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Neostigmine for Treating Acute Colonic Pseudo-Obstruction in Neurocritically Ill Patients

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Background and Purpose Acute colonic pseudo-obstruction (ACPO) is a common but understudied complication in neurocritically ill patients. The acetylcholinesterase inhibitor neostigmine can be used to treat ACPO in patients who do not respond to conventional treatment. This study investigated the effectiveness and adverse events when using neostigmine to manage ACPO in neurocritically ill patients.

Methods This retrospective study investigated patients with ACPO who were treated using neostigmine in the neurological intensive-care units at two centers between March 2017 and August 2020. Neostigmine was administered intravenously or subcutaneously (at doses ranging from 0.25 mg to 2 mg) according to the protocols at the two centers. The outcomes were bowel movements and the changes in colon diameters on abdominal radiographs. Safety events such as bradycardia, vomiting, salivation, and sweating were evaluated.

Results This study included 31 subjects with a mean age of 46.8 years (65.4% males). All patients had a bowel movement at a median of 120 minutes after administering neostigmine. The colon diameter decreased by a median of 17.5 mm (paired t-test: $p<0.001$) regardless of the dose and treatment protocols. Multilevel analysis confirmed that the mean colon diameter decreased from 66 mm pretreatment to 47.5 mm posttreatment ($p<0.001$), with an intraclass correlation coefficient of 13%. Three patients (9.7%) exhibited hypersalivation, sweating, bradycardia, and vomiting. Bradycardia (heart rate, 42 beats/minute) occurred in one patient (3.2%), and was successfully managed by injecting atropine.

Conclusions Neostigmine injection is a safe and effective treatment option for ACPO in neurocritically ill patients who fail to respond to conservative management.

Keywords neostigmine; intestinal pseudo-obstruction; critical illnesses.

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INTRODUCTION

Acute colonic pseudo-obstruction (ACPO; also called Ogilvie syndrome) is characterized by gross dilatation of the colon in the absence of a mechanical obstruction.[1-3] ACPO often occurs in critically ill patients due to the disturbance of gastrointestinal motility induced by severe medical illnesses. Regardless of the underlying condition, early recognition and timely management are important to avoid life-threatening complications of ACPO such as colonic ischemia, bowel perforation, and peritonitis.[1,2,4] Neostigmine is an acetylcholinesterase inhibitor exerting potent muscarinic effects that promote intestinal smooth-muscle contractions and augment peristalsis.[5-7] Previous studies have shown that neostigmine is a safe and effective treatment option for ACPO in patients who do not respond to conservative management.[5,8-10] However, the effect of neostigmine on APCO in neurological intensive-care unit (NeuroICU) patients has rarely been studied. Gastrointestinal motility problems are common in NeuroICU patients.[11-14] Both the severity of neurological illnesses and

the medications used such as opioids or drugs with strong anticholinergic effects put neurocritically ill patients at risk of developing ACPO. Despite this condition being observed frequently in clinical practice, very little has been published about its treatment. Therefore, we investigated the safety and effectiveness of neostigmine for the treatment of ACPO in neurocritically ill patients.

METHODS

Study population and clinical information

We retrospectively identified 31 consecutive patients with APCO who were treated using neostigmine in the NeuroICU at two centers (Center 1, Seoul National University Hospital, Seoul, Republic of Korea, *n*=15; Center 2 , University of Texas Houston Health Science Center, Houston, TX, USA, *n*=16) between March 2017 and August 2020. Information was collected on demographic characteristics including age and sex, comorbidities including history of bradyarrhythmia (heart rate, <50 beats/minute), and concomitant medications such as antiepileptic drugs, opioids, anticholinergics, beta adrenergic agonists or antagonists, prokinetics, and laxatives. Information was also collected on the primary diagnosis at admission and the history of diseases related to gastrointestinal motility from electronic medical records. We also retrospectively obtained abdominal CT findings from electronic medical records to differentiate the causes of colonic dilatation. ACPO was diagnosed based on typical clinical features as well as colonic dilatation found in radiological imaging.[6-10] This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (No. H-2010-153-1167) and the University of Texas Houston Health Science Center (No. HSC-MS-20-1123). The need for informed consent was waived by the IRBs.

