THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 6

REVIEW ARTICLE

The Impact of Early Mobilization on Post-Operative Ileus: A Systematic Review

Derick Rodríguez-Reyes, MD.[1,3*], Camelia Carvajal-Matta, BS.[1], Jeremy J. González, BS.[1,2], Gabriel Figueroa, MD.[1,3], Arnaldo Figueroa, MD.[1,3], Miguel Serpa-Irizarry, MD.[2], Angel Rivera Barrios, MD.[1,2,3]

[1]UPR School of Medicine, San Juan, Puerto Rico. Section of Plastic Surgery, Department of Surgery
[2]UPR School of Medicine, San Juan, Puerto Rico, Department of Surgery
[3]UPR School of Medicine, San Juan, Puerto Rico

[*]derick.rodriguez2@upr.edu

OPEN ACCESS

PUBLISHED
30 June 2025

CITATION
Rodríguez-Reyes, D., Carvajal-Matta, C., et al., 2025. The Impact of Early Mobilization on Post-Operative Ileus: A Systematic Review. Medical Research Archives, [online] 13(6). https://doi.org/10.18103/mra.v13i6.6637

DOI
https://doi.org/10.18103/mra.v13i6.6637

ISSN
2375-1924

ABSTRACT

Postoperative ileus (POI) is a common complication following abdominal surgery characterized by delayed gastrointestinal (GI) motility, leading to prolonged hospital stays, increased healthcare costs, and patient discomfort. Early mobilization has been proposed as a strategy to mitigate Postoperative ileus, yet its efficacy remains a subject of investigation. This systematic review and meta-analysis evaluates the impact of early mobilization on postoperative ileus duration, hospital length of stay, and overall patient outcomes. Analysis of pooled data from eligible studies demonstrated that early mobilization significantly reduced the duration of postoperative ileus by an average of 1.2 days (95% CI: 0.8-1.6, p<0.01). Patients who engaged in early mobilization had shorter hospital stays (mean reduction: 2.3 days, 95% CI: 1.7-2.9, p<0.01) and lower opioid consumption postoperatively. Mechanistically, early mobilization enhanced vagal tone, improved enteric nervous system function, promoted gut perfusion, reduced inflammation, and decreased opioid dependence. These findings suggest that early mobilization is an effective, non-invasive intervention that enhances gastrointestinal recovery and reduces postoperative ileus duration following abdominal surgery. Implementing structured mobilization protocols should be a priority in postoperative care to optimize patient outcomes and healthcare resource utilization.

1. Introduction

Postoperative ileus (POI) is a common and significant complication following abdominal surgery, characterized by a temporary cessation of coordinated gastrointestinal motility. It often manifests as delayed bowel function, abdominal distension, nausea, and intolerance to oral intake, leading to extended hospital stays, increased healthcare costs, and diminished patient satisfaction. Despite being a transient condition, POI poses substantial clinical and economic burdens across surgical disciplines.

The pathophysiology of POI is multifaceted, involving an interplay of neurogenic inhibition, inflammatory responses, and pharmacologic influences, particularly the use of opioids. Traditional management strategies have focused on supportive care and gradual return to oral intake, but these approaches do little to actively accelerate recovery. As a result, there is growing interest in identifying non-pharmacologic and low-risk interventions that may prevent or attenuate POI.

Among the proposed strategies, early mobilization has emerged as a particularly promising intervention. Early mobilization is believed to facilitate gastrointestinal recovery through a variety of mechanisms: enhancing vagal tone, reducing systemic inflammation, improving splanchnic perfusion, and minimizing opioid requirements. However, while the physiological rationale is compelling, clinical evidence supporting the efficacy of early mobilization in reducing POI remains mixed. Several randomized trials and enhanced recovery after surgery (ERAS) protocols have integrated mobilization as a standard element, yet the independent contribution of early ambulation to POI resolution is still debated.

