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Prophylactic Neostigmine Infusion After Radical Cystectomy; Phase I Clinical Trial

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Abstract

Background: Postoperative ileus (POI) occurs in 10% to 30% of patients following abdominal surgeries, leading to prolonged hospitalization, increased complications, and elevated treatment costs. Various strategies have been proposed to prevent POI and its associated complications. Neostigmine, an acetylcholinesterase inhibitor, has demonstrated effectiveness in treating acute colonic pseudo-obstruction (Ogilvie's syndrome). However, concerns exist regarding its use following surgeries that involve intestinal manipulation, and its impact on reducing the incidence of POI after radical cystectomy and urinary diversion has not been adequately investigated.

Objectives: This study aims at assessing the safety of neostigmine administration after radical cystectomy and urinary diversion, marking the first phase of a clinical trial.

Methods: Twenty-four hours after radical cystectomy, 1 mg of neostigmine was administered intravenously to the selected group of patients. Drug-related complications were carefully monitored.

Results: A total of 25 patients, with an average age of 63.20 ± 8.85 years, were included in the study. One patient expired 5 days post-surgery due to sepsis related to intra-abdominal abscess formation without intestinal leakage. In the remaining patients, drug-related complications were mild and self-limited.

Conclusions: This study indicates that intravenous administration of 1 mg of neostigmine is relatively safe for patients undergoing radical cystectomy. Future phases of the clinical trial should focus on evaluating the efficacy of neostigmine in preventing POI following radical cystectomy.

Keywords: Acetylcholinesterase Inhibitor, Drug Safety, Ileus, Prophylaxis, Surgical Anastomosis

1. Background

Postoperative ileus (POI) is characterized by an abnormal pattern of gastrointestinal motility following surgical procedures, occurring in the absence of mechanical obstruction. Clinically, POI manifests as symptoms such as abdominal distention, lack of stool passage, and intolerance to oral intake. Although POI is generally considered an uncomplicated sequel in most cases, it can lead to increased complications, higher healthcare costs, and prolonged hospital stays (1, 2). The incidence of POI after abdominal surgery ranges from 10% to 30% (3). When POI persists for more than 3 to 7 days, it is classified as "prolonged" or "pathologic" POI, which may result in serious complications (4). Patients undergoing radical cystectomy and urinary diversion are particularly susceptible to POI, influenced by factors such as intestinal resection, inflammatory mediators, opioid use, and electrolyte imbalances (5, 6).

To prevent POI and mitigate its associated complications, several strategies have been implemented. These strategies include the adoption of "enhanced recovery after surgery (ERAS)" protocols, as

well as the utilization of specific pharmaceutical therapies (1, 7). Neostigmine, an acetylcholinesterase inhibitor, is traditionally used in managing acute colonic pseudo-obstruction, also known as Ogilvie's syndrome (8-10). The most significant side effects of neostigmine are those related to its cholinergic activity. These side effects can include bradyarrhythmia, bronchospasm, miosis, abdominal cramps, increased secretions, vomiting, and nausea (11). Notably, neostigmine is contraindicated in individuals with hypersensitivity to the drug, as well as in cases of peritonitis or any mechanical obstruction in the gastrointestinal or urinary tract (9, 12). Given the prohibition of this medication in cases of documented intestinal obstruction, its use following gastrointestinal surgeries raises concerns (9).

2. Objectives

This study aims at investigating the safety of neostigmine administration after radical cystectomy and urinary diversion by designing the first phase of a clinical trial.

3. Methods

3.1. Study Design

This study represents the first phase of a clinical trial aimed at investigating the safety of postoperative administration of neostigmine after radical cystectomy on the incidence of POI. In this phase, we will evaluate the side effects and related complications associated with administering 1 mg of neostigmine intravenously in a selected group of patients following radical cystectomy.

3.2. Patient Selection

Patients diagnosed with bladder cancer and scheduled for radical cystectomy from April 2023 to May 2024 at Shahid Modarres Hospital were evaluated for inclusion in the study. During the screening period, 38 patients were assessed, and after excluding those who did not meet the criteria, 25 patients were ultimately included in the study.

