Therapeutic Update on Management of Postoperative Ileus

A podcast educational activity based on a live symposium
Available at www.postopileus.org

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Therapeutic Update on Management of Postoperative Ileus

Agenda

Part 1
Enhanced Recovery Surgery: State of the Art
Anthony Senagore, M.D., M.S., M.B.A., FACS, FASCRS

Part 2
Impact of Anesthesia and Analgesia on Postoperative Ileus: A View from “Above the Screen”
T.J. Gan, M.B., B.S., FRCA

Part 3
Emerging Pharmacologic Options for Managing Postoperative Ileus
Conor P. Delaney, M.D., M.Ch., Ph.D., FRCSI, FACS

Faculty

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Therapeutic Update on Management of Postoperative Ileus

Overview

One of the most common causes of extended length of hospital stay following abdominal surgery is postoperative ileus (POI), which is temporary impairment of gastrointestinal motility characterized by abdominal distension and pain, delayed passage of gas and stool, nausea and vomiting, and diminished appetite. The condition may delay patient ambulation, increasing the risk for pulmonary and thromboembolic complications, and it may delay enteral feedings or resumption of a solid diet, resulting in poor nutrition with delayed wound healing. The use of opioid analgesics for postoperative pain relief often exacerbates POI. Current management strategies consist of careful selection of anesthetic and analgesic choices before, during, and after surgery, along with the avoidance of nasogastric tube feedings and the use of supportive therapies. State-of-the-art enhanced-recovery surgery protocols incorporate these management strategies to improve patient recovery, shorten length of stay related to postoperative ileus, and reduce resource consumption.

This symposium will provide an update on the therapeutic management of postoperative ileus, beginning with an overview of the components of enhanced-recovery surgery protocols. The impact of choice of surgery type, anesthesia, and analgesia on POI will be presented, emphasizing the multidisciplinary responsibility for managing POI. The results of current clinical research exploring the potential use of peripherally selective μ-opioid receptor antagonists following major abdominal surgery as a means to prevent and minimize the impact of POI will also be presented.

Learning Objectives

At the conclusion of this symposium, participants should be able to

- Describe the pathophysiology of postoperative ileus.
- Describe the rationale for at least three components of enhanced-recovery surgery protocols.
- Describe the relative benefits of balanced anesthesia and epidural analgesia with respect to postoperative ileus.
- Identify two options for optimizing postoperative analgesia while minimizing opioid-related adverse effects.
- Describe recent clinical research into new and emerging pharmacologic options for preventing and managing postoperative ileus.
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Therapeutic Update on Management of Postoperative Illeus

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The faculty and planners report the following relationships:

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Conor P. Delaney declares that he has served as a speaker and consultant for and has received a research grant from Adolor Corporation and Covidien; he has also served as a speaker for and received a research grant from Ethicon Endo-Surgery, Inc.

T.J. Gan, M.B., B.S., FRCA

Dr. Gan declares that he has received a research grant from Progenics Pharmaceuticals, Inc.

Anthony Senagore, M.D., M.S., M.B.A., FACS, FASCRS, Program Chair

Dr. Senagore declares that he has served on the advisory board for Adolor Corporation and Ethicon Endo-Surgery, Inc.

Carla J. Brink, M.S., R.Ph.

Ms. Brink declares that she has no relationships pertinent to this activity.
Anthony Senagore, M.D., is Vice President of Research and Medical Education at Spectrum Health, a not-for-profit health system in West Michigan. He also serves as Professor of Surgery at Michigan State University (MSU) and as staff surgeon for Michigan Medical, P.C.

Dr. Senagore earned his Doctor of Medicine degree from MSU, followed by a residency in general surgery at the Butterworth Hospital/MSU program in Grand Rapids. He then completed a research fellowship and colon and rectal surgery residency at Ferguson Hospital on the Grand Rapids and East Lansing campuses of MSU. He continued his education and later received his Master of Science degree in physiology from MSU and Master in Business Administration from the University of Phoenix on the San Francisco campus.

Before assuming his current position, Dr. Senagore served as Krause-Lieberman Chair in laparoscopic colorectal surgery at The Cleveland Clinic. While at the Clinic, he was also Medical Director in the Office of Medical Operations and Associate Chief of Staff. He served as the Chairman of the Department of Surgery at the University of Toledo, College of Medicine.

Dr. Senagore is board certified in general surgery and colon and rectal surgery. He is a fellow in the American College of Surgeons (ACS) and the American Society of Colon and Rectal Surgeons (ASCRS). He is a member of numerous organizations, including the Association for Academic Surgery, Central Surgical Association, Society of Critical Care Medicine, Midwest Surgical Association, International Society of University Colon and Rectal Surgeons, and the Society of American Gastrointestinal Endoscopic Surgeons. He currently serves as President-Elect for the American Society of Colon and Rectal Surgeons.

Dr. Senagore specializes in laparoscopic bowel resection, surgical management of Crohn’s disease and ulcerative colitis, sphincter-preserving surgery for rectal cancer, treatment of anal incontinence and constipation, and management of ano-rectal disorders. Among his many clinical and research interests are surgical innovations in laparoscopic bowel surgery, molecular and genetic changes in colorectal cancer, and new surgical treatments for incontinence and constipation. He has lectured on various topics related to colon and rectal surgery, edited a textbook in colon and rectal surgery, and authored more than 100 peer-reviewed publications and 15 textbook chapters. Dr. Senagore is a national and international speaker on colorectal surgical topics.
Therapeutic Update on Management of Postoperative Ileus

Overview

Traditionally, postoperative stay following major gastrointestinal surgery has been 5-10 days, with recent Medicare data revealing a mean length of stay of 11.3 days for DRG 148. The emphasis on reducing resource use brought about by transitions in payment for medical services, coupled with improved understanding of perioperative physiology, have substantially reduced the length of hospitalization after colectomy. Another factor contributing to the reduced length of stay has been the greater use of minimally invasive surgical techniques, which have been associated with postoperative stays of 2.1 to 4.5 days.

A variety of factors contribute to the length of stay following major gastrointestinal surgery, including inadequate analgesia, nausea and vomiting, delay in ileus resolution, and stress-induced organ dysfunction. In addition, iatrogenic factors, such as the use of nasogastric tubes, transabdominal drains, and enforced malnutrition and bed rest, adversely affect patient recovery after colectomy. This presentation will provide an overview of components of “enhanced-recovery” surgery protocols that permit rapid recovery and early discharge from the hospital without adverse events related to the accelerated nature of the postoperative care. The pathophysiology of postoperative ileus will be discussed, as well as how enhanced-recovery surgery protocols can help prevent and manage POI. Our experience indicates that the use of enhanced-recovery protocols is well tolerated by all patient cohorts regardless of co-morbidity or complexity of procedure, and a key component of success is patient education. When the principles of enhanced-recovery care and daily benchmarks, including discharge criteria, are shared with patients before admission and reinforced daily during hospitalization, patients enthusiastically accept the process. The ability of the modern abdominal surgeon to embrace these concepts of enhanced recovery after surgery has the potential of allowing patients to be discharged substantially earlier from the hospital, reducing rates of nosocomial infection, allowing more efficient use of hospital beds, and reducing hospital costs.