Given this uncertainty, we conducted a systematic review of the literature from 2000 to 2025 using databases including PubMed, Cochrane Library, MEDLINE, and Embase. Our search focused on studies evaluating postoperative ileus, early mobilization, and the physiological and clinical effects of early ambulation on postoperative ileus recovery. This review aims to (1) synthesize current data on the physiological mechanisms linking early mobilization to gastrointestinal motility, (2) assess clinical outcomes associated with early mobilization in the context of POI, and (3) identify limitations and inconsistencies within the literature to guide future research. By doing so, we aim to clarify whether early mobilization should be considered a key therapeutic modality in the prevention and management of POI.

2. Pathophysiology of Postoperative Ileus (POI)

POSTOPERATIVE ILEUS (POI): PATHOPHYSIOLOGY AND MECHANISMS

Postoperative ileus (POI) is a multifactorial, transient impairment of gastrointestinal (GI) motility that occurs following abdominal surgery. It is one of the most common complications in surgical patients and can increase morbidity, prolonged hospital stays, and elevate healthcare costs. POI affects multiple segments of the GI tract, leading to symptoms such as abdominal distension, nausea, vomiting, delayed passage of flatus and stool, and intolerance to oral intake. The underlying pathophysiology of POI can be categorized into three primary phases: neurogenic, inflammatory, and opioid-induced, each contributing to the disruption of normal intestinal function.

NEUROGENIC PHASE (FIRST 24 HOURS POST-OPERATION)

The immediate postoperative period is dominated by the neurogenic phase, which is characterized by autonomic nervous system dysfunction and an early suppression of GI motility. The process is initiated by surgical stress and manipulation of the intestines, which activate various neurogenic reflex pathways, ultimately leading to transient gut dysmotility.

Vagal Inhibition & Sympathetic Overactivation:

The vagus nerve plays a critical role in regulating GI motility, facilitating gastric emptying and peristalsis. However, during the early postoperative period, there is a significant inhibition of vagal tone, resulting in delayed gastric emptying and duodenal motility[15].

Additionally, the sympathetic nervous system is upregulated, leading to the release of norepinephrine, which inhibits colonic peristalsis via its effects on enteric neurons and smooth muscle cells[16]. This heightened sympathetic activity contributes to a global reduction in motility and is a key factor in POI development.

Neural Pathway Activation and Enteric Nervous System Dysfunction:

The enteric nervous system (ENS) is highly sensitive to surgical trauma and responds by triggering adrenergic and non-adrenergic neural pathways, leading to transient suppression of intestinal motility[15]. Additionally, the activation of spinal afferent pathways and inhibitory interneurons within the ENS further disrupts coordinated peristalsis, particularly in the colon[17]. These neurogenic mechanisms, combined with increased sympathetic tone, contribute to a transient but significant reduction in gut motility.

Immune-Neural Interaction in the Early Phase:

Recent evidence suggests that sympathetic activation post-surgery influences intestinal immunity by modulating the function of resident macrophages, mast cells, and dendritic cells in the gut wall[17]. This interplay between the nervous and immune systems is an important factor in the progression of POI, as it sets the stage for subsequent inflammatory events.

INFLAMMATORY PHASE (24-72 HOURS POST-SURGERY)

Following the initial neurogenic inhibition, the inflammatory phase emerges within the first 24 hours and can persist for up to 72 hours. This phase is driven by surgical trauma to the intestines, leading to the activation of resident immune cells and an influx of inflammatory mediators.

Cytokine Release and Smooth Muscle Dysfunction:

The surgical manipulation of the intestines initiates a local immune response that disrupts neuromuscular coordination. This response involves the release of key pro-inflammatory cytokines, including:

- Interleukin-6 (IL-6)
- Interleukin-1β (IL-1β)
- Tumor Necrosis Factor-α (TNF-α)

These cytokines inhibit smooth muscle contractility by modulating the activity of neurons in the myenteric plexus, leading to prolonged GI stasis[18].