Efficacy and safety of neostigmine

All patients were initially treated with conservative managements including correction of electrolyte imbalances and altering or stopping offending medications, in accordance with published recommendations.[15,16] Neostigmine was considered if APCO did not respond to this conservative management. Neostigmine was administered using either an intravenous (IV) or a subcutaneous (SC) injection over 5 minutes according to the protocols at each center. The dose of neostigmine (0.25, 0.5, 1, or 2 mg) was chosen at the discretion of the neurointensivists in charge at each center (2 mg was used in Center 1, and 0.25, 0.5, 1, or 2 mg was used in Center 2).[5,9] Clinical responses were observed for up to 3 hours after administering neostigmine. If there was no bowel movement or relief of abdominal distension, an additional dose of neostigmine was administered.

Vital signs and electrocardiograms were monitored continuously before and after administering neostigmine. The primary efficacy outcome was the clinical response, defined by a bowel movement following neostigmine injection. The secondary efficacy outcomes were changes in the abdomen circumference and the colon diameter, including of the cecum, ascending colon, transverse colon, and descending colon on plain radiographs within 24 hours after the injection.[5,9,10] We also assessed clinical improvement outcomes such as success of initiating enteral feeding and endoscopic or surgical decompression during hospitalization. Safety outcomes of neostigmine were also assessed, including cardiac arrest, bradycardia, syncope, bronchospasm, vomiting, severe salivation, and severe lacrimation for up to 24 hours after administering the last dose of neostigmine.

Statistical analysis

Categorical variables are presented as numbers and percentages, continuous variables conforming to a normal distribution are presented as mean±standard deviation values, and variables that were not normally distributed are presented as medians and interquartile ranges (IQRs). Changes in the abdomen circumference and the colon diameter between before and after the neostigmine treatment were assessed using the paired *t*-test or the Wilcoxon test, as appropriate. Moreover, we performed multilevel logistic regression analysis using a linear mixed-effects model while adjusting for confounders including age, sex, route of neostigmine treatment, initial dose, and centers as a random effect in order to estimate center-specific effects.[2,15]

Statistical analyses were conducted and reviewed by a professional medical statistician. For all analyses, a two-tailed *p* value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS program (version 25.0, IBM Statistics, Armonk, NY, USA) and the SAS program (version 9.4, SAS Institute, Cary, NC, USA).

RESULTS

This study included 31 patients with a mean age of 46.8 years, of whom 20 (65.4%) were male. The admission diagnoses comprised stroke (ischemic stroke and hemorrhagic stroke; *n*=11, 35.5%), status epilepticus (*n*=7, 22.6%), anti-N-methyl-d-aspartate (NMDA) receptor encephalitis (*n*=4, 12.9%), traumatic brain injury (*n*=4, 12.9%), traumatic spinal cord injury (*n*=3, 9.7%), anaplastic astrocytoma (*n*=1, 3.2%), and cardiac arrest (*n*=1, 3.2%; Tables 1 and 2). No patient had bradyarrhythmia at baseline (Table 2). Fifteen of the included patients (48.4%) underwent abdominal CT to exclude