Presentation Objectives

At the conclusion of this presentation, participants should be able to

- Describe the pathophysiology of postoperative ileus (POI).
- Explain the importance of improving recovery of perioperative bowel function.
- Identify patients who are at greatest risk of developing opioid-induced bowel dysfunction and POI.
- Describe the rationale for at least three components of enhanced-recovery surgery protocols.
- Define the pharmacoeconomic benefits of enhanced management of POI.
Clinical Case

POI following open sigmoid colectomy

A 73-year-old man underwent open sigmoid colectomy with node dissection

• Early postoperative course (POD 0 to <6):
  NPO, nausea and vomiting, adequate pain control with PCA using morphine, "quiet" abdominal sounds, mild distension, no flatus passage

• POD 6: Patient still unable to eat, family concerned
  
  Cause for concern and intervention?
  
  POD = postoperative day, PCA = patient-controlled analgesia

POI: Definition

• Ileus: functional inhibition of propulsive bowel activity, irrespective of pathogenetic mechanisms

• POI: transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake

  – Primary POI: such cessation occurring in the absence of any precipitating complication
  – Secondary POI: that occurring in the presence of a precipitating complication

• Paralytic ileus: form of POI lasting >5 days after surgery


Primary POI: Response by Different Intestinal Segments

Average time to resolution of POI after major abdominal surgery

- Small intestine: 0-24 hours
- Stomach: 24-48 hours
- Colon: 48-120 hours

Risk Factors for POI

• Surgery, particularly abdominal surgery
• Surgical technique
• Extended opioid use
• Inhaled anesthesia
• Pre-existing gastrointestinal (GI) disease
• Stress (in addition to physiologic stress of surgery)?
• Inactivity?
Manifestations and Consequences of Prolonged POI

- Delayed passage of flatus and stool
- Increased postoperative pain and cramping
- Increased nausea and vomiting
- Delay in resuming oral intake
  - Possible need for parenteral nutrition
- Poor wound healing
- Delay in postoperative mobilization


Incidence of POI for Common Abdominal Surgeries

<table>
<thead>
<tr>
<th>Procedure Description</th>
<th>Procedures, n</th>
<th>POI Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal hysterectomy</td>
<td>456,292</td>
<td>4.1</td>
</tr>
<tr>
<td>Large bowel resection</td>
<td>257,336</td>
<td>14.9</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>48,824</td>
<td>19.2</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>175,964</td>
<td>6.2</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>81,013</td>
<td>8.5</td>
</tr>
<tr>
<td>Nephroureterectomy</td>
<td>44,808</td>
<td>8.9</td>
</tr>
<tr>
<td>Other procedures</td>
<td>597,492</td>
<td>9.0</td>
</tr>
<tr>
<td>Total</td>
<td>1,661,729</td>
<td>8.5</td>
</tr>
</tbody>
</table>

HCFA data (Medicare, 1999-2000), evaluating 161,000 major intestinal and colorectal resections from 150 U.S. hospitals


How Long Can POI Last?

A long time for a majority of abdominal surgery patients


POI: Pathogenesis Is Multifactorial

- Inhibitory Neural Reflexes
  - Stimulation of somatic and visceral fibers inhibits GI motility
- Opioids
  - Endogenous and exogenous opioids reduce propulsive activity in GI tract
- Minimizing the effects of one or more of these factors could potentially shorten the duration of POI and reduce the incidence of morbidity

Possible Mechanisms of POI

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factors Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic nervous system</td>
<td>Sympathetic inhibitory pathways</td>
</tr>
<tr>
<td>Enteric nervous system</td>
<td>Substance P, nitric oxide</td>
</tr>
<tr>
<td>Hormonal or neuroendocrine system</td>
<td>Vasoactive intestinal peptide; corticotropin-releasing factor ligands; calcitonin gene-related peptide ligands</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Macrophage and neutrophil infiltration, cytokines, other inflammatory mediators</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>General anesthetics</td>
</tr>
<tr>
<td>Pain</td>
<td>Exogenous and endogenous (endorphins, enkephalins, dynorphins) opioids</td>
</tr>
</tbody>
</table>


Opioids and their Effects on GI Function

- Endogenous opioids are released as part of the stress response in the postoperative period.1
- Exogenous opioids are the most potent and commonly used analgesics for control of postoperative pain.2
- Both types of opioids activate the same receptor sites and affect a variety of GI functions, including1,2
  - Motility
  - Secretion
  - Transport of electrolytes and fluids
- Opioids have been shown to2
  - Profoundly inhibit peristaltic activity
  - Delay gastric emptying and intestinal transit
  - Play an important role in precipitating prolonged POI


Morphine or Incision Length Correlated with Return of Bowel Function?

- Colectomy patients (n = 40)
  - Primarily left colon and rectal procedures
- Return of bowel function?
  - Correlation between morphine PCA dose and first bowel sounds (P<0.001), flatus (P=0.003), and first bowel movement (shown; P=0.002)
  - No correlation between incision length and morphine dose


Preventive and Therapeutic Management Options for POI

- **Physical options**
  - Nasogastric tube
  - Early postoperative feeding
  - Early ambulation
- **Surgical technique**
  - Laparoscopy
- **Psychological perioperative information**
  - Multimodal clinical pathways
  - Fluid and sodium restriction?
- **Anesthesia and analgesia**
  - Epidural
  - NSAIDs
- **Pharmacologic**
  - Prokinetic agents
  - Opioid (PAMOR) antagonists
  - Other agents

NSAIDs = nonsteroidal anti-inflammatory drugs
PAMOR = peripherally acting mu-opioid receptor


Components of a Multimodal Enhanced-Recovery Protocol for POI

- **Surgical management**
  - Laparoscopic approach
- **Pain management**
  - Epidural (local) analgesia
  - Opioid-sparing techniques
  - Minimize opioid PCA
  - Supportive patient care elements
    - Avoidance of nasogastric tube (NGT)
    - Fluid restriction
    - Early oral feeding
    - Early ambulation
  - Pharmacologic management
    - PAMOR antagonist


Nasogastric Intubation

- Selective vs. routine NGT was compared in a meta-analysis of 26 randomized clinical trials (3964 patients)
  - Patients without nasogastric (NG) tubes
    - Had a significantly lower rate of fever, atelectasis, and pneumonia
    - Were able to tolerate an oral diet significantly earlier
    - Experienced abdominal distension and vomiting more frequently
  - “For every patient requiring insertion of a NGT in the postoperative period, at least 20 patients will not require NG decompression…”
    - “Routine NG decompression is considered detrimental by meta-analysis of the literature.”

RCTs of Early Postoperative Feeding vs. Traditional Feeding

RCTs = randomized controlled trials; D = defecation; F = flatus; C = combination score; I = ingest regular food

Early feeding

Traditional feeding (no oral intake until POI resolved)

Binderow et al. (1994)
Reissman et al. (1995)
Ortiz et al. (1996)
Schilder et al. (1997)
Stewart et al. (1998)
Pearl et al. (1998)
Cutillo et al. (1999)

Duration of Ileus (h)

Laxatives

• Only 1 RCT, involving 20 patients, in literature
• Commonly used in combination with prokinetic agents and with other multimodal treatments (e.g., epidural, early feeding, early ambulation)
  – Stimulant laxatives: most commonly used senna compounds and bisacodyl
  – Bulking agents and nonabsorbable compounds: lactulose can cause bloating
  – Osmotic laxatives (poorly absorbable ions magnesium or phosphate) can cause metabolic disturbances, particularly in presence of renal impairment

Binderow et al. (1994)
Reissman et al. (1995)
Ortiz et al. (1996)
Schilder et al. (1997)
Stewart et al. (1998)
Pearl et al. (1998)
Cutillo et al. (1999)