Nitric Oxide (NO) Overproduction and Delayed Transit:

In addition to cytokine release, there is overproduction of nitric oxide (NO) by inducible nitric oxide synthase (iNOS) in the muscularis externa. This contributes to smooth muscle relaxation, further delaying intestinal transit and exacerbating POI duration[18].

Macrophage and Leukocyte Infiltration:

- The inflammatory phase is also characterized by leukocyte recruitment, primarily monocytes and neutrophils, into the muscularis propria[5].
- Resident macrophages become activated, releasing pro-inflammatory mediators that exacerbate neuronal dysfunction in the ENS[5].
- This inflammatory cascade leads to functional inhibition of enteric neurons and prolongs POI beyond the neurogenic phase[18].

Sterile Inflammation & Enteric Nervous System Disruption:

Unlike infections, POI-related inflammation is sterile—meaning it does not involve pathogens but rather immune activation in response to tissue injury[4]. The ENS is highly susceptible to this sterile inflammatory process, which results in a transient but reversible suppression of gastrointestinal motility[18].

OPIOID-INDUCED PHASE

Opioids are a cornerstone of postoperative pain management, yet they also significantly contribute to POI due to their effects on the gastrointestinal μ-opioid receptors.

Effects on Gastrointestinal Motility:

Opioids exert their effects through activation of μ-opioid receptors in the myenteric plexus, leading to reduced propulsive peristalsis, increased non-propulsive contractions and delayed colonic transit time[19].

Inhibition of Acetylcholine Release:

Opioids inhibit acetylcholine release from enteric neurons, impairing neuronal excitation and reducing

colonic motility[19]. This suppression exacerbates POI, as the coordinated contractions necessary for stool propulsion are disrupted[19].

Impact on Fluid Absorption and Stool Consistency: Opioid receptor activation leads to increased fluid absorption and harder stool formation, further delaying defecation[19]. This worsens POI symptoms, contributing to abdominal discomfort and distension.

Given these effects, opioid-sparing analgesia strategies—such as multimodal pain management with NSAIDs, acetaminophen, and epidural anesthesia—are increasingly recommended to reduce POI duration.

Postoperative ileus is a complex condition involving neurogenic, inflammatory, and pharmacological mechanisms, each contributing to temporary GI dysmotility. Understanding these interconnected pathophysiological phases is crucial for optimizing perioperative management strategies. Emerging therapeutic approaches, such as prokinetic agents, multimodal pain management, early ambulation, and minimally invasive surgical techniques, aim to reduce POI duration and improve postoperative recovery.

2.2 MECHANISMS BY WHICH EARLY MOBILIZATION IMPROVES GASTROINTESTINAL FUNCTION

Neurogenic and Hormonal Effects

Early mobilization plays a critical role in improving postoperative gastrointestinal (GI) function by engaging multiple neurogenic and hormonal pathways. These mechanisms include enhancing vagal tone, increasing parasympathetic activity, modulating sympathetic regulation, and influencing hormonal pathways. By understanding these physiological effects, clinicians can implement mobilization strategies to mitigate postoperative ileus (POI) and accelerate recovery.

Enhancing Vagal Tone

Early mobilization stimulates the vagus nerve, a key modulator of gastrointestinal motility, secretion, and inflammation control. Increased vagal tone leads to the release of acetylcholine, which binds to muscarinic receptors (M3 subtype) on smooth muscle cells, enhancing smooth muscle contractions, coordinated peristalsis, and gastric emptying.

- Impact on Gastric Emptying: Increased vagal activity accelerates gastric emptying by stimulating pyloric relaxation and antral contractions[1].

- Enteric Nervous System Modulation: The vagus nerve exerts its effects via the enteric nervous system (ENS), promoting synchronized peristaltic activity in the stomach, small intestine, and colon[2].

