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ORIGINAL ARTICLE

Neostigmine In Unavoidable Post Operative Ileus: A Randomized Clinical Trial

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ABSTRACT

Background: This study was aimed to show the effective way to decrease the rate of postoperative ileus.
Design: Prospective clinical randomized trial of neostigmine in 42 patients with ileus after abdominal surgery.
Intervention: Intravenous administration of 2.5 mg of neostigmine in 500 N/S over 30 min, or placebo. Patients who had no response to the initial injection were eligible to receive open-label neostigmine three hours later.
Setting: Abdominal circumference, time to first flatus and defecation, HR and BP after 3 hours of administration, and radiographic colonic measurements were recorded. Patients were followed for recurrence of ileus. All organic causes of ileus excluded from the study.
Result: 20 out of 21 neostigmine patients (95.23%) passed flatus and stools with first administration of Neostigmine administration, whereas none of the placebo-treated patients passed stools (P < 0.001). In pre study abdominal circumference, there was no significant difference, whereas after 3 hours of intervention, it was decreased significantly (100.85 ±14.61 case group, 124.71 ± 16.15, P<0.0001). No acute serious adverse effects occurred in both groups.
Conclusion: In patients with acute colonic pseudo-obstruction who have not had a response to conservative therapy, treatment with neostigmine rapidly decompresses the colon.

Key words: Neostigmine, Post Operative, Ileus

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Introduction

Postoperative ileus (POI), in the absence of any mechanical obstruction, remains a commonly encountered clinical problem; it is often considered an unavoidable consequence of major abdominal surgery and of other types of surgery as well. The idea that POI is "unavoidable", may be changing. Consistent, effective mitigation, and possibly even prevention of POI, may soon become attainable goals of standard approaches to perioperative care. On the other hand, the important aspect of our study, is the economic burden of POI. One recent attempt to study the prevalence and economic burden of POI, used data from the year 2002 from Premier's Perspective™ Comparative Database, which includes 5 million discharges annually[1].

Data from controlled trials have shown that many of the methods used to date in an effort to mitigate POI—for example, use of nasogastric intubation, administration of metoclopramide, delay of solid diet—cannot be relied on, to

shorten the duration of POI. So, this study was aimed to show the effective way to decrease the rate of postoperative ileus (POI).

Methods

Patients

Patients with acute colonic pseudo-obstruction, who were 18 years of age or older, were recruited for the study between August 2007 and February 2008, from inpatient medical and surgical wards of hospitals affiliated with the University of Baqiyatallah. Acute colonic pseudo-obstruction was defined as marked colonic distention in the absence of mechanical obstruction. To be eligible for the study, patients had to have a caecal diameter of at least 10 cm on plain radiographs[2]. Mechanical obstruction was ruled out by the finding of air throughout all colonic segments including the rectosigmoid, on plain abdominal radiographs. When air was not demonstrable in the rectosigmoid colon, mechanical obstruction was ruled out by radiographical contrast enemas. Patients were enrolled in the study if colonic distention, documented by clinical examination and abdominal radiographs, failed to improve after 24 hours of conservative management that included administering nothing by mouth, nasogastric suction, and intravenous fluid and electrolyte replacement. Any drug that could adversely affect colonic motility, specifically narcotics and anticholinergic agents, was discontinued when possible. One patient, who was subsequently randomly assigned to the placebo group, was enrolled after only 18 hours of conservative therapy, when the consulting gastroenterologist determined that urgent decompression was warranted.

Exclusion criteria included a base-line heart rate of less than 60 beats per minute or systolic blood pressure of less than 90 mm Hg; signs of bowel perforation with peritoneal signs on physical examination or free air on radiographs; active bronchospasm requiring medication; treatment with prokinetic drugs such as cisapride or metoclopramide in the 24 hours before evaluation; a history of colon cancer or partial colonic resection; active gastrointestinal bleeding; pregnancy; a positive history of myocardial infarction and intestinal resection or a serum creatinine concentration of more than 3 mg per deciliter (265 μmol per liter). The Human-Subjects Committee of the University of Baqiyatallah and its affiliated hospitals approved the study protocol. All patients provided written informed consent.

Study Design

Patients were randomly assigned (by flipping a coin) to receive 2.5 mg of neostigmine intravenously in 500 ml of normal saline over a period of thirty minutes or identical-appearing saline placebo. The injections were given by a physician who was unaware of the patient's treatment assignments. All patients were monitored by electrocardiography; atropine was available at the bedside, and 1.0 mg was given intravenously as needed, for symptomatic bradycardia. Patients were instructed to remain supine for at least 60 minutes after the injection. Vital signs were recorded immediately before the injection, and five minutes and three hours afterwards.

The physician administering the infusion monitored the clinical response for 30 minutes after the injection. The maximal abdominal circumference and the diameter of the caecum, ascending colon, and transverse colon on plain radiographs, were measured before and three hours after the injection by an investigator who was unaware of the patient's treatment assignments.