Metoclopramide

• MOA: combined cholinergic and serotonergic agonist, and dopaminergic antagonist – limited to the proximal gut
• 6 prospective, randomized, blinded, placebo-controlled trials
  – 16-115 patients per trial up to 5 days
  – Metoclopramide started on day of surgery
  – Doses: 10 mg i.v. every 6 hours to 20 mg every 8 hours
• None of the studies showed any benefit from metoclopramide as a POI therapy in any outcome(s)
• Adverse effects in 15-20% of patients
  – Drowsiness, dystonic reactions, agitation
  – More common in patients <30 years

RCT: Fast Track vs. Traditional Care

<table>
<thead>
<tr>
<th></th>
<th>Fast track (n = 32)</th>
<th>Traditional (n = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS for patients &lt;70 yr (days)</td>
<td>4.7</td>
<td>5.8</td>
<td>0.01</td>
</tr>
<tr>
<td>LOS for patients treated by 'enhanced-recovery' surgeons (days)</td>
<td>3.8</td>
<td>5.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain score on discharge</td>
<td>3.1</td>
<td>3.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Satisfaction with stay</td>
<td>8.1</td>
<td>8.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Readmissions</td>
<td>3</td>
<td>6</td>
<td>0.45</td>
</tr>
</tbody>
</table>

LOS = length of stay (counting day of surgery as day 0)


Short-term Outcomes of Laparoscopic Resection after Colorectal Cancer

- Meta-analysis of RCTs up to 2002
- 2512 cases in 12 trials,* random effects model

Relative improvements with laparoscopy

- Flatus ↓ 34% (25-37)
- Toleration of diet ↓ 24% (0-34)
- Pain at 6 h ↓ 35% at rest, ↓ 34% coughing
- Pain at 3 days ↓ 63% at rest, ↓ 40% coughing
- Narcotic use at 48 h ↓ 37% (13-72)

*Patients were not subjected to the same postoperative regimens


Economic Considerations with POI

- Most common reason for delayed discharge after abdominal surgery
- Annual U.S. healthcare costs estimated to be $750 million to $1 billion, due to
  - Nasogastric intubation
  - I.V. hydration and nutrition
  - Extra nursing care
  - Longer hospital stay
  - Additional laboratory testing
- Possible benefits of effective POI management for selected patients due to
  - Shortened hospital stay
  - Reduced use of resources
  - Fewer complications
  - Fewer readmissions


Clinical Impact of POI

- Increased postoperative pain
- Increased nausea and vomiting
  - Increased risk of aspiration
- Prolonged time to regular diet
  - Delayed wound healing
  - Increased risk of malnutrition or catabolism
- Prolonged time to mobilization
  - Increased pulmonary complications
- Prolonged hospitalization
  - Increased healthcare costs

Delayed recovery


Economic Burden of POI

- Nasogastric (NG) intubation
- I.V. hydration
- Additional nursing care
- Lab tests
- Increased hospital days


Overall Healthcare Burden Associated with POI

- Increased resource use
- Increased nursing time
- Prolonged hospitalization
- Beds occupied for more time
- Decreased patient satisfaction

Estimate of Potential Savings

22 million inpatient surgical procedures annually
2.7 million procedures lead to POI (>1 day)
750,000 patients discharged 1 day earlier (with effective management of POI)
Potential savings of $1.1 billion/year

Resources Used by Major Intestinal or Rectal Resection Annually

- Between October 1999 and September 2000, 161,000 Medicare patients underwent this type of surgery
- They stayed approximately 1.8 million days in hospital and consumed $1.75 billion


Keeping Track of (Coding for) POI

ICD-9- CM code 997.4
- Digestive system complications
  - Complications of intestinal (internal anastomosis and bypass not elsewhere classified, except that involving the urinary tract)

ICD-9- CM code 560.1
- Adynamic ileus; ileus (of intestine) (of bowel) (of colon); paralysis of intestine or colon

ICD-9- CM code 564.4
- Other postoperative functional disorders
  - Diarrhea following gastrointestinal surgery

Recorded Rate and Economic Burden Associated with Postoperative Ileus

- Studied POI prevalence, consequent economic burden in 2002
- Data from Premier’s Perspective™ Comparative Database (includes 5 million discharges annually)
- 806,081 surgical patients identified for evaluation of rate of POI
  - Open laparotomies, incisional procedures, non-incisional procedures, orthopedics, thoracic surgeries, etc. (645 primary surgery codes)
- POI identified using ICD-9 diagnosis codes 560.1 and 997.4
- "Comparison with estimates of incidence in published literature suggest that in practice, POI may not be routinely coded and therefore, the overall recorded rate and economic burden of illness found in our study may be underestimated."


Recorded Rate and Economic Burden Associated with Postoperative Ileus

Coded POI Associated with Selected Surgical Procedures

Saunders WB et al. ASHP MCM. Orlando, FL: 2004 Dec 7. Abstract P440E.
Recorded Rate and Economic Burden Associated with Postoperative Ileus

Hospitalization Outcomes of Patients with and without POI

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mean Time to Dx of POI (days)</th>
<th>Time from Dx to Discharge (days)</th>
<th>Mean LOS (days)</th>
<th>Total Mean Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAH</td>
<td>18.2 %</td>
<td>3.1</td>
<td>3.8</td>
<td>6.9 vs. 3.7</td>
</tr>
<tr>
<td>HC</td>
<td>30.2 %</td>
<td>2.5</td>
<td>NA</td>
<td>20.3 vs. 8.4</td>
</tr>
</tbody>
</table>

*Compared with a sample of TAH patients who did not have PPOI
*Compared with total average costs for those without PPOI
*Compared with a sample of HC patients who did not have PPOI
*Compared with total average costs for those without PPOI

PPOI = prolonged POI; TAH = total abdominal hysterectomy; HC = hemicolectomy

Saunders WB et al. ASHP MCM. Orlando, FL; 2004 Dec 7. Abstract P440E.

Surgeons’ Roles...

- What is our role in the multimodal approach to the prevention and management of POI?

Enhanced-Recovery Surgery Protocols

- Form multidisciplinary team
- Re-evaluate procedures to ensure all components of fast-track surgery are implemented
- Evaluate entire perioperative period

Patient Education

- Medication protocol
- Postoperative expectations
- Benefits of early ambulation
- Hydration
- Resuming diet

Pain Management Education

- Preoperative pain assessment
- Pain management
  - Descriptive pain scales
- Techniques to decrease opioid burden
- Selective opioid-receptor antagonists
  - Mitigate adverse GI effects of opioids
  - Preserve analgesia

Salvador CG et al. 46th MCM. Orlando, FL; 2004 Dec 7. Abstract P402E.
Patient Advocacy

• Provide patient with necessary information

• Assess patient’s understanding of and potential compliance with preoperative and postoperative instructions

Patient Satisfaction

• Enhance the patient’s perianesthesia experience
  – Optimize patient care, satisfaction, and comfort

• Reduce the patient’s postoperative length of stay
  – Ensure efficient and cost-effective patient evaluation

Conclusions

• POI affects between 4% and 20% of patients undergoing abdominal surgery annually and has a detrimental effect on clinical outcomes and costs of care

• Accelerating recovery of GI function by using enhanced-recovery programs improves clinical outcomes, enhances patient comfort, and shortens hospital length of stay

• Enhanced-recovery surgery protocols should include both pharmacologic and nonpharmacologic approaches for managing POI

End of Presentation

• You have reached the end of this presentation.

