10mg significantly reduced length of PI (time to first bowel movement after elective colonic surgery decreased from 110 to 81 hours [4mg group] or 79 hours [10mg group]).[50] In another randomised, clinical trial where propanolol was administered with neostigmine versus neostigmine alone or placebo, the patients receiving propanolol 10mg plus neostigmine had significantly shorter PI than the placebo group (68 vs 90 hours to bowel movements), but no significant difference was seen in PI between patients receiving propanolol plus neostigmine compared with neostigmine alone (68 vs 82 hours).[51] In a recent randomised trial of 27 patients receiving propanolol 80–160 mg/day, no difference in clinical resolution of PI (passage of flatus or faeces) was seen.[52]

3.3 Dihydroergotamine

Dihydroergotamine potentially enhances gastrointestinal motility via an inhibitory effect on α-receptors. In a randomised, clinical trial in 85 patients undergoing major abdominal surgery, length of PI (time to first passage of stool) did not vary between groups (88 vs 94 hours for the active vs placebo group, respectively).[54] However, in another trial in 46 patients undergoing open cholecystectomy, PI was significantly improved with administration of dihydroergotamine, with bowel movement occurring 57 hours after surgery in the treated group compared with 102 hours after surgery in the placebo group.[53] Both these studies are almost 20 years old and no newer evidence has been presented on dihydroergotamine in the treatment of PI.

3.4 Neostigmine

Neostigmine is an acetylcholinesterase inhibitor, which causes an increase in cholinergic activity in the gut wall, thereby stimulating colonic motility. In a double-blind, randomised study of 90 patients with prolonged PI, injections of neostigmine did not have any effect on the resolution of PI.[56] In contrast, a recent study administering neostigmine to postsurgical patients as well as to healthy volunteers found neostigmine to improve colonic motility as measured by manometry/barostat recordings in postsurgical patients as well as in healthy volunteers.[55] However, no clinical data on length of PI was presented and previous studies indicate that length of PI is relatively independent of such technical registrations.[1] Furthermore, administration of neostigmine seems effective in acute colonic pseudo-obstruction.[75] The clinical usefulness of neostigmine in postoperative patients may be limited by adverse effects including abdominal cramps, excess salivation, vomiting

Table II. Pharmacologic strategies in the treatment of postoperative ileus (PI) from randomised, controlled trials

Agent	Mechanism of action	Effect on duration of PI
Propanolol	β-Receptor antagonist	Decreased[50]
		None[51,52]
Dihydroergotamine	α-Receptor antagonist	Decreased[53]
		None[54]
Neostigmine	Acetylcholinesterase inhibitor	Decreased[55]
		None[56]
Erythromycin	Motilin agonist	None[57,58]
Cisapride	Acetylcholine agonist	Decreased[59-62]
	Serotonin receptor agonist	None[63-66]
Metoclopramide	Cholinergic stimulant	None[67-70]
	Peripheral dopamine antagonist	
Cholecystokinin	Prokinetic peptide	None[71]
Ceruletide	Cholecystokinin agonist	Decreased[72,73]
Vasopressin	Stimulation of defecation	None[74]

and bradycardia. Moreover, the potentially increased risk of anastomotic leakage with neostigmine needs to be clarified.[55]

3.5 Gastrointestinal Peptides

Experimental studies have demonstrated that agonists to gastrointestinal peptides, such as VIP, which inhibit release of other gastrointestinal peptides,[13] antagonists to inhibitory gastrointestinal peptides (substance P)[14] or immunoneutralisation (GCRP) may reverse PI.[15] Somatostatin inhibits the release of several of the gastrointestinal peptides and the somatostatin analogue octreotide increases gastrointestinal transit in experimental studies.[76,77] However, no clinical studies have investigated the effect of octreotide on clinically relevant outcomes of PI.

3.6 Vasopressin

Vasopressin (anti-diuretic hormone) is released as part of the stress response to surgery. Since vasopressin in pharmacological doses stimulates colonic motility, it has been postulated that vasopressin may be effective in the treatment of PI.[74] However, in one randomised study of 73 patients undergoing major abdominal operations, postoperative administration of vasopressin did not affect length of PI.[74] Thus, on the basis of the available evidence, vasopressin cannot be recommended to treat PI.

3.7 5-HT_4-Receptor Agonists

As a 5-HT_4 receptor agonist, cisapride has previously been demonstrated to have beneficial effects on PI in some studies (table II).[1] However, since cisapride has been withdrawn from the marked because of cardiac adverse events,[78] it is not an option to treat PI.

A new serotonin 5-HT_4 receptor agonist, prucalopride has recently been developed, and has been found to increase gastrointestinal transit after surgical stimulation in an experimental study.[79] Clinical data in PI are not yet available.