3.2.1. Inclusion Criteria

- Candidates for radical cystectomy due to muscle-invasive bladder cancer.

- Undergoing radical cystectomy with urinary diversion involving intestinal and colonic reconstruction (e.g., ileal conduit, orthotopic ileal or sigmoid pouch, etc.).

3.2.2. Exclusion Criteria

- Contraindications to neostigmine administration, including hypersensitivity to neostigmine, chronic kidney disease, reactive airway disease, uncontrolled arrhythmias, and recent myocardial infarction.

3.3. Data Collection

Twenty-four hours after radical cystectomy, 1 mg of neostigmine was ordered for the selected patients. Intravenous infusion administration was supervised by a urological oncology fellow and the patients were monitored; also, a nurse conducted vital sign examinations every 10 minutes during infusion and then every hour during the next 24 hours and then every 3 hours during the rest days of the hospitalization period. Patients were observed for any side effects and complications related to neostigmine administration including blurred vision, headache, increased sweating, nausea, chest pain or discomfort, diarrhea or any intestinal anastomosis complication, hives, muscle cramps and spasms, confusion, cough or increase of respiratory secretion, difficulty in moving, dysphagia, xerostomia, loss of consciousness, abdominal pain, fainting, halos around lights, itching, muscle pain or stiffness, difficult or labored breathing, disturbed color perception, dizziness, double vision, drowsiness. Additionally, the following outcomes were recorded: Time taken to normalize bowel sounds, time to first passage of gas, time to first defecation, fluid tolerance, and solid food tolerance. All data were meticulously recorded and analyzed to assess the effects of the intervention.

3.4. Ethical Statement

This research was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, with approval number IR.SBMU.LASER.REC.1402.025. Potential risks and benefits were explained to all patients. Also, written informed consent was obtained from all the patients. The information obtained from the patients was kept confidential throughout the survey.

4. Results

A total of 25 patients participated in our study. Participants' characteristics are summarized in Table 1.

Table 1. Participants' Characteristics

Variables	Mean ± SD or No. (%)
Age (y)	63.20 ± 8.85
Gender	
Male	21 (84)
Female	4 (16)
Duration of surgery (min)	251.60 ± 69.02
Method of urinary diversion	
Ileal conduit	10 (40)
Orthotopic ileal pouch	8 (32)
Orthotopic sigmoid pouch	7 (28)

Due to the small sample size, we did not have any missing data or follow-up information. The average time to auscultation of normal bowel sounds following surgery was 28.52 ± 11.86 hours. The average times for the first occurrences of various recovery milestones post-surgery were as follows: (A) Gas passage: 39.92 ± 16.35 hours; (B) defecation: 61.80 ± 24.23 hours; (C) fluid tolerance: 44.48 ± 30.81 hours; (D) solid food tolerance: 67.28 ± 34.90 hours.

We closely monitored the patients for any side effects and complications related to neostigmine administration. Unfortunately, one patient expired 5 days post-surgery and 4 days after infusion of neostigmine. In the autopsy report, the death etiology was explained due to sepsis related to intra-abdominal abscess formation without intestinal leakage. In the remaining 24 patients, side effects were mild and self-limited, with no reports of cardiovascular complications. Additionally, there were no cases of peritonitis or leaks from intestinal anastomosis. Details regarding side effects associated with neostigmine are presented in Table 2.

Table 2. Details of Side Effects Associated with Neostigmine Administration

Variables	Patients [a]
Headache	2 (8)
Abdominal cramps	3 (12)
Vomiting and nausea	2 (8)
Increased respiratory secretions	1 (4)

[a] Values are expressed as No. (%).

Early therapeutic interventions required due to neostigmine administration were classified according to the Clavien-Dindo grading system, as shown in Table 3. None of the patients experienced severe complications (grade IV or V). Two patients required anti-nausea medication (grade I), and two others required analgesics for headache relief (also grade I).

Table 3. Clavien-Dindo Classification of Early Therapeutic Interventions

Grade	Patients [a]
Grade I	4 (16)
Grade II	0 (0)
Grade III a	0 (0)
Grade III b	0 (0)
Grade IV a	0 (0)
Grade IV b	0 (0)
Grade V	0 (0)

[a] Values are expressed as No. (%).