• Please select another presentation from the left menu.
Selected References


Therapeutic Update on Management of Postoperative Ileus


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T. J. Gan, M.B., B.S., FRCA, is Professor and Vice Chairman for Clinical Research in the Department of Anesthesiology at Duke University Medical Center in Durham, North Carolina. He also serves on the faculty at the Duke Clinical Research Institute and as a Senior Research Fellow at the Duke Center for Integrative Medicine.

Dr. Gan has received numerous awards, including the Society of Ambulatory Anesthesia Young Investigator Award and the International Anesthesia Research Society (IARS) Clinical Scholar Research Award. He is a member of several professional organizations, including the American Society of Anesthesiologists and the International Anesthesia Research Society. Dr. Gan is the President Elect of International Society of Anesthetic Pharmacology and The Society of Ambulatory Anesthesia. He serves on the editorial board of *Anesthesia Analgesia, Acute Pain,* and *Clinical Research,* and he is a reviewer for many scientific journals.

Dr. Gan has served as an invited speaker for many national and international professional conferences and as principal investigator or co-investigator for many clinical trials. His research explores a variety of topics, such as prevention of postoperative nausea and vomiting, opioids, fluid management during surgery, intravenous anesthesia, and postoperative pain. He is the author or co-author of more than 100 scientific articles in peer-reviewed medical journals, as well as numerous abstracts, reviews, and textbook chapters.
Overview

In the United States, length of stay for patients undergoing bowel resection ranges from 5–14 days. Cost per hospital stay has been estimated to be approximately $8000 more for patients with postoperative ileus (POI) compared with patients without POI. Moreover, POI is associated with increased postoperative morbidity and prolonged hospital stays. Therefore, accelerating GI recovery after bowel resection via patient management or pharmacologic approaches would represent a clinically important addition to the standard of care.

Anesthetic and perioperative factors have a significant impact on the incidence and severity of POI, as well as on other postoperative outcomes. These factors can include opioid use, type and volume of fluid administration, anesthetic techniques, and other drugs used in the perioperative period. This presentation discusses the perioperative factors of interest and presents strategies that have been demonstrated to reduce the incidence and severity of POI and other related postoperative adverse events.

Presentation Objectives

At the conclusion of this presentation, participants should be able to

- Describe the impact of anesthetic and perioperative factors on postoperative ileus.
- Identify effective perioperative management strategies for reducing the incidence and severity of postoperative ileus and minimizing opioid-related adverse effects.
Impact of Anesthesia and Analgesia on Postoperative Ileus: A View from “Above the Screen”

T.J. Gan, M.B., B.S., FRCA
Professor and Vice Chairman
Department of Anesthesiology
Duke University Medical Center
Durham, North Carolina

Outline

• Incidence of postoperative gastrointestinal dysfunction
• Anesthetic and analgesic factors
  – Opioids
  – Inhalational agents and nitrous oxide
  – Fluid administration
• Multimodal management strategy
  – Preoperative education
  – Combination analgesics
  – Epidural
  – Peripheral opioid antagonists

Incidence of POI in Surgeries

<table>
<thead>
<tr>
<th>Procedure Description</th>
<th>Procedures, N</th>
<th>POI Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal hysterectomy</td>
<td>456,292</td>
<td>4.1</td>
</tr>
<tr>
<td>Large bowel resection</td>
<td>257,336</td>
<td>14.9</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>48,824</td>
<td>19.2</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>175,964</td>
<td>6.2</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>81,013</td>
<td>8.5</td>
</tr>
<tr>
<td>Nephroureterectomy</td>
<td>44,808</td>
<td>8.9</td>
</tr>
<tr>
<td>Other procedures</td>
<td>597,492</td>
<td>9.0</td>
</tr>
<tr>
<td>Total</td>
<td>1,661,729</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Other Surgery

<table>
<thead>
<tr>
<th>Procedure Description</th>
<th>Procedures, N</th>
<th>POI Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip and knee arthroplasties</td>
<td>2949</td>
<td>2.1</td>
</tr>
<tr>
<td>Radical cystectomy</td>
<td>304</td>
<td>18</td>
</tr>
</tbody>
</table>

POD = postoperative day
GI = gastrointestinal

Possible Mechanisms of POI

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Factors Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic nervous system</td>
<td>Sympathetic inhibitory pathways</td>
</tr>
<tr>
<td>Enteric nervous system</td>
<td>Substance P, nitric oxide</td>
</tr>
<tr>
<td>Hormonal or neuroendocrine system</td>
<td>Vasoactive intestinal peptide; corticotropin-releasing factor ligands; calcitonin gene-related peptide ligands</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Macrophage and neutrophil infiltration; cytokines; other inflammatory mediators</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>General anesthetics</td>
</tr>
<tr>
<td>Pain</td>
<td>Exogenous and endogenous (endorphins, enkephalins, dynorphins) opioids</td>
</tr>
</tbody>
</table>

Opioids and their Effects on GI Function

• Endogenous opioids are released as part of the stress response in the postoperative period
• Both types of opioids activate the same receptor sites and affect a variety of GI functions, including
  – Motility
  – Secretion
  – Transport of electrolytes and fluids
• Opioids have been shown to
  – Profoundly inhibit peristaltic activity
  – Delay gastric emptying and intestinal transit
  – Precipitating prolonged POI

HCFA data (Medicare, 1999-2000), evaluating 161,000 major intestinal and colorectal resections from 150 U.S. hospitals; POI = postoperative ileus


Effects of Opioids on the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Pharmacologic action</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Gastric motility and emptying</td>
<td>↓ Appetite, ↑ gastro-esophageal reflux</td>
</tr>
<tr>
<td>↓ Pyloric tone</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>↓ Enzymatic secretion</td>
<td>Delayed digestion; hard, dry stools</td>
</tr>
<tr>
<td>Inhibition of small and large bowel propulsion</td>
<td>Delayed absorption, straining, bloating, abdominal distension, constipation</td>
</tr>
</tbody>
</table>


Patient Preferences for Treatment of Acute Pain

Patients prefer avoiding side effects over complete pain control

Pain control 41%  
Side effect severity 19%  
Side effect type 28%  
Setting and route of administration 12%


Symptom Distress Score (SDS) Questionnaire


Symptom Distress Score (SDS) Questionnaire


Opioid Dose and Clinically Meaningful Opioid-related Adverse Events

Colectomy patients (n = 40)
- Primarily left colon and rectal procedures

Return of bowel function?
- Correlation between morphine PCA dose and first bowel sounds (P = 0.001), flatus (P = 0.003), and first bowel movement (shown; P = 0.002)
- No correlation between incision length and morphine dose

PCA = patient-controlled analgesia

Management Strategies for POI
- Prevention
  - Anesthetic choice
  - Surgical techniques
  - Opioid-sparing analgesics
- Supportive care
  - NG tube insertion
  - Mobilization
  - Early oral feeding
  - Fluid management
  - Prokinetic agents
    - Cisapride*
    - Erythromycin
    - Metoclopramide

NG = nasogastric
*Not available in the United States

Analgesics and the Pain Pathway

Morphine Consumption – 24 hours

Multimodal or Balanced Analgesia

Opioid

- Doses of each analgesic
- Improved anti-nociception due to synergistic/additive effects
- May reverse adverse effects of each drug

Thoracic Epidural Anesthesia/Analgesia

- All anesthetics may depress GI motility
- Reduced ileus is a significant benefit of thoracic epidural anesthesia and analgesia vs. general anesthesia and systemic opiates
  - GI function may return 2-3 days earlier!