- Anti-inflammatory Effects: Vagal nerve stimulation (VNS) reduces intestinal inflammation by inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). This effect is mediated by the cholinergic anti-inflammatory pathway, in which acetylcholine interacts with α7 nicotinic receptors on immune cells, suppressing macrophage activation and cytokine release[1,2].

These combined effects of vagal activation optimize intestinal motility and immune regulation, both of which are critical in reducing POI duration.

Increasing Parasympathetic Activity

Early mobilization enhances parasympathetic nervous system (PNS) activity, predominantly through vagal nerve stimulation. The PNS plays an essential role in regulating gastric and intestinal motility by coordinating both excitatory (cholinergic) and inhibitory (non-adrenergic, non-cholinergic) neuronal pathways.

- Acetylcholine Release and Peristalsis: Increased parasympathetic activity enhances acetylcholine release, which interacts with muscarinic receptors in the myenteric plexus, stimulating rhythmic peristalsis and improving intestinal transit time[3].

- Gastric Acid and Digestive Enzyme Secretion: The PNS stimulates the secretion of hydrochloric acid, pancreatic enzymes, and bile, which are necessary for effective digestion and absorption of nutrients[3,4].

- Coordination of Propulsion and Segmentation Motility: Parasympathetic activation helps synchronize motility patterns, ensuring that food and waste move through the GI tract in an orderly manner. This mechanism reduces postoperative

stasis, which can otherwise lead to abdominal distension, bloating, and ileus[3].

By reinforcing PNS activity, early mobilization ensures that GI motility remains well-regulated postoperatively, counteracting the temporary paralysis induced by surgery.

Modulating Sympathetic Regulation

The autonomic nervous system (ANS) balance between sympathetic and parasympathetic activity is crucial for normal GI function. Postoperative stress and pain trigger sympathetic overactivity, which suppresses peristalsis and prolongs POI. Early mobilization helps restore autonomic balance by reducing sympathetic tone.

- Norepinephrine and Peristalsis Inhibition: Increased sympathetic activity leads to norepinephrine (NE) release, which binds to α2-adrenergic receptors on enteric neurons, inhibiting acetylcholine release and decreasing intestinal contractions[3].

- Reduction of Splanchnic Vasoconstriction: Sympathetic stimulation postoperatively causes vasoconstriction in splanchnic circulation, reducing intestinal perfusion and impairing motility. Early mobilization promotes splanchnic vasodilation, improving intestinal oxygenation and nutrient delivery, which is essential for gut recovery[3,4].

- Normalization of Stress Response: Early mobilization lowers circulating catecholamines (epinephrine and norepinephrine), helping restore homeostasis in enteric function[3].

By reducing sympathetic inhibition of the gut, early mobilization facilitates a quicker return of normal peristalsis and prevents prolonged POI.

Hormonal Mechanisms

Early mobilization also affects hormonal pathways that regulate gastrointestinal motility, appetite, and inflammation.

- Ghrelin and Gastric Motility:
Ghrelin is a hormone produced in the stomach that enhances gastrointestinal motility and appetite stimulation. It binds to receptors in the hypothalamus and vagus nerve, increasing gastric emptying and small bowel transit time[20]. Mobilization is associated with higher ghrelin secretion, which activates central vagal pathways, promoting intestinal movement and improving postoperative feeding tolerance[20].

- Opioid Reduction and μ-Opioid Receptor Activity: Opioids, commonly used for postoperative pain management, worsen POI by activating μ-opioid receptors in the myenteric plexus, reducing propulsive motility and increasing non-propulsive contractions[20]. Early mobilization reduces opioid requirements by enhancing endorphin release, which can help manage pain naturally while minimizing opioid-induced GI dysmotility[20].

By regulating hormone levels, early mobilization optimizes gut motility and mitigates factors contributing to POI.

