Postoperative ileus: New Considerations

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POI is a transient cessation of coordinated bowel motility after surgical intervention. It prevents effective transit of intestinal contents or tolerance of oral intake.
Etiology

- Sympathetic reflexes:
  - Ultrashort reflexes confined to gut wall
  - Short reflexes involve prevertebral ganglia efferent stimuli to the bowel
  - Long reflexes involve afferent stimuli to the cord
Etiology

- Motilin, substance P, VIP, cytokines
- Stimulated by local factors and body response to trauma
- Inhibition diminishes ileus
- Opioids:
  - Exogenous and endogenous
  - Decrease propulsive movement
  - Act on myenteric plexus at mu receptors
  - Jejunum > ileum
Higher levels of endogenous morphine were significantly related to delayed gastrointestinal recovery and length of hospital stay.
Activation of mast cells, monocytes and macrophages

Histamine
TNF-α
Prostanoids
Interleukins
Reactive oxygen species

Postoperative ileus

Nausea
Vomiting
Distension
Absolute constipation

Somatic and visceral trauma

Gut handling and anastomosis

Fluid overload

Opioid analgesia

Interference with electromechanical coupling

Intestinal oedema and stretch → STAT-3 activation and ↓ MLC phosphorylation

Activation of opioid receptors; decreased intestinal motility

Changes in gut peptides: motilin, VIP, substance P
Risk factors

**Risk factors for postoperative ileus.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Possible mechanisms</th>
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<tbody>
<tr>
<td>Increasing age [22,24].</td>
<td>Reduced overall capacity for the body to recover from surgical insult [24].</td>
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<td>Male gender [17].</td>
<td>Increased inflammatory response to surgery [19].</td>
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<td>Low preoperative albumin [24].</td>
<td>Increased pain threshold in males [16], resulting in higher catecholamine release [20].</td>
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<tr>
<td>Acute and chronic opioid use [15,22].</td>
<td>Increased oedema and stretch of gut</td>
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<td>Previous abdominal surgery [22].</td>
<td>µ-opioid receptor stimulation ameliorates peristalsis [18,23].</td>
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<td>Pre-existing airways/peripheral vascular disease [17].</td>
<td>Increased need for adhesiolysis, increased bowel handling</td>
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<td>Long duration of surgery [15,17].</td>
<td>Reduced physiological reserve</td>
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<tr>
<td>Emergency surgery [16,19]</td>
<td>Increased bowel handling [21] and opiate use</td>
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<tr>
<td>Blood loss and need for transfusion [15,17,22,24].</td>
<td>Increased inflammatory and catecholamine response; secondary causes of POI</td>
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<tr>
<td>Procedures requiring stomas [19].</td>
<td>Increased crystalloid administration resulting in oedema</td>
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<td>Oedema in abdominal wall muscle and cut bowel</td>
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Prevention

- General anesthesia: no effect
- Regional anesthesia: no effect
- Epidural:
  - Block afferent and efferent inhibitory reflexes
  - Thoracic vs. lumber
  - Bupivacaine vs. opioids
- Routine NG
  - Increases morbidity
  - Doesn’t diminish duration of ileus
  - In treatment of established ileus
Prevention

- Mobilization:
  - Not demonstrated to diminish duration of postoperative ileus

- Early feeding:
  - Most of recent studies showed significant decrease of postoperative ileus

- Laparoscopic surgery:
  - Less stress, less endo morphine, smaller incision
  - Minimal improvement over open if early feeding in both
Salt and water overload

- Surgery causes an increase in ADH, cortisol and aldosterone leading to salt and water retention.
- Liberal perioperative fluid \( \rightarrow \) 2–3 kg wt gain, with redistribution of fluid to the interstitial space.
- Oedema can also increase the risk of POI and anastomotic leak.
- The Na\(^+\)/H\(^+\) ion exchange protein (NHE) is activated by oedema-induced mechanical stretch.
- NHE reduces contractility, providing a clue to the mechanism behind the inhibition of peristalsis resulting from oedema-induced mechanical stretch.
Alvimopan