Table 1. Characteristics of the included patients at the two centers

Patient no.	Sex	Age, years	Diagnosis	Dose	Route	Clinical response
Center 1						
1	F	70	Multiple embolic infarction	2 mg (×1)	IV	BM (+)
2	F	72	Anaplastic astrocytoma	2 mg (×1)	IV	BM (+)
3	M	49	Status epilepticus	2 mg (×1)	IV	BM (+)
4	F	28	Post cardiac arrest	2 mg (×2/day)	IV	BM (+)
5	F	58	Status epilepticus	2 mg (×1)	IV	BM (+)
6	F	18	Status epilepticus	2 mg (×1) 2 mg (×1); repeated injection at 3 days after first treatment	IV IV	BM (+) BM (+)
7	F	35	Bilateral MCA infarction	2 mg (×1)	IV	BM (+)
8	F	36	Status epilepticus	2 mg (×1) 2 mg (×1); repeated injection at 1 day after first treatment	IV IV	BM (+) BM (+)
9	M	65	Bilateral MCA infarction	2 mg (×1)	IV	BM (+)
10	M	18	Status epilepticus	2 mg (×1) 2 mg (×1); repeated injection at 1 day after first treatment	IV IV	BM (+) BM (+)
11	F	18	Anti-NMDA-receptor encephalitis	2 mg (×1)	IV	BM (+)
12	F	21	Anti-NMDA-receptor encephalitis	2 mg (×1)	IV	BM (+)
13	F	29	Anti-NMDA-receptor encephalitis	2 mg (×1)	IV	BM (+)
14	M	23	Status epilepticus	2 mg (×1)	IV	BM (+)
15	F	21	Anti-NMDA-receptor encephalitis	2 mg (×1) 2 mg (×1); repeated injection at 1 day after first treatment	IV IV	BM (+) BM (+)
Center 2						
1	M	82	Acute left traumatic SDH	0.25 mg (×2)	SC	BM (+)
2	M	70	Right PICA infarction	1 mg (×2)	IV	BM (+)
3	M	55	C3 transverse process fracture	2 mg (×1)	IV	BM (+)
4	M	46	Cerebellar AVM-related left PICA aneurysmal SAH with IVH	2 mg (×1)	IV	BM (+)
5	M	70	IVH with hydrocephalus	2 mg (×1)	IV	BM (+)
6	M	33	Left parietal AVM rupture	1 mg (×1)	IV	BM (+)
7	M	77	Traumatic left SDH, SAH, and left temporal contusion	1 mg (×1)	IV	BM (+)
8	M	55	Perimesencephalic SAH	1 mg (×1) 1 mg (×1); repeated injection at 1 day after first treatment	IV IV	BM (+) BM (+)
9	M	40	Basilar artery occlusion	1 mg (×2) 1 mg (×1); repeated injection at 1 day after first treatment	IV IV	BM (+) BM (+)
10	M	54	Traumatic right SDH, bifrontal SAH, and right posterior temporal contusion	0.5 mg (×1)	IV	BM (+)
11	M	50	Right MCA infarction	0.25 mg (×1)	IV	BM (+)
12	M	42	Left basal ganglia ICH with IVH	0.25 mg (×1) 0.25 mg (×1); repeated injection at 1 day after first treatment 0.25 mg (×1) and 0.5 mg (×1); repeated injection at 2 days after first treatment 2 mg (×1); repeated injection at 3 days after first treatment	SC SC SC IV	BM (+) BM (+) BM (+) BM (+)
13	M	41	Spinal cord injury (C6-C7 fracture)	0.25 mg (×3) 0.25 mg (×3); repeated injection at 3 days after first treatment 0.25 mg (×3); repeated injection at 4 days after first treatment 0.5 mg (×4); repeated injection at 5 days after first treatment 0.5 mg (×2); repeated injection at 6 days after first treatment	SC SC SC SC SC	BM (+) BM (+) BM (+) BM (+) BM (+)
14	M	71	Traumatic right SDH, left temporal SAH, C5-C6 hyperextension injury, and central cord syndrome	0.5 mg (×1)	IV	BM (+)
15	M	46	Spinal cord injury (C3-C4 retropulsion)	0.5 mg (×1)	IV	BM (+)
16	M	57	Status epilepticus	0.25 mg (×1) 1 mg (×1); repeated injection at 2 days after first treatment	IV IV	BM (+) BM (+)

AVM: arteriovenous malformation, BM: bowel movement, ICH: intracerebral hemorrhage, IV: intravenous, IVH: intraventricular hemorrhage, MCA: middle cerebral artery, NMDA: N-methyl-d-aspartate, PICA: posterior inferior cerebellar artery, SAH: subarachnoid hemorrhage, SC: subcutaneous, SDH: subdural hemorrhage.

