Neostigmine treatment protocols applied in acute colonic pseudo-obstruction disease: A retrospective comparative study

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ABSTRACT

Background/Aims: *When conservative methods fail, neostigmine is recommended in the pharmacological treatment of acute colonic pseudo-obstruction (ACPO). The objective of this study was to analyze the response of patients to different neostigmine protocols.*

Materials and Methods: *Patients diagnosed with ACPO in the intensive care unit between January 2015 and September 2017 were retrospectively studied. Either of the two neostigmine protocols, the bolus dose (BD) or continuous infusion (CI), was applied to the ACPO patients who were unresponsive to conservative treatments, and the results were analyzed.*

Results: *In 79 of 122 (64%) patients, the resolution of symptoms was observed with conservative treatments. Of 43 patients who did not respond to conservative treatments, 20 were applied neostigmine as BD, and 23 were applied by CI. A total of 55% of patients in the BD group and 60.9% patients in the CI group responded to neostigmine therapy after the first dose. The group-specific protocols were re-applied in patients unresponsive to the first dose. A total of 25% in the BD group and 8.7% in the CI group responded to the second dose treatment. As a result, 80% of patients from the BD group and 69.6% from the CI group responded to neostigmine therapy. Although an overall response rate was higher in the BD group, there was no significant difference between groups (P=0.322). Colonic complications were observed in 2 patients, 1 from each group. There were no major side effects requiring treatment cessation.*

Conclusion: *The safety and effectiveness of both neostigmine protocols applied to ACPO patients were similar. Clinical and radiological responses were obtained without serious side effects with CI.*

Keywords: *Colonic pseudo-obstruction, gastrointestinal motility, neostigmine*

INTRODUCTION

Intestinal motility disorders are frequently encountered in critically ill patients (1). Acute colonic pseudo-obstruction (ACPO) disease, also known as Ogilvie's syndrome, is defined as the abnormal dilatation of the colon, although no mechanical obstruction is present (2). It is usually seen in patients hospitalized due to serious medical or surgical diseases (3). Although the underlying pathogenesis of the syndrome is not completely understood, excessive parasympathetic suppression or sympathetic stimulation, which might be generated by an imbalance in the autonomic innervation of the colon, is thought to be the cause (3,4). It is asserted that transient neural impairment in the sacral plexus may cause atony in the distal tract that leads to functional obstruction and proximal dilatation (5). Severe complications of the syndrome are ischemia and perforation. The risk of spontaneous colonic perforation is 3%, and the mortality is approximately 50% (6). The rate of ischemia and perforation dramatically increases if the duration of distension exceeds 6 days (5,7). If the cecal diameter exceeds 10 cm, an intervention is required (8).

Neostigmine is an anticholinesterase-effective parasympathomimetic drug, used in the treatment of myasthenia gravis, postoperative urinary retention, and in the reversal of non-depolarizing neuromuscular blockade. Adverse drug events might include bradycardia, asystole, hypotension, restlessness, seizures, tremor, miosis, bronchoconstriction, hyperperistalsis, nausea, vomiting, salivation, diarrhea, and sweating due to parasympathetic stimulation (8). Depending upon the duration of application and dosing, a response rate of up to 92% can be achieved with neostigmine therapy in the ACPO disease (3). In our study, we have investigated the efficacy and safety of two neostigmine protocols applied in patients with ACPO.

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MATERIALS AND METHODS

Definitions, patient selection, and inclusion criteria

After obtaining an approval from the scientific and ethical committee of the Selçuk University School of Medicine Hospital, patients with ACPO who had stayed in the Anesthesiology and Reanimation Intensive Care Unit between January 1, 2015, and September 1, 2017, were retrospectively analyzed. Demographic data, medications, routes of neostigmine applications (BD or CI), clinical-radiological findings, treatment outcomes, side effects, and complications were analyzed.

The intensive care patients with ACPO who had cecal diameters ≥10 cm on plain abdominal radiographs with dilated colonic segments including rectosigmoideum and progressive abdominal distension without any improvement in the next 24 hours, even after conservative treatments, were included in the study.