- μ-opioid receptors are the primary mediators of opioid analgesic effects in the central nervous system, and also the origin of gastrointestinal side effects.
- Alvimopan is a peripherally acting μ-opioid receptor antagonist, does not cross the BBB.
- A meta-analysis alvimopan vs. placebo on POI after major abdominal surgery:
  - alvimopan accelerated recovery of GIT by 1.3 days Hazard Ratio (HR) 1.16 to 1.45 d, P < 0.00001
- Postoperative analgesic effects were not diminished.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism</th>
<th>Benefit</th>
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<tbody>
<tr>
<td>Salt and fluid overload</td>
<td>↓ gut oedema and stretch</td>
<td>++</td>
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<tr>
<td>Carbohydrate loading</td>
<td>↓ insulin resistance</td>
<td>±</td>
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<tr>
<td>Routine nasogastric tubes</td>
<td>Prophylactic drainage of stomach</td>
<td>–</td>
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<tr>
<td>Intravenous lidocaine</td>
<td>Anti-inflammatory; opioid-sparing</td>
<td>+</td>
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<tr>
<td>Coffee</td>
<td>Stimulatory effect</td>
<td>+</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>Stimulatory effect</td>
<td>+</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Opioid sparing; anti-inflammatory</td>
<td>++</td>
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<tr>
<td>Early enteral nutrition</td>
<td>Anabolic; ↓ insulin resistance; stimulatory</td>
<td>++</td>
</tr>
<tr>
<td>Laparoscopic surgery</td>
<td>↓ tissue trauma; ↓ bowel handling; ↓ inflammatory reaction</td>
<td>++</td>
</tr>
<tr>
<td>Alvimopan</td>
<td>μ-opioid receptor antagonist</td>
<td>++</td>
</tr>
<tr>
<td>Mid-thoracic epidural anaesthesia</td>
<td>↓ inflammatory response; ↓ sympathetic stimulation; ↓ opioid requirement</td>
<td>++</td>
</tr>
<tr>
<td>Early mobilisation</td>
<td>? anabolic effect</td>
<td>+/-</td>
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<tr>
<td>Nicotine</td>
<td>Colonic prokinetic</td>
<td>+</td>
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<tr>
<td>Daikenchuto</td>
<td>Anti-inflammatory on acetylcholine receptors</td>
<td>+</td>
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<tr>
<td>Magnesium sulphate</td>
<td>Anaesthetic effect</td>
<td>+</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>Prokinetic effect</td>
<td>±</td>
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</tbody>
</table>
Novel therapeutic strategies

- Neural blockade with local anaesthetic or antagonists
- Suppression of the inflammatory cascade
  - systemic administration of corticosteroids
  - focused approach whereby specific pathways in the response to the surgical insult may be targeted
Novel therapeutic strategies

- Manipulation of gastrointestinal neuropeptides
  - Octreotide inhibits the release of many GIT hormones via direct action on neurons in the ENS
  - Octreotide, in a canine model, accelerated postoperative GIT transit at low doses
  - In healthy human volunteers Octreotide accelerated gastric emptying but delayed mouth-to-caecum transit time
Novel therapeutic strategies

- A more generalized approach to the manipulation of gastrointestinal neuropeptides in the postoperative period may be achievable by gum chewing.

- It was initially postulated that this ‘sham feeding’ would stimulate the cephalic phase of digestion and produce a neurohormonal milieu conducive to gut recovery.
Novel therapeutic strategies

- Oral water-soluble hyperosmotic contrast media, such as gastrografin, have been shown to be of therapeutic benefit by drawing fluid out of the bowel wall into the gut lumen, thereby reducing dysfunction and promoting peristalsis.
Conclusions

- The pathophysiological 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.

- Novel therapeutic strategies should target individual pathways in the pathogenesis of ileus, such as neural blockade, suppression of inflammation, mechanical reduction of oedema and gut neuropeptide manipulation.