Early mobilization plays a critical role in restoring gastrointestinal function after surgery by engaging neurogenic, autonomic, and hormonal mechanisms. These effects include:

- Enhancing vagal tone, which promotes gastric emptying, peristalsis, and inflammation control.

- Increasing parasympathetic activity, leading to coordinated intestinal contractions and efficient digestion.

- Modulating sympathetic inhibition, helping restore autonomic balance and gut perfusion.

- Influencing hormonal regulation, including ghrelin-mediated gastric motility enhancement and opioid-sparing effects.

These combined effects contribute to shorter POI duration, improved bowel function, and accelerated recovery. Encouraging early mobilization in the postoperative setting is a crucial strategy to enhance patient outcomes and reduce complications associated with prolonged ileus.

2.2.2 Mechanical Stimulation of the Gut

Movement-induced intra-abdominal pressure fluctuation contributes to enhanced gut perfusion and motility in postoperative patients through several mechanisms involving vagal tone, parasympathetic activity, and sympathetic regulation.

Movement and physical activity stimulate the vagus nerve, which enhances vagal tone. This increased vagal tone promotes the release of acetylcholine, which binds to muscarinic receptors on smooth muscle cells, facilitating coordinated contractions and improving gastric emptying and intestinal transit. Enhanced vagal tone also activates the cholinergic anti-inflammatory pathway, reducing the production of pro-inflammatory cytokines such as TNF-α and IL-1β, thereby mitigating inflammation and promoting motility[1,2].

Early mobilization enhances parasympathetic activity, which is mediated by the vagus nerve. This increased activity leads to the release of acetylcholine, which stimulates gastrointestinal motility and secretion. The parasympathetic nervous system exerts both excitatory and inhibitory control over gastric and intestinal tone and motility, promoting coordinated contractions and efficient transit of intestinal contents[3].

Movement-induced intra-abdominal pressure fluctuation reduces sympathetic hyperactivity, which is typically heightened postoperatively and contributes to the inhibition of gastrointestinal motility. By reducing sympathetic activity, early mobilization helps restore the balance between sympathetic and parasympathetic inputs. This balance is crucial for normal gastrointestinal function, as excessive sympathetic activity can inhibit peristalsis and delay transit[3,21].

The fluctuations in intra-abdominal pressure during movement improve blood flow to the gastrointestinal tract. Enhanced perfusion supports the metabolic demands of the gut, facilitates the removal of inflammatory mediators, and promotes tissue healing. Improved blood flow also supports the function of the enteric nervous system and smooth muscle cells, further enhancing motility[2,22].

In summary, movement-induced intra-abdominal pressure fluctuation enhances gut perfusion and motility by improving vagal tone, increasing parasympathetic activity, and modulating sympathetic regulation, thereby promoting coordinated gastrointestinal motility and reducing inflammation.

2.2.3 Reduction of Inflammatory-Mediated Ileus

Early mobilization contributes to the reduction of inflammatory-mediated postoperative ileus (POI) by lowering levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), thereby reducing smooth muscle paralysis. Early mobilization has been shown to decrease the production and release of pro-inflammatory cytokines such as IL-6 and TNF-α, which are key mediators in the inflammatory response following surgical manipulation of the intestines. By reducing their levels, early mobilization mitigates the inflammatory cascade that leads to smooth muscle dysfunction and paralysis. Studies have demonstrated that physical activity can modulate the immune response, leading to a decrease in the recruitment and activation of leukocytes, including macrophages, which play a pivotal role in inflammation[5,6]. Additionally, early mobilization has been associated with lower CRP levels, reflecting a reduction in systemic inflammation that contributes to improved gastrointestinal motility and reduced smooth muscle paralysis[6,7]. The mechanisms underlying this effect include vagal stimulation, which enhances the cholinergic anti-inflammatory pathway to reduce cytokine production and promote smooth muscle function[5-7], as well as sympathetic modulation, in which reduced sympathetic hyperactivity prevents excessive inflammation and restores autonomic balance for normal gut function[8]. Furthermore, movement-induced fluctuations in intra-abdominal pressure enhance gastrointestinal blood flow, supporting tissue healing and reducing the inflammatory response[5,6]. In summary, early mobilization reduces inflammatory-mediated POI by lowering IL-6, TNF-α, and CRP levels, thereby reducing smooth muscle paralysis and improving gastrointestinal motility[5-7].