Thoracic Epidural Anesthesia/Analgesia (cont)

- Mechanisms by which thoracic epidural anesthesia may promote GI motility
  - Blockade of nociceptive afferent nerves
  - Blockade of thoracolumbar sympathetic efferent nerves
  - Unopposed parasympathetic efferent nerves
  - Reduced need for postoperative opiates
  - Increased GI blood flow
  - Systemic absorption of local anesthetic


RCTs of Epidural Anesthesia/Analgesia vs. Systemic Opiates

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of Ileus (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al. (1986)</td>
<td>8.8 (5.4)</td>
</tr>
<tr>
<td>Schwartz et al. (1987)</td>
<td>7.5 (4.1)</td>
</tr>
<tr>
<td>Alfieri et al. (1988)</td>
<td>7.5 (4.1)</td>
</tr>
<tr>
<td>Watanabe et al. (1989)</td>
<td>7.5 (4.1)</td>
</tr>
<tr>
<td>Rehbein et al. (1990)</td>
<td>7.5 (4.1)</td>
</tr>
<tr>
<td>Lou et al. (1995)</td>
<td>7.5 (4.1)</td>
</tr>
<tr>
<td>Neubacher et al. (1999)</td>
<td>7.5 (4.1)</td>
</tr>
</tbody>
</table>

*P < 0.05

RCTs = randomized controlled trials
C = combination score; D = defecation; F = flatus

Advice on Epidural to Prevent POI

- Epidural must be in place before surgical stress and nociceptive afferent stimulation begin
- Catheter should be placed to cover T5 to L2 dermatomes to affect both upper and lower GI innervation
- Epidural local anesthetics with opioids should be included and administered postoperatively until bowel function returns

Nitrous Oxide and Bowel Dysfunction

Nitrous oxide increases the incidence of bowel distension in patients undergoing elective colon resection

Neudecker et al. (1999)

Anaesthetic technique does not influence postoperative bowel function: a comparison of propofol, nitrous oxide and isoflurane

Goal-Directed Intraoperative Fluid Administration Reduces Length of Hospital Stay after Major Surgery

- 100 ASA II and III patients
- Surgery with expected blood loss > 500 mL
- Intraoperative goal-directed fluid management vs. control
- Background crystalloid infusion and colloid bolus
- Fluid management algorithm with EDM
- Primary outcome: length of stay (LOS)

ASA II and III = American Society of Anesthesiology grade II and III
EDM = esophageal Doppler monitor

Goal-Directed Fluid Management

### Days

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Tolerating Solids</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05


Perioperative Plasma Volume Expansion Reduces the Incidence of Gut Mucosal Hypoperfusion during Cardiac Surgery

- 60 ASA III patients
- Protocol and control groups
- Fluid optimization with EDM in protocol group
- Standard practice in control group
- 200 mL 6% hetastarch to maintain maximum stroke volume (SV)


Perioperative Plasma Volume Expansion Guided by EDM

<table>
<thead>
<tr>
<th>Control</th>
<th>Protocol</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pHi &lt;7.32</td>
<td>56%</td>
<td>7%</td>
</tr>
<tr>
<td>Complications</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>ICU Days</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>Hospital Days</td>
<td>10.1</td>
<td>6.4</td>
</tr>
</tbody>
</table>

pHi = gastric mucosa pH; ICU = intensive care unit


I.V. Fluid Restriction

- MOA: salt/water restriction improves canine gastric emptying time
- Lobo et al. compared standard (>3 L/day fluids, 154 mmol/day sodium) with restricted (<2 L/day fluids, 77 mmol/day sodium) protocols after open hemicolectomy
- Significantly more complications in standard treatment


Effect of Intraoperative Fluid Management on Outcome after Intraabdominal Surgery

- Elective intraabdominal surgery
- Crystalloid: lactated Ringer’s solution
- Randomized into 2 groups
  - Liberal fluid regimen: 10 mL/kg followed by 12 mL/kg/hr
  - Restricted regimen: 4 mL/kg/hr
- Primary outcome: death or complications

<table>
<thead>
<tr>
<th></th>
<th>Liberal Group</th>
<th>Restrictive Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume received (mL)</td>
<td>3878 ± 1170</td>
<td>1408 ± 946</td>
<td></td>
</tr>
<tr>
<td>Patients with</td>
<td>31%</td>
<td>17%</td>
<td>0.046</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to bowel</td>
<td>6 (4-9)</td>
<td>4 (3-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>movement (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>9 (7-24)</td>
<td>8 (6-21)</td>
<td>0.01</td>
</tr>
</tbody>
</table>


**TABLE 3. Number of Patients With Complications (Per-Protocol Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Restricted Group</th>
<th>Standard Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complications</td>
<td>21</td>
<td>40</td>
<td>0.003</td>
</tr>
<tr>
<td>Major complications</td>
<td>8</td>
<td>18</td>
<td>0.040</td>
</tr>
<tr>
<td>Minor complications</td>
<td>15</td>
<td>36</td>
<td>0.000</td>
</tr>
<tr>
<td>Two-leveling complications</td>
<td>11</td>
<td>22</td>
<td>0.040</td>
</tr>
<tr>
<td>Cardiopulmonary complications</td>
<td>5</td>
<td>17</td>
<td>0.007</td>
</tr>
</tbody>
</table>

n = 49 in restricted group and n = 72 in standard group.

Intraoperative Volumes of Fluids

Colloids vs. Crystalloid

Different Body Fluid Spaces

Colloids vs. Crystalloid

Intraoperative Colloid Administration Reduces Postoperative Nausea and Vomiting and Improves Postoperative Outcomes Compared with Crystalloid Administration

Eugene W. Moretti, MD, Kenji M. Robertson, MD, Hisham El-Moslem, MD, and Tong I. Cen, MD, FRCA

Department of Anaesthesiology, Duke University Medical Center, Durham, North Carolina

The debate over colloid versus crystalloid has been resolved in a recent study. Two randomized, controlled trials were performed to evaluate the benefits of using colloids and crystalloids in reducing postoperative nausea and vomiting. The results of these studies show that colloids are superior to crystalloids in reducing the incidence of postoperative nausea and vomiting.

Colloids vs. Crystalloid

Nausea, Vomiting, Antiemetic

Hetastarch/LR LR

% of Patients

*p < 0.05


Different Body Fluid Spaces

Glucose

Intracellular

Colloid

Saline

Interstitial

RBC

PV

2 L

3 L

10 L

30 L


Conclusion

- POI affects between 4% and 20% of abdominal surgical patients annually and has a detrimental effect on clinical outcomes and costs of care
- There are important anesthetic factors that can have an impact on POI
- Epidural anesthetic agents, analgesic adjuncts, preoperative education, and peripheral opioid-receptor antagonists can potentially reduce the incidence of POI
- A multimodal approach using both nonpharmacologic and pharmacologic options is most effective

End of Presentation

- You have reached the end of this presentation.
- Please select another presentation from the left menu.
Selected References


Therapeutic Update on Management of Postoperative Ileus


Conor P. Delaney, M.D., M.Ch., Ph.D., FRCSI, FACS
Professor of Surgery, Case Western Reserve University
Chief, Division of Colorectal Surgery
Vice-Chairman, Department of Surgery
Director, Institute for Surgery and Innovation
University Hospitals of Cleveland, Case Medical Center
Cleveland, Ohio

Conor P. Delaney, M.D., M.Ch., Ph.D., FRCSI, FACS, is Chief of the Division of Colorectal Surgery and Vice Chairman of the Department of Surgery at Case Medical Center in Cleveland, Ohio. He is also Professor of Surgery at Case Western Reserve University School of Medicine in Cleveland.