Table 2. Efficacy and safety of neostigmine in the treatment of acute colonic pseudo-obstruction in all patients (*n*=31)

Parameter	Value
Age, years	46.8±19.5
Sex (male)	20 (65.4)
Diagnosis at admission	
Stroke (ischemic and hemorrhagic)	11 (35.5)
Status epilepticus	7 (22.6)
Anti-N-methyl-d-aspartate-receptor encephalitis	4 (12.9)
Traumatic brain injury	4 (12.9)
Traumatic spinal cord injury	3 (9.7)
Cardiac arrest	1 (3.2)
Astrocytoma	1 (3.2)
History of bradyarrhythmia	0 (0.0)
Route	
IV	28 (90.3)
SC	2 (6.5)
IV and SC	1 (3.2)
Efficacy	
Time to BM following initiation of neostigmine, minutes	120 [60–210]
Change in colon diameter, mm	-17.5 [-12.8 to -26.3]
BM	31 (100.0)
Enteral feeding after neostigmine	28 (90.3)
Adverse events	4 (12.9)
Bradycardia	1 (3.2)
Bronchospasm	0 (0.0)
Vomiting	1 (3.2)
Severe salivation	1 (3.2)
Severe lacrimation	0 (0.0)
Severe sweating	1 (3.2)

Data are presented as mean±standard deviation, *n* (%), or median [interquartile range].
BM: bowel movement, IV: intravenous, SC: subcutaneous.

mechanical causes of bowel obstruction. Before the administration of neostigmine, all patients were taking more than three medications (prokinetics or laxatives) for ACPO (Supplementary Table 1 in the online-only Data Supplement). Neostigmine was administered intravenously in 90.3% patients (*n*=28) (Table 2).

For the primary outcome, all patients had bowel movements after the first injection of neostigmine, and the median time from the administration of neostigmine to defecation was 120 minutes (IQR, 60–210 minutes). Five patients (16.1%) received an additional dose of neostigmine on the same day as the first round of neostigmine treatment. Patients with a lower dose of neostigmine tended to require repeated neostigmine treatment (Table 3). Nine patients (29.0%) were treated using another round of neostigmine injection at a median of

Table 3. Association between initial dose and repeated injection on the same day

	No repeated dose	Repeated dose	*p*
Total	26 (83.9)	5 (16.1)	
Initial dose, mg			0.034
0.25	2 (7.7)	3 (60.0)	
0.5	3 (11.5)	0 (0.0)	
1	4 (15.4)	1 (20.0)	
2	17 (65.4)	1 (20.0)	

Data are presented as *n* (%).

1 day after the initial treatment (IQR, 1–2.5 days) due to a partial response to neostigmine treatment or the recurrence of APCO. The secondary outcome of the colon diameter on plain radiographs significantly decreased by a median of 17.5 mm (IQR, -12.8 to -26.3 mm; paired *t*-test: $p<0.001$) (Fig. 1 and Table 2). The treatment effects of neostigmine on the colon diameter were consistently significant at each center (Fig. 2 and Supplementary Tables 2 and 3 in the online-only Data Supplement). Multilevel analysis considering the center as a random effect revealed that the administration of neostigmine was significantly effective in reducing the colon diameter [least-square mean: from 66 mm (95% confidence interval, 43.9–89.2 mm) pretreatment to 47.5 mm (95% confidence interval, 24.8–70.1 mm) posttreatment, $p<0.001$), with an intraclass correlation coefficient of 13% for each center. Moreover, the abdomen circumference, which was measured only in Center 1 and at a median of 24 hours (IQR, 3.5–24.0 hours) after neostigmine injection, decreased by a median of 1.75 cm (IQR, 0.98 to 2.50 cm; paired *t*-test: $p=0.001$) after the administration of neostigmine (Supplementary Table 2 in the online-only Data Supplement and Supplementary Fig. 1 in the online-only Data Supplement).

Regarding the clinical outcomes during hospitalization, enteral feeding was initiated in 28 patients (90.3%) after neostigmine treatment, and no patient required endoscopic or surgical decompression (Table 2). In addition, 10 patients (32.3%) were being treated using opioids prior to neostigmine therapy, but the effect of neostigmine was not influenced by the use or nonuse of opioids (colon diameter: median, -21.1 mm; IQR, -27.0 to -12.6 mm in opioid nonusers vs. median, -16.3 mm; IQR, -23.5 to -11.1 mm in opioid users; $p=0.569$) (Supplementary Table 1 in the online-only Data Supplement). In addition, one patient was treated using quetiapine (300 mg/day, minimal anticholinergic effect), and no patient was taking beta adrenergic agonists or antagonists (Supplementary Table 1 in the online-only Data Supplement).