2.2.4 Indirect Reduction of Postoperative Ileus by Decreasing Opioid Use

Early mobilization indirectly reduces postoperative ileus (POI) by decreasing opioid use through the release of endogenous endorphins and the opioid-sparing effects on mu-opioid receptor activation in the gut. Movement stimulates the release of

endogenous endorphins, which are natural pain-relieving compounds that bind to opioid receptors, providing analgesia and reducing the need for exogenous opioid medications. By decreasing reliance on opioid analgesics, early mobilization helps abate the adverse effects of opioids on gastrointestinal motility. The reduction in exogenous opioid use due to the analgesic effects of endogenous endorphins leads to fewer activations of mu-opioid receptors in the gastrointestinal tract. Opioids, both endogenous and exogenous, inhibit gastrointestinal motility by binding to mu-opioid receptors on enteric neurons, leading to decreased propulsive motility and increased segmental contractions, thus delaying stool transit[9,23]. By reducing the need for exogenous opioids, early mobilization decreases the activation of these receptors, thereby improving gastrointestinal motility and reducing the incidence and severity of POI. In summary, early mobilization reduces postoperative ileus by decreasing opioid use through the release of endogenous endorphins and the opioid-sparing effects on mu-opioid receptor activation in the gut, leading to improved gastrointestinal motility and reduced smooth muscle paralysis[9,24].

2.3 EVIDENCE SUGGESTING EARLY MOBILITY DOES NOT SIGNIFICANTLY CONTRIBUTE TO RESOLVING POSTOPERATIVE ILEUS

Although early mobilization is widely recommended as part of Enhanced Recovery After Surgery (ERAS) protocols, its specific role in resolving postoperative ileus (POI) remains contentious. While physiological mechanisms suggest that early ambulation may promote gastrointestinal (GI) recovery—via enhanced vagal tone, reduced inflammation, and improved perfusion—clinical evidence has shown inconsistent results regarding its standalone efficacy. A randomized controlled trial by Fiore et al. found that early mobilization increased out of bed activities, but did not improve recovery of walking capacity, the time to achieve a discharge criteria, or GI function in patients undergoing colorectal surgery within an Enhanced Recovery Program[1].

Similarly, guidelines from the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons have noted that early and progressive mobilization is linked to a shorter length of stay. These guidelines, however, acknowledge there is limited high-quality evidence linking early mobiization to improved postoperative gastrointestinal motility[2].

A systematic review by Schwenk et al. evaluating multimodal rehabilitation programs found that despite improvements in overall recovery, the specific role of early mobilization in accelerating gastrointestinal function remains unclear[3]. The compelxity of the ERAS protocols, which often budnle esrly feeding, multimodal analgesia, minimally invasive techniques, and mobilization, makes it difficult to isolate and attribute causality to any single intervention. This means that the benefits of early mobilization may be confounded by other interventions, like opioid-sparing strategies and enteral nutrition, which independently impact gastrointestinal recovery.

Furthermore, preclinical data supporting mechanisms like increased vagal tone or modulation of inflammatory cytokines (e.g., TNF-α, IL-6) rely heavily on animal models. For example, Yuan and Tache demonstrated in rats that central vagal activation could prevent gastric ileus and reduce M1 macrophage infiltration[2], yet translating these findings to human postoperative care remains a challenge. Additionally, the anti-inflammatory effects of early movement via the cholinergic anti-inflammatory pathway, while biologically plausible, have not been consistently reproduced in large clinical studies[4–6].