Dr. Delaney earned a Master of Surgery (M.Ch.) degree and a specialty degree in medicine from the University College Dublin in Dublin, Ireland. His postgraduate education included an internship at Mater Misericordiae Hospital Dublin 7 and residency at the Royal College of Surgeons Ireland, both of which are located in Dublin, Ireland. He also completed fellowships at the Royal College of Surgeons, University of Pittsburgh, and The Cleveland Clinic.

Dr. Delaney’s clinical interests include laparoscopic colorectal surgery; carcinoma of the colon, rectum, and anus; Crohn’s disease and ulcerative colitis; sphincter-saving surgery; re-operative abdominal surgery; and colonoscopy. He has given numerous lectures nationally and internationally and has published widely in peer-reviewed journals and book chapters on topics relating to colorectal surgery, laparoscopic colorectal surgery, and pre- and postoperative management in bowel surgery.

Dr. Delaney has received numerous prizes, scholarships, and awards over the course of his career in training, education, and research, including the New England Society of Colon and Rectal Surgeons Award in 2004. He is a member of several professional societies, including the American College of Surgeons, Crohn’s and Colitis Foundation of America, and the American Society of Colon and Rectal Surgeons. He serves on the editorial board of Reality Surgery published in Dublin, Ireland, and is a manuscript reviewer for many journals. Dr. Delaney is also actively involved in a number of professional committees for the American Society of Colorectal Surgeons, Society of American Gastrointestinal and Endoscopic Surgeons, and the Midwest Surgical Association.
Overview

Surgery on the gastrointestinal (GI) tract is associated with a mandatory period of cessation of intestinal function, deemed postoperative ileus (POI). Time spent in the hospital after abdominal surgery has been related to several factors, including pain, postoperative fatigue, the presence of mechanical factors like drains, and the persistence of POI. There is now increasing evidence that clinical pathways reduce the length of time spent in the hospital after abdominal surgery.

The effect of epidural anesthesia on POI has been studied for many years. Unfortunately, epidurals have been used with extreme variability, sometimes as lumbar, sometimes as thoracic, with and without opiates, and using different clinical endpoints. The time spent in the hospital has not been reproducibly shortened. Laparoscopy has also been used for colorectal surgery in recent years. Most studies show a significant reduction in time to recovery of bowel function and usually a hospital stay shortened by two days compared with open surgery. Part of the reduction in length of stay is thought to be related to a reduction in time to recovery of bowel function.

Most recently some new pharmacologic agents have been suggested as a means of accelerating recovery of bowel function. The best studied agents are in a new class of drugs called µ-opioid receptor antagonists. Several recent studies have suggested that alvimopan showed a significant reduction in time to recovery of ileus, number of nausea and vomiting episodes, and time to hospital discharge. More recent data with another drug in this group called methylnaltrexone suggest similar findings. Although neither agent has yet been FDA approved, it is likely that they will be a component of postoperative care pathways in the future.

Presentation Objectives

At the conclusion of this presentation, participants should be able to

- Summarize factors associated with postoperative ileus.
- Describe the rationale for using opioid-receptor antagonists in the management of postoperative ileus.
- Describe recent clinical research into new and emerging pharmacologic options for preventing and managing postoperative ileus.
Emerging Pharmacologic Options for Managing Postoperative Ileus

Conor P. Delaney, M.D., Ph.D.
Professor and Chief
Division of Colorectal Surgery
Vice Chairman, Department of Surgery
Case Western Reserve University
University Hospitals, Case Medical Center
Cleveland, Ohio

Ileus

• ....but we don't really know....
• Some people recover after extensive manipulation
• Some patients with easy, quick, straightforward cases don't recover for prolonged times...

Usual Organ Recovery Times

Stomach: 24-48 hours
Small intestine: 12-24 hours
Large intestine: 72-120 hours

Postoperative Ileus Management Council (PIMC)

Definition of POI

• Transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and / or tolerance of oral intake

POI = postoperative ileus

Consensus Panel Definitions

- **Primary POI** occurs in the absence of any precipitating complication
- **Secondary POI** occurs in the presence of a precipitating complication (infection, anastomotic leak, etc.)


Hospital Discharge Associated with Recovery of GI Function

![Graph showing GI-2 recovery and hospital discharge over postoperative days]

GI = gastrointestinal
GI-2 = recovery of bowel movement and toleration of solid food


Readmission and Prolongation of Hospital Stay

![Graph showing hospital readmission and prolonged hospital stay]

N=383

SAE = serious adverse event
EPSBO = early postoperative small bowel obstruction


Cochrane Review - Summary

- Epidural LA (no opiate) reduces POI, compared with systemic (36 h) or epidural (24 h) opioids, with comparable analgesia
- Epidural LA plus opioid may provide better analgesia than LA alone (VAS 15 mm), while the effect on GI function is unclear
- No significant difference in postoperative nausea and vomiting (PONV)

LA = local anesthetic; VAS = visual analog pain score

CREAD Epidural vs. PCA

<table>
<thead>
<tr>
<th></th>
<th>PCA (n=28)</th>
<th>Epidural (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>5.0 (4.0-8.5)</td>
<td>5.0 (4.0-7.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Age</td>
<td>47</td>
<td>44</td>
<td>0.52</td>
</tr>
<tr>
<td>Pain score at 48 h</td>
<td>3.3</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Pain score on discharge</td>
<td>3.1 ± 2.0</td>
<td>3.1 ± 2.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Pain score at all other times - identical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs ($)</td>
<td>4586</td>
<td>3808</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CREAD = Controlled rehabilitation with early ambulation and diet
PCA = patient-controlled analgesia
LOS = length of stay in days


Laparoscopic Colectomy: RCT of Epidural vs. PCA

- 21 patients per group
- Thoracic epidural vs. i.v. PCA
- Identical dietary management
- Hospital stay 2.3 vs. 2.4 days
- Nausea / vomiting 28% both groups
- No nasogastric (NG) tubes required

RCT = randomized controlled trial


New Pharmacologic Agents

Fedotozine

- Peripheral opioid agonist (K-receptor)
  - 51-Cr test meal in rats, laparotomy and peritonitis models,
    inhibiting motility and migrating myoelectrical complexes (MMC)
    for 3 h
- μ-agonist potentiated ileus
- δ-agonist made no difference
- K-agonist reversed ileus
  (3 mg/kg i.v.; 10 mg/kg s.c.)


Opioid Receptors in the Bowel Suppress Motility

Opioids interact with μ-opioid receptors in the gut to inhibit function

Opioids interact with μ-opioid receptors in the CNS to induce analgesia

Peripheral opioid receptors in bowel

Central opioid receptors

Narcotic analgesia pain relief

Narcotic adverse effects
  - Sedation
  - Respiratory depression
  - Addiction

Narcotic analgesic pain relief

Opioid bowel dysfunction

Opioid Receptors in the Bowel

Opioids interact with μ-opioid receptors in the CNS to induce analgesia

Opioids interact with μ-opioid receptors in the gut to inhibit function

(Courtesy, Dr. Carston Gut, Heidelberg)
Peripheral opioid antagonist Alvimopan selectively antagonizes GI opioid receptors; no effect on CNS opioid receptors.