3.8 Metoclopramide

As recently reviewed,[1,80] administration of metoclopramide does not significantly reduce PI. In a total of six randomised, clinical trials, PI was not improved in four studies[67-70] and showed limited, if any, effect in the remaining two studies, with inadequate study design and report.[81,82]

3.9 Cholecystokinin

Cholecystokinin is a peptide with prokinetic effects, however, in a randomised, double-blind study in 60 patients scheduled for cholecystectomy, length of PI was not significantly affected by cholecystokinin administration (69 vs 84 hours to defecation for the cholecystokinin vs placebo groups, respectively).[71] Ceruletide, a cholecystokinin agonist, has been shown to reduce PI slightly in two studies.[72,73] However, adverse effects with nausea and vomiting limit the clinical use.

3.10 Magnesia

In a randomised, double-blind trial of bisacodyl administration versus placebo twice daily from the first postoperative day, the patients treated with bisacodyl had significantly earlier bowel movement (25 vs 56 hours) compared with placebo recipients.[83] Other studies with sodium phosphate solution,[84] or magnesia and biscolic suppositories,[85] are inconclusive because of the lack of a control group. Further studies are needed to assess the effect of laxatives on PI.

3.11 Erythromycin

Erythromycin has prokinetic effects, since it is an agonist of the prokinetic peptide motilin. However, in two prospective, randomised clinical trials erythromycin did not affect length of PI[57,58] (table II). These findings are not surprising, since erythromycin only stimulates motilin receptors in the small intestines and PI in humans is mostly due to colonic inertia.[86]

In summary, the effects of the various prokinetic agents attempts to reduce PI has mostly

been disappointing, with the possible exception of cisapride.

4. Other Perioperative Interventions

4.1 Minimally Invasive Surgery

Minimally invasive surgery leads to a decrease in the inflammatory response to surgery,[87] and laparoscopic surgery reduced PI in two of four randomised clinical studies comparing laparoscopic versus open colonic surgery,[88,89] whereas laparoscopic surgery did not reduce PI (time to defecation) in the remaining two studies,[90,91] although time to flatus was significantly reduced in one of the studies.[91] Several non-randomised controlled studies report a reduction in PI by the introduction of laparoscopic colonic surgery.[92] However, no specific perioperative care protocols were followed in these studies and, therefore, the belief in benefits from laparoscopic surgery and changes in perioperative management may have introduced bias to improve outcome in these non-blinded studies.

4.2 Feeding Protocols

Traditional recommendations of postoperative feeding include the use of nasogastric tubes and advancing postoperative feeding after the presence of bowel sounds. However, routine use of nasogastric tubes after elective surgery is not indicated[93,94] and does not reduce PI. In addition, the presence of bowel sounds is reflective of fasted state motility in the intestinal tract with myoelectric migratory complexes (MMCs). It is established from several studies, that the presence of MMCs does not reflect length of PI.[1] Thus, bowel sounds in the fasting patient may not reflect gastrointestinal motility in the fed state. In a recent review of randomised, clinical trials assessing the effect of early enteral feeding on PI, the ileus-reducing effect of early enteral feeding *per se* was minimal and probably not of clinical significance.[1] However, the effect of feeding in these studies may be masked by concomitant opioid analgesia, counteracting a potential benefit of early feeding.

Ingestion of a dietary fibre-enriched food may theoretically improve PI as a result of a stimulatory effect on gastrointestinal motility. A randomised study of preoperative intake of bran-enriched diet found that length of PI was significantly decreased in patients with high preoperative fibre intake, with 14 versus four patients (in two groups of 21 patients each) having bowel movements within the first 2 postoperative days after major abdominal surgery.[95]

4.3 Perioperative Fluid Management

Fluid excess may potentially contribute to PI as a result of the presence of intestinal oedema.[27] In a randomised study of 102 patients undergoing major surgical procedures, 'regulated' postoperative fluid intake (i.e. hourly volumes of oral fluids) versus 'unregulated' postoperative fluid intake (i.e. patients would drink as desired) did not affect length of PI.[96] In a more well-designed study, length of PI was significantly decreased (4.0 vs 6.5 days) with restrictive postoperative fluid treatment (maximum of two litres of water and 77 mmol sodium per day) compared with a 'standard' postoperative fluid regimen (minimum of three litres of water and 154 mmol sodium per day) in a randomised trial in 20 patients scheduled for elective colonic surgery.[97] In one study, an albumin concentration below 35 g/L did not correlate with increased duration of PI when compared with patients where the concentration of albumin was maintained above 35 g/L with albumin infusions after vascular surgery.[98]

4.4 Other Approaches

On the basis of the hypothesis that electric stimulation may shorten the length of PI, 50 patients undergoing major abdominal surgery were randomised to a group receiving pulsed electromagnetic energy twice daily postoperatively versus traditional care.[99] Although the patients receiving electrical stimulation had a more rapid return of bowel sounds, no difference in the time until flatus was passed was found between groups.[99] In a prospective, randomised study of guided imagery