Three hours after the infusion, patients who did not have a reduction in colonic distention on both clinical examination and radiographs, were eligible to receive open-label neostigmine (2.5 mg intravenously) administered by a physician who was unaware of the identity of the study drug. The three-hour period was chosen because of the short half-life of neostigmine. Three

hours later, abdominal circumference, colonic diameters, and clinical response were again measured. Patients were monitored for adverse effects during the initial treatment and during open-label treatment, and were then followed for the remainder of their hospitalization. The treatment assignments were not revealed to the investigators, treating physicians, or patients until the last patient had been discharged from the hospital.

Statistical Analysis

On the basis of prior reports, we estimated that 22 patients would be required in each group for the study, to have the power at an alpha level of 0.05, with a beta error of 0.2, to detect a significant difference between groups, assuming a response rate of 80 percent in the neostigmine group (CI: 73-100% , 95%, 91% in previous studies) and 30 percent in the placebo group. We used Fisher's exact test to compare the frequency of clinicalresponses and treatment failures in the two groups. We evaluated the changes in abdominal circumference and colonic diameters with the use of student□s T test and U Mann-Whitney for non parametric variables. All tests were two-tailed.

Assessment of Outcomes

The outcomes assessed, included an immediate clinical response to the study drug, changes in abdominal girth and colonic diameters on abdominal radiographs three hours after treatment, and the need for colonoscopic decompression or surgery during hospitalization. An immediate clinical response was defined as the passage of flatus or stool with a reduction in abdominal distention on physical examination, within 30 minutes after the injection. Treatment was considered to have failed if open-label neostigmine, colonoscopic or surgical intervention, or both were required because of the recurrence or persistence of colonic distention.

Results

Two patients were excluded from the study. Refused consent and a base-line heart rate of less than 60, were the reasons for exclusion. Twenty one patients were randomly assigned to receive neostigmine, and 21 to receive a saline placebo. All patients had acute abdominal distention. The two groups were similar with regard to age, sex, duration and degree of colonic distention, use of narcotics and anticholinergic medications, history of recent surgical procedures, and severity of illness [Table/Fig 1]. The underlying surgical diagnoses included laparoscopic cholecystectomy in 8 patients, laparoscopic appendectomy in 10 patients, total knee replacement in 5 patients and total hip replacement in 3 patients, amputation of diabetic foot in 2 patients, prostatectomy in 11 patients, lumbar laminectomy, exploratory laparotomy after a gunshot wound, and open reduction of multiple fractures with internal fixation, in one patient each.

(Table/Fig 1) Characteristic Of The Patients Base Line

Result	Neostigmine (N=21)	Placebo (N=21)
Immediate Clinical Response-No. (%)	20(95.23%)*	0(0%)*
Abdominal Circumference Before intervention-cm	121.42±17.13†	128.38±16.70†
Abdominal Circumference 3hrs After intervention-cm	100.85±14.61‡	124.71±16.51‡

*P<0.001 by Fisher's exact test.
†P> 0.05 by Fisher's exact test
‡P<0.001 by U Mann-Whitney test.

After treatment, there was prompt evacuation of flatus or stool with a reduction in abdominal distention on physical examination in 20 patients in the neostigmine group (95.23 percent), and none in the placebo group (P<0.001) [Table/Fig 2]. The median time to response was 6 minutes (range, 3 to 30). There were also significant reductions in abdominal circumference and colonic diameters in the neostigmine group as compared to the placebo group [Table/Fig 2].

(Table/Fig 2) Result of Initial Treatment

Result	Neostigmine* (n=21)	Placebo* (n=21)
Age	65±14	63±12
Sex- (M/F)	16/5	14/7
Cecal Diameter- cm†	17±5	15±4
Abdominal Circumference	121.42±17.13	128.38±16.70
Duration of Pseudo Obstruction(days‡)	4±2	3±4

* P > 0.05 by Fisher's exact test in all variables
†The diameter was measured on plain radiographs.
‡The duration of pseudo-obstruction was measured from the time of radiologic diagnosis to randomization.

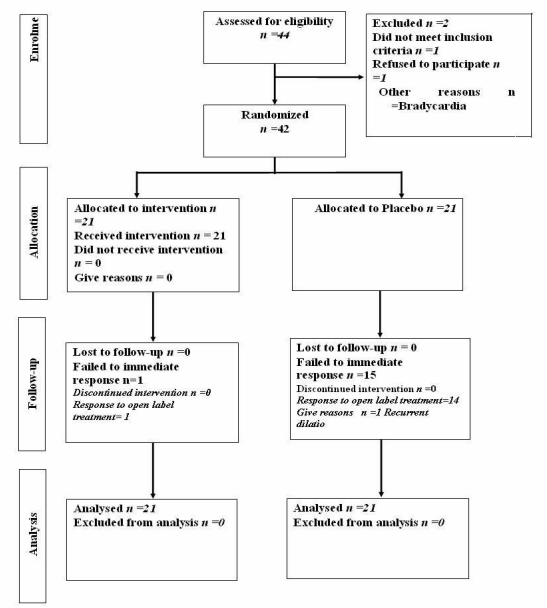
Treatment was considered to have failed in one patient who received neostigmine (4.7 percent), and in fifteen who received placebo (71.42 percent, P=0.04). Only the one patient (5%) in the neostigmine group had no immediate clinical response to initial treatment, but did have a response to open-label therapy, with no recurrence of dilation.