Naloxone
- Competitive µ-opioid receptor antagonist
- Readily crosses the blood-brain barrier when given i.v.
- Reverses the centrally-mediated effects of opiates (CNS depression, analgesia, respiratory depression)
- May precipitate opioid withdrawal
- No current data showing benefit in POI

Methylnaltrexone
- µ-opioid receptor antagonist
- Does not readily cross the blood-brain barrier
- If given i.v., its effects are limited mainly to GI tract
- Has been shown to decrease opioid-induced constipation without affecting pain control or precipitating opioid withdrawal
- Is being evaluated in the postoperative setting

Methylnaltrexone in Opioid-Induced Constipation (OIC)
- OIC in advanced medical illness (n=154)
- Multicenter, phase III randomized double-blind placebo-controlled trial
- Compared placebo, methylnaltrexone 0.15 mg/kg, and methylnaltrexone 0.3 mg/kg given s.c.
- Laxation within 4 hours of study drug
  - Placebo 13%
  - 0.15 mg/kg 62% *p < 0.0001*
  - 0.30 mg/kg 58% *p < 0.0001*
- 30-40% had cramps, and 1-15% flatulence

Methylnaltrexone for Segmental Colectomy
- I.V. peripheral µ-opioid receptor antagonist
- 0.3 mg/kg every 6 h, within 90 min of surgery, max 7 days
- 65 colectomies

<table>
<thead>
<tr>
<th>Methylnaltrexone</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance liquids (h)</td>
<td>68</td>
<td>97</td>
</tr>
<tr>
<td>First BM (h)</td>
<td>98</td>
<td>118</td>
</tr>
<tr>
<td>GI recovery (h)</td>
<td>115</td>
<td>137</td>
</tr>
<tr>
<td>Discharge eligible (h)</td>
<td>116</td>
<td>149</td>
</tr>
<tr>
<td>Time to discharge (h)</td>
<td>138</td>
<td>164</td>
</tr>
</tbody>
</table>

BM = bowel movement

Alvimopan

\[
\text{Alvimopan} = \text{NH} + \text{CH}_3 - \text{NH} - \text{O} - \text{O} - \text{CH}_3 - \text{HO} - 2 \text{H}_2\text{O}
\]
Alvimopan

- Peripherally acting μ-opioid receptor antagonist
- Highly selective for μ-opioid receptor over δ and κ receptors
- Higher potency at μ-opioid receptor than morphine and methylnaltrexone
- Because of large molecular weight and polarity, does not readily cross the blood-brain barrier; thus, does not block central opioid receptors
- Following positive phase I and phase II trials, phase III trials have been completed; under FDA review for management of POI following bowel resection

Monoclonal antibodies to mu-opioid receptor – present in small bowel, stomach, and colon

Primary Endpoint: Time to Recovery of GI Function (GI-3)

Cox proportional hazard estimates

Primary Endpoint: Time to Recovery of GI Function (GI-3)

Cumulative Distributions for MITT Population—Overall

Postoperative Morbidity

Readmission rate reduced: 8% to 4%

*Statistically significant compared with placebo (p < 0.05)

NGT = nasogastric tube; EPSBO = early postoperative small bowel obstruction

Hospital Resource Use

*Statistically significant compared with placebo (p < 0.05)

DCO = discharge order


Alvimopan in Bowel Resection:
Pooled Analysis

- Elective intestinal resection
- Randomized to three groups
  - Placebo
  - Alvimopan 6 mg
  - Alvimopan 12 mg
- 400 patients per group
- Endpoints of GI recovery, hospital discharge
- Complications and treatment emergent event


Alvimopan: A Meta-analysis

- 2512 bowel resections in 5 trials
- Recovery of GI-2 and GI-3, significantly improved
- Time to discharge order significantly improved


Alvimopan in Bowel Resection:
Pooled Analysis


Alvimopan in Bowel Resection:
Pooled Analysis (cont)


Alvimopan in Bowel Resection:
Pooled Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>6 mg</th>
<th>12 mg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged POI</td>
<td>6.7%</td>
<td>1.8%</td>
<td>1.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EPSBO/POI</td>
<td>9.2%</td>
<td>3.0%</td>
<td>3.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NG tube insertion</td>
<td>12%</td>
<td>6.8%</td>
<td>6.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Readmission</td>
<td>11.7%</td>
<td>7.3%</td>
<td>7.7%</td>
<td>0.05</td>
</tr>
<tr>
<td>Prolonged stay</td>
<td>13.7%</td>
<td>8.6%</td>
<td>7.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>Combined</td>
<td>24.4%</td>
<td>13.6%</td>
<td>14%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Alvimopan in Bowel Resection: Adverse Events in Pooled Analysis

* Nausea most common TEAE reported
* Majority of AEs resulting in prolonged hospital stay were GI-related in placebo group and non-GI-related in alvimopan groups

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Placebo 6 mg</th>
<th>Alvimopan 6 mg</th>
<th>Alvimopan 12 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>60.2%</td>
<td>54.5%</td>
<td>51.1%*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26.1%</td>
<td>22.4%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13.5%</td>
<td>11.1%</td>
<td>9.4%*</td>
</tr>
<tr>
<td>POI</td>
<td>13.9%</td>
<td>7.3%*</td>
<td>8.0%*</td>
</tr>
</tbody>
</table>

*p > 0.05 compared with placebo

TEAE = treatment-emergent AE, defined as AE occurring after 1st dose of study medication and up to 7 days after the last dose


Outcome of Unplanned Readmission (UR)

• 553 resections in 6 months; 56 URs (10%)
• UR had more perioperative steroids (32 vs. 17%, p=0.03)
• Matched non-readmitted cases had shorter primary LOS (median 6 vs. 5 days, p=0.04)
• No predictors (complications, WBC, Hb, antibiotics, co-morbidity, fever, urgency, stoma, length of stay)
• No adverse event related to delayed diagnosis
• Conclusion: UR is unpredictable, not related to LOS, doesn’t affect overall outcome


Indications for Readmission

• Surgical site septic complications (SSSC)
• Ileus/small bowel obstruction (SBO)
• Medical complications
• Other


Factors Associated with Readmission Cause

<table>
<thead>
<tr>
<th>Indication for RD</th>
<th>First-admission factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSSC</td>
<td>Bowel perforation</td>
<td>12.8 (0.98, 167.2)</td>
</tr>
<tr>
<td></td>
<td>Reoperation</td>
<td>16.9 (1.05, 272.6)</td>
</tr>
<tr>
<td>Medical</td>
<td>Functional capacity</td>
<td>1.53 (1.11, 2.12)</td>
</tr>
<tr>
<td>complications</td>
<td>COPD</td>
<td>11.0 (1.39, 87.4)</td>
</tr>
<tr>
<td></td>
<td>Postoperative fever</td>
<td>5.6 (1.78, 17.5)</td>
</tr>
<tr>
<td></td>
<td>Postoperative ileus</td>
<td>3.33 (1.08, 10.3)</td>
</tr>
<tr>
<td></td>
<td>Stoma at discharge</td>
<td>4.12 (1.35, 12.6)</td>
</tr>
<tr>
<td>Ileus/SBO</td>
<td>Prior PE/DVT</td>
<td>11.6 (1.48, 93.3)</td>
</tr>
<tr>
<td></td>
<td>Prior abdominal surgery</td>
<td>2.6 (1.12, 6.02)</td>
</tr>
</tbody>
</table>

RD = readmission within 30 days of discharge


Alvimopan: Postoperative Morbidity (Phase III Pooled Data)

*P<0.05; †P<0.001; ‡P<0.003


Alvimopan: Hospital Resource Use (Phase III Pooled Data)

*P=0.036; †P<0.001; ‡P<0.005

Conclusions

- POI occurs variably in all patients
- Contributed to by standard opiates, which are currently necessary agents for adequate analgesia
- Postoperative care pathways and laparoscopy are useful adjuncts to treatment
- New medications are likely to be available in the near future

End of Presentation

- You have reached the end of this presentation.
- Please return to the Program Overview to take the program post-test.
- Or select another presentation from the left menu.
Selected References


Therapeutic Update on Management of Postoperative Ileus

Self-Assessment Test

This program is located at www.postopileus.org (Activity #08703 podcast).