(mediated by audio tapes) in 130 patients undergoing colorectal surgery, length of PI was significantly decreased from 92 to 58 hours in the group assigned to guided imagery.[100] In another randomised trial in 40 patients undergoing intra-abdominal operations, preoperative education led to a significant decrease in PI (time to flatus reduced from 4.1 to 2.6 days).[101] In a recently published randomised trial in 50 patients undergoing elective colonic surgery, application of postoperative mechanical massage of the abdominal wall led to a significant decrease in length of PI (1.8 vs 3.5 days to passage of flatus).[102] However, pain relief in this study was inadequate, with postoperative analgesia consisting only of propacetamol, and with exceptionally high pain scores varying from 7–8 (on a 10 point VAS scale) in the first 2 postoperative days, thus hindering further interpretation of the study results.[102]

Obviously, the approaches in these studies need confirmation before clinical recommendations can be given.

5. Multimodal Approaches for the Prevention of Postoperative Ileus

Multimodal rehabilitation programmes were developed as a logical consequence of the individually positive effects on postoperative recovery (and PI) of single-modality interventions such as thoracic epidural analgesia, opioid-sparing analgesia, minimally invasive surgery and early nutrition.[5,49]

5.1 Multimodal Studies

In most studies with postoperative epidural local anaesthetics, especially, the positive effects on PI were not utilised, for example to try to feed and mobilise patients earlier.[1]

In a multi-modal rehabilitation programme consisting of continuous thoracic epidural analgesia with local anaesthetics, no nasogastric tubes, no or short-term use of drains, early feeding and enforced mobilisation in 100 consecutive patients undergoing open colonic resection, 95 patients had defecation within the first 48 hours postoperatively (and median time to hospital discharge was 2 days).[103,104]

Similar results were seen in 31 consecutive patients undergoing abdominal rectopexy within a multimodal rehabilitation programme including early mobilisation, early oral feeding, epidural analgesia and a pre-planned 2-day hospital stay, as bowel movement occurred at a median of 2 days postoperatively.[105] Gastrointestinal motility was assessed by a scintigraphic technique after ^{111}-Indium ingestion with the same multimodal rehabilitation programme in 12 patients undergoing open colonic surgery and was compared with 12 matched volunteers. The results from the post-surgical patients and healthy volunteers were similar, since 57% of the tracer was excreted in patients and 53% in volunteers within 48 hours, and the median time to defecation was 1 day.[106] Thus, there was no clinical or scintigraphic evidence of PI in these 12 patients after a colonic resection. In 50 consecutive patients undergoing laparoscopic surgery with a similar multimodal rehabilitation programme, median time to defecation was 2 days, with defecation occurring in 92% of the patients within the first 3 postoperative days.[107]

In two recent prospective studies in patients undergoing colorectal surgery within a multimodal rehabilitation programme with no nasogastric tubes, early diet and ambulation (one study with laparoscopic surgery and postoperative thoracic epidural local anaesthetics,[108] the other study with open surgery and no epidurals[109]) patients were discharged only after resolution of PI at a mean of 2.8 days[108] and 4.3 days, respectively.[109] However, specific data on length of PI in these two studies were not presented.

A prospective study in 15 patients undergoing radical cystectomy with a multimodal rehabilitation regimen of early oral nutrition and enforced mobilisation, demonstrated a reduction in PI from 4 to 3 days compared with an historic control group with no specific perioperative rehabilitation programme.[110] Similar results were found in another prospective study from the same institution, in which a multimodal approach including individu-

ally adjusted postoperative epidural local anaesthetics and enforced mobilisation led to a significant decrease in PI as assessed by bowel sounds on the first postoperative day in patients undergoing esophagectomy.[111]

5.2 Summary of Multimodal Approaches

Preliminary results from multimodal rehabilitation programmes suggest that an approach with continuous epidural analgesia including local anaesthetics, early oral feeding and mobilisation may significantly reduce PI to a duration of 1–2 days after colonic surgery. These promising results should therefore be assessed in other major abdominal procedures. Most importantly, no data are available from acute abdominal operations where the inflammatory component is more pronounced and where the clinical benefits of reducing PI may have major implications.

6. Conclusions

PI is traditionally believed to be an obligatory response to surgery, but new evidence from studies with multimodal rehabilitation programmes including continuous thoracic epidural analgesia with local anaesthetics, early feeding and mobilisation indicate PI may be reduced to 1–2 days after colonic surgery. Further options to reduce PI include laparoscopic surgery and the new selective peripheral opioid-antagonists. Future research strategies should evaluate the relative role and indication for these treatment modalities, as well as exploring the place for new prokinetic agents and laxatives. Reduction of PI has major clinical implications because of the reduction of patient discomfort and hospital stay.[1,5] Finally, reduction of PI may allow early oral (enteral) nutrition, which separately has been shown to reduce postoperative morbidity.[112]

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