Neostigmine was applied to patients consecutively after failed conservative treatments as BD until March 2016 and then CI until September 2017. Among the conservative treatments were discontinuation of oral intake, placement of a nasogastric tube for proximal gut decompression, correction of fluid and electrolyte imbalances (e.g., calcium, potassium, magnesium, phosphate levels) and metabolic abnormalities (including thyroid functions), treatment of any underlying concomitant illnesses, and the cessation of medications such as narcotics and anticholinergics that negatively affect colonic motility. In addition, patients' position was frequently changed from supine to right- and left-lateral decubitus, and patients were mobilized when it was possible.

Acute colonic pseudo-obstruction is defined as significant colonic distension without the presence of mechanical obstruction. In our study, mechanical obstruction was thus excluded via plain abdominal radiography or abdominal computed tomography by displaying air in the rectosigmoideum or other colonic segments. When air was not visible in plain radiography or tomography, and mechanical obstruction was excluded via radiographic contrast enema. A favorable clinical response was considered in cases of ≥10% reduction in abdominal distention, large-volume flatus, or defecation greater than 100 ml. A favorable radiological response was considered in the presence of a ≥20% regression in the cecal diameter on plain abdominal radiography. Plain abdominal radiographs were taken at an initial and after the bolus dose applications at the 3rd, 8th, and 24th hours. The same workup was also performed for the continuous infusion group. Patients not responding to neostigmine for 24 hours or with relapse dilatation demonstrated on plain radiographs were considered to be unresponsive to first dose therapy. Relapsed dilatation was accepted if the cecal diameter of a patint was ≥8 cm or a ≥10% increase over the baseline resolution was present. A response to neostigmine therapy without relapse for 24 hours was defined as a sustained response. The time between the neostigmine application and a clinical-radiological response was defined as time to response.

Exclusion criteria

The presence of atrioventricular conductance disturbances, sinus bradycardia (heart rates <60 bpm) or nodal rhythms, hypotension (systolic blood pressures <90 mmHg), serum creatinine levels >3 mg/dl, intestinal perforation signs (peritoneal irritation findings upon physical examination or intra-abdominal free air displayed on radiological workup), colon cancer or partial colon resection, gastrointestinal bleeding, active bronchospasm, and pregnancy or lactation were included in the exclusion criteria.

Protocol

Based on previous studies, patients who had been still unresponsive to conservative treatments for 2 days were divided into the BD and CI groups. The BD group was given 2 mg neostigmine in 15 min (9). In the CI group, 5 mg neostigmine was prepared in 50 ml 0.9% NaCl solution and infused at a rate of 4 ml/h (0.4 mg neostigmine/h). If no response was received in 8 hours, the infusion rate was doubled and continued for 24 hours (10). Clinical and radiological response was considered to be the primary endpoint. Prolongation of the PQ interval in the electrocardiogram, cramping abdominal pain, excessive salivation and sputum production, and bronchospasm were considered to be secondary endpoints, and they required cessation of the therapy. Within 24 hours after the first dose, patients who were still unresponsive or with relapsed disease were reapplied neostigmine. Despite repeated neostigmine applications, the patients who were definitely unresponsive to treatment underwent decompression by colonoscopy and were applied a rectal tube for 24 hours.

Measurements

Disease severity was determined by the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) score, which was calculated within 24 hours after the admission to the intensive care unit (ICU). Possible neostig-

mine-related complications and ICU mortalities were recorded. All patients, as long as they were in ICU, were continuously monitored for their body temperature, heart rate, oxygen saturation, and electrocardiogram. Before and after the injections, the blood pressure was measured at least every 30 minutes by invasive or noninvasive means. Atropine for bradycardia (heart rate <50 bpm) and ephedrine for hypotension (systolic pressure <90 mmHg) were made available. Physicians and nurses were informed about potential complications and clinical outcomes of the treatment.