5. Discussion

This study intended to investigate the safety of administering neostigmine following radical cystectomy surgery with intestinal anastomosis, focusing on associated side effects and complications. We monitored 25 patients who received neostigmine postoperatively. While one patient tragically passed away 5 days after surgery, it is important to note that this complication is unlikely to be directly related to the prescribed dose of 1 mg IV of neostigmine. Among the remaining 24 patients, no serious complications were reported. The side effects observed were mild and self-limited, suggesting that neostigmine can be administered safely in this context.

The POI is a common complication following abdominal surgeries, with a reported prevalence ranging from 10% to 30% (13). Researchers identify several predisposing factors for the occurrence of POI, including tissue trauma, intestinal manipulation, inflammation, fluid overload, and the use of opioid analgesics (13, 14). This condition is characterized by intestinal paralysis, leading to the accumulation of intestinal contents. The POI is characterized by intestinal paralysis, which leads to the accumulation of intestinal contents. Clinical signs of POI include abdominal pain and distension, nausea and vomiting, feeding intolerance, and cessation of flatus and

defecation. These symptoms arise from the buildup of liquid and gas in the gastrointestinal tract (15, 16).

The implications of POI extend beyond patient discomfort; it significantly increases the length of hospitalization and treatment costs. In the United States, annual costs associated with POI have been estimated to reach as high as 1.47$ billion, creating a significant financial strain on society (17). Additionally, POI is associated with a heightened risk of more serious complications, including pulmonary embolism, pulmonary aspiration, electrolyte imbalance, wound dehiscence, and even sepsis (3, 18, 19).

Given the potential complications associated with POI, researchers have focused on identifying effective prevention and treatment strategies. In some medical centers, the routine use of nasogastric tubes following abdominal surgeries is common. However, studies suggest that prophylactic nasogastric decompression does not significantly alleviate symptoms associated with POI; its use is recommended only for selected patients (20). Conversely, emerging evidence indicates that chewing gum may effectively reduce the duration of ileus after elective surgeries (21, 22). A recent randomized controlled trial by Muwel et al. further demonstrated that chewing gum can reduce POI following surgery for gastroduodenal perforation peritonitis (23).

Additionally, the effects of coffee and caffeinated drinks on POI are being explored and debated. A meta-analysis by Yang et al. reported that coffee or caffeine consumption after elective colorectal surgeries can aid in the prevention and treatment of POI (24). While the impact of coffee on bowel movements has been confirmed in other studies (25, 26), some research presents conflicting results. For instance, one randomized controlled trial found that coffee consumption does not significantly improve bowel function following minimally invasive surgeries (27). Furthermore, pharmacological prophylaxis for POI has been investigated; a randomized controlled trial by Delaney et al. found that the administration of alvimopan significantly reduced the incidence of POI after bowel resection (28).

Neostigmine is an acetylcholinesterase inhibitor that has demonstrated beneficial effects in treating acute colonic pseudo-obstruction, also known as Ogilvie's syndrome (10). In this study, we aimed at investigating the safety of neostigmine administration following radical cystectomy. According to the results, this study suggests the second phase of a clinical trial be designed to evaluate the effect of prophylactic neostigmine on the occurrence of POI after radical cystectomy. The main limitation of our study was the relatively small sample size. The limited number of participating patients decreases the generalizability of our results. Future multicenter studies with larger sample sizes and greater diversity in race and gender will help produce more widely applicable findings.

Footnotes

Authors' Contribution: Study concept and design: M. S.; Acquisition of data: A. Am., M. F., and M. M.; Analysis and interpretation of data: F. A.; Drafting of the manuscript: A. Al., N. M.; Critical revision of the manuscript for important intellectual content: F. A.; Administrative, technical, and material support: F. A.; Study supervision: M. S.

Clinical Trial Registration Code: IRCT20170826035911N2 .

Conflict of Interests Statement: Some authors are part of the journal's review team.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available.

Ethical Approval: This study is approved under the ethical approval code of IR.SBMU.LASER.REC.1402.025 .

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Informed Consent: Written informed consent was obtained from all the patients.

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