None of the patients required colonoscopic decompression for recurrence of colonic distention.

One of the 15 patients who were assigned to the placebo group did not respond to open-label therapy again. At the discretion of their attending physicians, the patient was treated with conservative measures alone, and colonic distention gradually resolved over the next 48 to 72 hours.

Of the sixteen patients who received open-label therapy, one had previously received neostigmine, and fifteen had received placebo. The majority of patients had an immediate clinical response, and none required colonoscopic or surgical decompression. Of the 37 patients who received neostigmine, either initially or during open-label treatment, 36 (97 percent) had an immediate clinical response, and 1 (3 percent) had recurrent colonic dilation [Table/Fig 3].

The most frequent adverse effect of neostigmine treatment was abdominal pain, which occurred in 9 patients; it was described as mild cramping by 5 patients, and as moderate-to-severe cramping by the other 4. In all patients, the abdominal pain was transient and had no sequelae. Eight patients had excessive salivation,



(Table/Fig 3) Flow Chart Describing The Progress Of Patients Through The Trial

and four vomited. Symptomatic bradycardia requiring atropine occurred in one patient, who felt lightheaded within minutes after the infusion. None of the patients in the placebo group had an adverse effect.

Discussion

The definition of POI universally is discussed [3],[4] Notably, POI also can be associated with other abdominal and nonabdominal procedures [5],[6],[7]. Causative factors are thought to be related directly to the surgical procedure itself. Neurogenic (sympathetic hyperactivity), inflammatory (cellular and hormonal factors, including endogenous opioid peptides) and hormonal factors, all play some role in the maintenance of POI, prolonging its duration and/or leading to an increase in pain, distention, and other symptoms [8]. However, we restrict our data to POI. Based on this fact, various approaches have appeared over the years in an attempt to reduce POI, and to involve all surgical-team members to a greater or lesser degree.

Fast-track strategies should include only methods or pharmacologic agents that

have been documented as effective in helping to reduce the duration of POI, or to diminish the risk of its development. Despite widespread belief that metoclopramide reduces POI, there are no data from randomized controlled trials to support this notion[3]. However, extensive reviews of trials and clinical experience have found that NG intubation does not improve POI, and indeed, may exacerbate it[9]. Removal of NG tubes after anaesthesia is recommended to avoid other adverse effects, which can include pneumonia, as well as fever, atelectasis, and an increase in the number of days to toleration of solid diet[5]. Cisapride does in fact improve POI; however, this drug is no longer available in the United States and some countries, because it increases the risk for serious adverse cardiac effects[10]. The absolute benefit of laxatives with respect to helping reduce POI remains unproven; studies have shown variable results[3]. A study of aggressive postoperative bowel stimulation with magnesium hydroxide showed an early return (3 days) of bowel function following radical hysterectomy[11].

We found that neostigmine decompressed the colon in patients, with acute colonic pseudo-obstruction better than in previous studies[12]. The rate of failed attempt was much lesser than in other studies[12],[13,[14],[15].The last study with 2 mg of neostigmine was too small to evaluate the effect of neostigmine treatment on the risk of colonic perforation and mortality[12]. The dose of neostigmine (2.5 mg), its efficacy and no difference in complication rates, are benefits of our study in comparison of other studies. However, our results confirm those of uncontrolled studies[13],[14],[15].

We honestly declare that the use of parasympathomimetic agents such as neostigmine is not without risk. Patients with underlying bradyarrhythmias or those receiving β-adrenergic antagonists may be more susceptible to neostigmine-induced bradycardia. Similarly, neostigmine increases airway secretions and bronchial reactivity, which may exacerbate active bronchospasm. Recently, it was discovered that a new class of drugs—peripherally acting mu-opioid receptor antagonists—may help enhance multimodal management of POI.

Although the cost benefit of the new class of drugs is debated it has been suggested that the individual components of multimodal protocols—for example, laparoscopy—may reduce certain post surgical morbidities (including POI).

But do not by them prevent POI. Therefore, combinations of strategies with demonstrated effectiveness—early feeding [16], epidural analgesia, laparoscopic surgery, and use of peripherally acting mu-opioid-receptor antagonists—may help transform the reactive approach to POI, into a proactive multimodal paradigm that effectively targets the diverse aetiologic factors leading to this common clinical problem [12].

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