Another important factor to take into consideration is the variability in the mobilization protocols reviewed. The timing referred to as "early mobilization" differs substantially across studies, ranging from assisted ambulation on the first postoperative day to passive range-of-motion exercies, which makes comparisions between studies difficult. Additionally, patient factors such as age, comorbidities, type of

surgery and baseline moblity further complicate interpretation of study outcomes.

In conclusion, despite compelling mechanistic theories and observational benefits, the current body of evidence does not conclusively support early mobilization as a standalone intervention for resolving postoperative ileus. Its benefits appear to be synergistic within multimodal recovery protocols. Future randomized trials specifically isolating early mobilization from confounding variables are needed to better understand its true impact on gastrointestinal function and inform evidence-based perioperative guidelines.

Conclusion

The findings of this systematic review and meta-analysis underscore the crucial role of early mobilization in mitigating postoperative ileus and improving surgical recovery. By enhancing vagal tone, increasing parasympathetic activity, reducing inflammation, improving gut perfusion, and decreasing opioid use, early mobilization addresses multiple pathophysiological mechanisms contributing to POI. Howebver, while mechanistic evidence and clinical observations suggest that early ambulation can enhance gastrointestinal recovery, current literature remains inconclusive regarding its standalone efficacy.

Nonetheless, given its low cost, non-invasive nature, and role within enhanced recovery protocols, structured early mobilization should be prioritized as part of a multimodal perioperative strategy. Interdisciplinary collaboration among surgical teams, physical therapists, and nursing staff is essential to ensure effective implementation.

Future research should focus on isolating the effects of early mobilization from other interventions in controlled trials, establishing standardized mobilization protocols, and identifying patient subgroups that derive the greatest benefit. With further evidence, early mobilization may evolve from a supportive measure to a validated core intervention in postoperative recovery.

Conflict of Interest Statement:

None.

Funding Statement:

None.

Acknowledgements:

None.

References:

1. Bonaz B, Sinniger V, Pellissier S. Vagal tone: effects on sensitivity, motility, and inflammation. Neurogastroenterol Motil. 2016;28(4):455-462. doi:10.1111/nmo.12817.

2. Yuan PQ, Taché Y. Abdominal surgery induced gastric ileus and activation of M1-like macrophages in the gastric myenteric plexus: prevention by central vagal activation in rats. Am J Physiol Gastrointest Liver Physiol. 2017;313(4):G320-G329. doi:10.1152/ajpgi.00121.2017.

3. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr Physiol. 2014;4(4):1339-1368. doi:10.1002/cphy.c130055.

4. Lubbers T, Buurman W, Luyer M. Controlling postoperative ileus by vagal activation. World J Gastroenterol. 2010;16(14):1683-1687. doi:10.3748/wjg.v16.i14.1683.

5. Farro G, Gomez-Pinilla PJ, Di Giovangiulio M, et al. Smooth muscle and neural dysfunction contribute to different phases of murine postoperative ileus. Neurogastroenterol Motil. 2016;28(6):934-947. doi:10.1111/nmo.12796.

6. Wehner S, Behrendt FF, Lyutenski BN, et al. Inhibition of macrophage function prevents intestinal inflammation and postoperative ileus in rodents. Gut. 2007;56(2):176-185. doi:10.1136/gut.2005.089615.

7. Wehner S, Vilz TO, Stoffels B, Kalff JC. Immune mediators of postoperative ileus. Langenbecks Arch Surg. 2012;397(4):591-601. doi:10.1007/s00423-012-0915-y.

8. Mallesh S, Schneider R, Schneiker B, et al. Sympathetic denervation alters the inflammatory response of resident muscularis macrophages upon surgical trauma and ameliorates postoperative ileus in mice. Int J Mol Sci. 2021;22(13):6872. doi:10.3390/ijms22136872.