Statistical analysis

Statistical analysis of the data was performed with the Statistical Package for Social Sciences 20.0 Windows (IBM Corp.; Armonk, NY, USA) package program. The descriptive statistics of demographic data and continuous variables were presented as medians with quartiles. In the inter-group comparisons of continuous variables, Student's t-test was used for parametric data and the Mann-Whitney U-test was used for non-parametric data. The chi-squared test was applied to analyze intra-group distribution of categorical variables. The $p<0.05$ was considered to be statistically significant.

Table 1. Characteristics of the patients in the bolus dose and continuous infusion groups at presentation

Parameter	Bolus Dose (n=20)	Continuous Infusion (n=23)	p
Male	10	12	0.887
Age	72 (21-80)	70 (26-80)	0.562
APACHE II	20.5 (13-38)	19.0 (13-37)	0.560
Opioid/Benzodiazepine (n)	5	10	0.205
Noradrenaline (µg/kg/dk)	0.22	0.23	0.966
Mechanic ventilation (n)	10	17	0.106
Recent surgery (n)	2	3	0.756
Cecal diameter (cm)	12.6 (11.7-13.5)	12.6 (11.6-13.6)	0.865
Abdominal circumference (cm)	115 (107-123)	115 (105-125)	0.889
Colon decompression (n)	4	7	0.434
Colon complication (n)	1	1	1.000
ICU mortality	6	7	0.975

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation; ICU: intensive care unit

RESULTS

Resolution of symptoms was observed with conservative treatments in 79 (64%) of 122 patients, diagnosed with ACPO between January 1, 2015, and September 1, 2017. Of the 43 patients who did not respond to conservative treatments, 20 were given BD, and 23 were given CI neostigmine treatment. There was no significant difference between the BD and CI groups in terms of gender, age, the APACHE II score, opioid-benzodiazepine intake, noradrenalin support, mechanical ventilation, recent surgery, the cecal diameter, abdominal circumference, colonic decompression and related complications, and 28-day ICU mortality (Table 1). Five of the patients had a recent surgical procedure. The rest of them were admitted to ICU for nonsurgical medical reasons.

Eleven of 20 patients in the BD group and 14 of 23 patients in the CI group responded to the first dose of neostigmine therapy. The treatment protocols were reapplied in the first-dose unresponsive 9 patients from the BD and 9 patients from the CI groups. Five patients in the BD group, and 2 patients in the CI group responded to the second dose of therapy. As a result, 16 of 20 patients from the BD group and 16 of 23 patients from the CI group responded to neostigmine therapy. Although the overall response rate was higher in the BD group, there was no statistically significant difference between groups (p=0.322) (Figure 1; Table 2). The mean duration required to reach a favorable response was 165 minutes for the BD group and 510 minutes for the CI group, and there was a significant difference between the groups (p=0.001) (Table 2). On the other hand, clinical and radiological responses were obtained in all second-dose unresponsive patients who underwent decompression by colonoscopy. Colonic complications

Table 2. Results of neostigmine administration

		Bolus Dose	Continuous Infusion	p
Response to neostigmine	sustained response on first dose (%)	55%	60.9%	0.744
	sustained response on second dose (%)	25%	8.7%	0.322
	overall response rate (%)	80%	69.6%	0.378
Time to response	mean	165 minutes	510 minutes	0.001
	range	(30-510)	(90-1620)	

were observed in 2 patients, 1 from each group. The patient in the BD group did not respond to the first- and second-dose neostigmine applications. He had cardiac arrest and afterwards was presented with low cardiac output and multiple organ failure syndrome. He died due to intestinal necrosis on the 7th day of the study. The patient in the CI group had been admitted to ICU for cerebrovascular disease and pneumonia. She responded to the first dose of neostigmine therapy but was diagnosed with ischemic colonic necrosis on the 8th day of the study and finally underwent intestinal resection surgery.

No significant difference was found between groups regarding side effects such as sinus bradycardia, abdominal pain, vomiting, bronchospasm, salivation and sputum production (p>0.05) (Table 3). The most common side effect in both groups was cramping abdominal pain, as reported by 8 patients. Two patients who responded to the second dose of neostigmine therapy developed symptomatic bradycardia and were treated with 0.5 mg atropine. Three patients experienced vomiting, and an antiemetic medication was provided to them. In either group, no one had hypotension. Bronchospasm developed only in 1 patient, and the patient was treated with oxygen inhalation, bronchodilators, and steroids. Increased salivation and sputum production in 6 patients were treated by suction.