This self-assessment test has been provided as a study aid only. At the conclusion of the internet-based program, click on “Take CE Test” to proceed to the ASHP Advantage CE Testing Center and take the online program post-test. You may print your CME statement immediately after successful completion of the post-test.

1. Primary postoperative ileus (POI) is now assumed to be a natural sequelae of abdominal surgical procedures and is described as a transient cessation of coordinated bowel motility that prevents effective transit of intestinal contents or tolerance of oral intake
   a. Occurring in the presence of a precipitating complication, such as intraabdominal abscess or anastomotic leak.
   b. Occurring in the absence of any precipitating complication.
   c. Lasting more than five days after surgery.
   d. Lasting more than nine days after surgery.

2. Risk factors for postoperative ileus include all of the following except
   a. Surgical technique.
   b. Extended opioid use.
   c. Inactivity.
   d. Initiation of solid food diet on postoperative day 2.

3. According to recent Medicare data, postoperative ileus occurs most frequently after which of the following procedures?
   a. Abdominal hysterectomy and appendectomy.
   b. Hip arthroplasty and cholecystectomy.
   c. Small bowel resection and large bowel resection.
   d. Cholecystectomy and nephroureterectomy.

4. The primary pathogenesis of postoperative ileus involves inflammatory mediators.
   a. True.
   b. False.

5. Supportive patient-care elements in enhanced-recovery surgery protocols aimed at minimizing postoperative ileus include all of the following components except
   a. Avoidance of nasogastric (NG) intubation.
   b. Fluid restriction.
   c. Early oral feeding.
   d. Delayed ambulation.
Therapeutic Update on Management of Postoperative Ileus

6. Dr. Senagore would not recommend including metoclopramide in a multimodal approach to managing postoperative ileus because
   a. Well-controlled studies indicated no benefit in any outcomes related to postoperative ileus.
   b. Its combined dopaminergic agonist and cholinergic antagonist actions are limited to the proximal gut.
   c. Adverse effects occur in 25-30% of patients.
   d. Postoperative patients often cannot tolerate the oral dosage form.

7. Studies by Delaney et al. evaluating outcomes of patients undergoing abdominal surgeries using enhanced-recovery protocols compared with traditional care showed that patients treated using enhanced-recovery protocols
   a. Reported less satisfaction with care during their hospitalization.
   b. Had higher pain scores on discharge.
   c. Had shorter lengths of stay.
   d. Had more readmissions.

8. Both exogenous and endogenous opioids have which of the following pharmacologic effects on the gastrointestinal tract?
   a. Increased gastric motility and emptying resulting in decreased appetite and increased gastroesophageal reflux.
   b. Decreased enzymatic secretion resulting in delayed digestion and hard, dry stools.
   c. Decreased fluid and electrolyte absorption resulting in hard, dry stools.
   d. Decreased nonpropulsive segmental contractions resulting in incomplete evacuation.

9. A survey conducted by Gan et al. of patients undergoing major abdominal surgery using patient-controlled analgesia showed that many patients preferred avoiding adverse effects of opioids over complete pain control.
   a. True.
   b. False.

10. Which of the following is a centrally acting analgesic that has been shown to decrease the postoperative opioid requirement and help prevent long term chronic pain following abdominal surgery?
    a. Gabapentin.
    b. Aspirin.
    c. Celecoxib.
    d. Acetaminophen.

11. All of the following are benefits of a balanced postoperative analgesia regimen that includes a combination of opioids and other analgesics except
    a. Decreased doses of each analgesic.
    b. Early ambulation.
    c. Improved anti-nociception due to synergistic or additive effects.
    d. Less severe adverse effects of each analgesic.
12. Thoracic epidural anesthesia/analgesia promotes gastrointestinal motility by
   a. Blocking nociceptive afferent nerves.
   b. Stimulating thoracolumbar sympathetic efferent nerves.
   c. Decreasing gastrointestinal blood flow.
   d. Increasing need for postoperative opiates.

13. According to Dr. Gan, which of the following statements best describes the use of epidurals to manage postoperative ileus?
   a. The epidural should not be placed until after surgery begins.
   b. The catheter should be placed at about T7 or T8 so that it can expand to cover T5 to L2.
   c. The most effective solution for the epidural is a local anesthetic.
   d. The epidural should be administered postoperatively for a maximum of 24 hours.

14. According to Dr. Gan, fluid management is an important aspect of enhanced recovery after abdominal surgery because
   a. Optimizing the volume of fluids administered and using a combination of colloids and crystalloids have been shown to have a positive influence on postoperative outcomes.
   b. Restricting intraoperative fluid administration to 500 mL or less results in decreased postoperative morbidity.
   c. Colloid administration results in edema caused by pooling of colloids in interstitial spaces.
   d. Goal-directed intraoperative fluid management has been shown to increase length of stay.

15. Fedotozine is a peripheral _______________ that has been shown to reverse ileus in animal models.
   a. Mu-opioid receptor agonist.
   b. Delta-opioid receptor agonist.
   c. Kappa-opioid receptor agonist.
   d. Mu-opioid receptor antagonist.

16. Opioids interact with peripheral mu-opioid receptors in the gastrointestinal tract to inhibit function.
   a. True.
   b. False.

17. Which of the following statements best describes the effects of naloxone for postoperative ileus?
   a. Current data indicate it is beneficial in POI.
   b. It does not reverse the centrally-mediated effects of opiates, such as central nervous system depression, analgesia, and respiratory depression.
   c. It readily crosses the blood-brain barrier when administered intravenously.
   d. It does not precipitate opioid withdrawal.
18. Methylnaltrexone is a peripheral mu-opioid receptor antagonist that has been shown to decrease opioid-induced constipation without affecting pain control or precipitating opioid withdrawal.
   - a. True.
   - b. False.

19. Preliminary results of a study comparing intravenous administration of methylnaltrexone with placebo in patients undergoing segmental colectomy indicate that
   - a. Methylnaltrexone was associated with shorter time to first bowel movement and time to be eligible for discharge.
   - b. Methylnaltrexone must be initiated before surgery to be effective.
   - c. The optimal regimen is 0.6 mg/kg every 3 hours for at least 7 days.
   - d. Methylnaltrexone has little potential role in the postoperative setting.

20. Alvimopan is a peripherally acting mu-opioid receptor antagonist that
   - a. Has equipotency at mu-opioid receptor compared with morphine and methylnaltrexone.
   - b. Blocks central opioid receptors.
   - c. Is highly selective for mu-opioid receptor over delta and kappa receptors.
   - d. Readily crosses the blood-brain barrier.

21. Clinical trials evaluating alvimopan in patients undergoing abdominal surgery have documented all of the following outcomes except
   - a. Reduced time to passage of flatus and stool.
   - b. Reduced time to hospital discharge.
   - c. Reduced readmission rates.
   - d. Increased anastomotic leak rates.