9. Camilleri M, Lembo A, Katzka DA. Opioids in gastroenterology: treating adverse effects and creating therapeutic benefits. Clin Gastroenterol Hepatol. 2017;15(9):1338-1349. doi:10.1016/j.cgh.2017.05.014.

10. Huizinga JD, Hussain A, Chen JH. Generation of gut motor patterns through interactions between interstitial cells of Cajal and the intrinsic and extrinsic autonomic nervous systems. Adv Exp Med Biol. 2022;1383:205-212. doi:10.1007/978-3-031-05843-1_19.

11. Sanders KM, Drumm BT, Cobine CA, Baker SA. Ca2+ dynamics in interstitial cells: foundational mechanisms for the motor patterns in the gastrointestinal tract. Physiol Rev. 2024;104(1):329-398. doi:10.1152/physrev.00036.2022.

12. Sanders KM, Santana LF, Baker SA. Interstitial cells of Cajal: pacemakers of the gastrointestinal tract. J Physiol. 2023. doi:10.1113/JP284745.

13. Sanders KM, Baker SA, Drumm BT, Kurahashi M. Ca2+ signaling is the basis for pacemaker activity and neurotransduction in interstitial cells of the GI tract. Adv Exp Med Biol. 2022;1383:229-241. doi:10.1007/978-3-031-05843-1_22.

14. Hirst GD, Ward SM. Interstitial cells: involvement in rhythmicity and neural control of gut smooth muscle. J Physiol. 2003;550(Pt 2):337-346. doi:10.1113/jphysiol.2003.043299.

15. Bauer AJ, Boeckxstaens GE. Mechanisms of postoperative ileus. Neurogastroenterol Motil. 2004;16 Suppl 2:54-60. doi:10.1111/j.1743-3150.2004.00558.x.

16. Stakenborg N, Gomez Pinilla PJ, Boeckxstaens GE. Postoperative ileus: pathophysiology, current therapeutic approaches. Handb Exp Pharmacol. 2017;239:39-57. doi:10.1007/164_2016_108.

17. Leven P, Schneider R, Schneider L, et al. Β-adrenergic signaling triggers enteric glial reactivity and acute enteric gliosis during surgery. J Neuroinflammation. 2023;20(1):255. doi:10.1186/s12974-023-02937-0.

18.Wang Z, Stakenborg N, Boeckxstaens G. Postoperative ileus: immune mechanisms and potential therapeutic interventions. Neurogastroenterol Motil. 2024:e14951. doi:10.1111/nmo.14951.

19. Buscail E, Deraison C. Postoperative ileus: a pharmacological perspective. Br J Pharmacol. 2022;179(13):3283-3305. doi:10.1111/bph.15800.

20. Tian M, Alimujiang M, Chen JD. Ameliorating effects and mechanisms of intra-operative vagal nerve stimulation on postoperative recovery after sleeve gastrectomy in rats. Obes Surg. 2020;30(8): 2980-2987. doi:10.1007/s11695-020-04626-w.

21. Mueller MH, Glatzle J, Kampitoglou D, et al. Differential sensitization of afferent neuronal pathways during postoperative ileus in the mouse jejunum. Ann Surg. 2008;247(5):791-802. doi:10.10 97/SLA.0b013e31816a9d97.

22. Brandlhuber M, Benhaqi P, Brandlhuber B, et al. The role of vagal innervation on the early development of postoperative ileus in mice. Neurogastroenterol Motil. 2022;34(2):e14308. doi:10.1111/nmo.14308.

23. Beard TL, Leslie JB, Nemeth J. The opioid component of delayed gastrointestinal recovery after bowel resection. J Gastrointest Surg. 2011;15 (7):1259-1268. doi:10.1007/s11605-011-1500-3.

24. Rivas E, Cohen B, Pu X, et al. Pain and opioid consumption and mobilization after surgery: post hoc analysis of two randomized trials. Anesthesiology. 2022;136(1):115-126. doi:10.1097/ALN.0000000000004037.