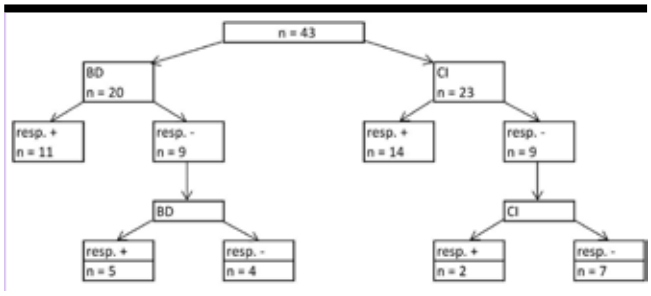

Figure 1. Results
BD: Bolus dose vs.; CI: Continue infusion; n: number of patients; resp.+: responders; resp.-: non responders

Table 3. Adverse effects of neostigmine therapy

Adverse Effect	Bolus Dose	Continuous Infusion	p
Sinus bradycardia	2	0	0.883
Abdominal pain	5	3	0.645
Vomiting	2	1	0.601
Hypotension	0	0	1
Bronchospasm	1	0	0.926
Saliva and sputum	3	3	1

DISCUSSION

The reversible cholinesterase inhibitor, neostigmine, increases the activation of muscarinic receptors by inhibiting the breakdown of acetylcholine, thereby stimulating colonic motor activity and decreasing the intestinal transit time (3,11,12). Oral intake of neostigmine in the ACPO disease is not recommended due to its irregular absorption from the gastrointestinal tract (3).

Most ACPO patients respond to conservative methods within 3 days (13-15). Medical treatment, decompression by colonoscopy, or surgical intervention are other performed methods when no response is obtained with conservative treatments. Colonoscopic decompression leads to a decreased cecal diameter in 70% of patients with ACPO, which can be displayed on radiographic images (6,16). Surgical intervention in patients with ACPO, on the other hand, is associated with a high mortality rate (17,18).

Neostigmine is widely used in the treatment of patients with ACPO who are unresponsive to conservative methods; however, there are various therapy protocols. When literature was searched, no comparative study of the BD and CI protocols was found. In the majority of previous studies, 2 or 2.5 mg neostigmine was given as bolus for durations ranging from 1 to 60 min (19). Only in one study conducted by Van der Spoel et al. (10), a continuous neostigmine infusion was practiced. In that study, patients with critical illness-related colonic ileus (CIRCI) were investigated. Also, it was stated that Ogilvie's syndrome might be a variant of CIRCI. In addition, case reports that mention the effects of CI protocol were discussed (20).

In our study, spontaneous resolution in 64% of the ACPO patients within 48 hours was observed with conservative treatments. However, Mehta et al. (9) found that spontaneous resolution had occurred in 30% of their patients. Notwithstanding, the results of our study in general were consistent with previous studies (7,13-15,21). On the other hand, the rate of spontaneous resolution was lower in the study by Mehta et al. (9) probably because they had set less time (24 hours) to observe the results of conservative treatments.

Because of its efficacy and cheapness, the ease of administration, less invasiveness, no colonic preparation required, lack of major side effects that necessitate cessation of therapy, and because it has not been associated with mortality in any report, we preferred pharmacologic

neostigmine therapy in patients with ACPO who had not responded to conservative measures, prior to colonoscopic decompression and surgical intervention (6,22).

The number of patients that received neostigmine therapy (n=43) was higher in our study than any other similar study (19). In the study by Ponec et al. (22) neostigmine was applied as 2 mg bolus, and a sustained response was acquired in 73% of patients after the first dose. Conor et al. (2) had sustained response in 61% of their patients after the first dose. In the study of Mehta et al. (9) a sustained response after the first dose was acquired in 63% of patients, and the overall response after the second dose was 79%. In our study, a sustained response after the first dose in the BD group was 55%, and the overall response rate after the second dose was 80%.

The overall response rate was 79% in the unique study by Van Der Spoel et al. (10) in which a continuous neostigmine infusion was applied at rates between 0.4 and 0.8 mg/hour for 24 hours. In our study, sustained response after the first dose of neostigmine in the CI group was 60.9%, and the overall response after the second dose was 69.6%. Van Der Spoel et al. (10) did not include patients with Ogilvie's syndrome, but they included patients with CIRCI into their study. That might be the reason why they had more success.

Two groups were compared in terms of treatment response. The BD group had a lower success rate after the first-dose application (BD: 55% vs. CI: 60.9%), but a higher overall response rate after the second-dose application (BD: 80% vs. CI: 69.6%). However, that was not statistically significant. The mean time required to obtain a treatment response was shorter in the BD group (BD: 165 min vs. CI: 510 min) and that was statistically significant. The reason for that was probably the lasting of continuous infusion for 24 hours as a protocol requisite.

One of the patients with ACPO who was unresponsive to a 2.5 mg neostigmine bolus dose responded to the continuous infusion protocol by Van Der Spoel et al. (10). The reason for that might be neostigmine's short duration of action (23). The mean half-life of neostigmine is approximately 1 hour. Continuous infusion may lead to intense peristalsis in the short span and mild protracted peristalsis in the long span. Despite not being statistically significant, the CI protocol seems to be more successful because the first-dose success rate is higher in the CI group than in the BD group. However, its success does not last for a long time since patients exhibit a low response to second dose. In fact, if a response to the first-dose 24-hour infusion is not present, response to the second-dose infusion is limited, and an overall response rate lags behind the BD protocol.

Neostigmine therapy has serious side effects like bronchospasm, bradycardia, and hypotension. The incidence of side effects may be reduced by applying a slow infusion instead of a rapid bolus infusion or by reducing the bolus dose from 2 mg to 1 mg (24). Both neostigmine protocols have been well tolerated in our study. There were no major side effects requiring treatment cessation. Side effects except for salivation and sputum production were more common in the BD group. The difference was not statistically significant, though.

Because the study was conducted in the ICU, abdominal pain that could only be noticed by patients' expressions might be under-presented in both groups. The sedation status of the patients is shown in Table 1 as opioid-benzodiazepine intake. Although sedation is a factor that affects describing abdominal pain, conscious states of non-sedated intensive care patients, hence their perception and expression of pain, vary much according to a number of factors, including their concomitant diseases. For this reason, being non-sedated is not a standard indicator for a good level of consciousness in identifying abdominal pain.

Mehta et al. (9) applied colonoscopic decompression to 4 patients who were unresponsive to the second dose of neostigmine, and they received complete response. Rex et al. (6) indicated that after a successful colonoscopic decompression, approximately 40% of the patients had recurrent colonic distension. Jetmore demonstrated that serial colonoscopic decompressions are required in one-third of patients (16). In our study, a sustained response was obtained by colonoscopic decompression clinically and radiologically for 24 hours in all second-dose unresponsive patients (BD: 4 vs. CI: 7).

There have been some restrictions in our study. First, only 5 (11%) of the patients had recently undergone a surgical procedure. Hence, the majority of the investigation (89%) was performed on nonsurgical patients, and neostigmine response of surgical patients could not be adequately assessed. Second, the sustained response obtained by neostigmine applications or colonoscopic decompressions was followed for 24 hours. Therefore, it was not possible to observe a possible long-term relapse. Third, if two protocols were applied diagonally to the first dose

in unresponsive patients, the superiority of the BD and CI protocols over one another could have been compared.

In conclusion, the reliability and efficacy of both neostigmine protocols are similar in pharmacological treatment of the ACPO disease. Clinical and radiological responses are obtained with continuous infusion of neostigmine without serious side effects. Success rates of both protocols can be increased by reapplication treatments. To understand better which protocol is more effective, extensive studies should be carried out, and the protocols should be cross applied to unresponsive patients.

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