Safety outcomes were monitored for up to 24 hours following the administration of the last dose of neostigmine. Four patients (12.9%) experienced adverse events including hy-

persalivation, sweating, and vomiting, which did not require additional management. Among them, one patient had an episode of transient bradycardia (42 beats/minute) at 1 hour after the IV administration of neostigmine (2 mg), which subsided after injecting atropine (0.5 mg). There was no sudden decrease in the blood pressure or respiration rate. None of the patients experienced syncope, bronchospasm, or cardiac arrest after the administration of neostigmine.

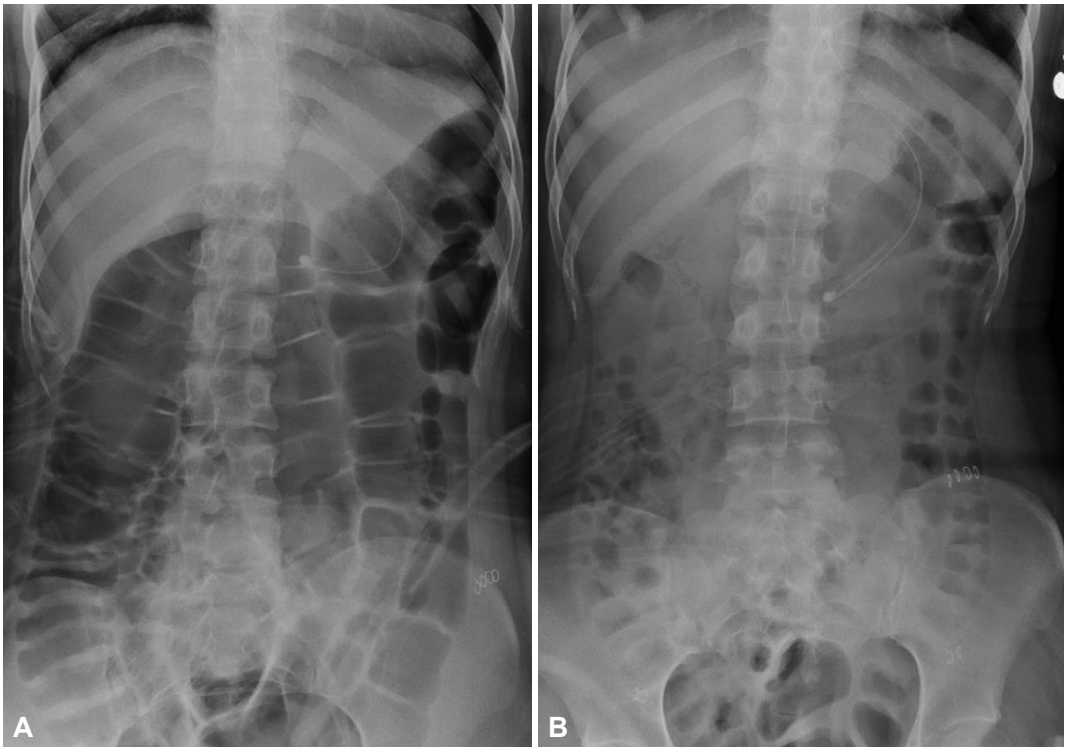

Fig. 1. Treatment effect of neostigmine on ACPO. Plain abdominal radiographs obtained before (A) and after (B) the intravenous administration of neostigmine (2 mg) in a 23-year-old female with anti-N-methyl-d-aspartate receptor encephalitis. (A) Initial imaging shows massive colonic dilatation consistent with ACPO. (B) A bowel movement occurred 2.5 hours after the neostigmine injection, and follow-up imaging performed 24 hours after the injection showed an improvement in colonic dilatation with a decrease in the diameter of the colon. ACPO: acute colonic pseudo-obstruction.

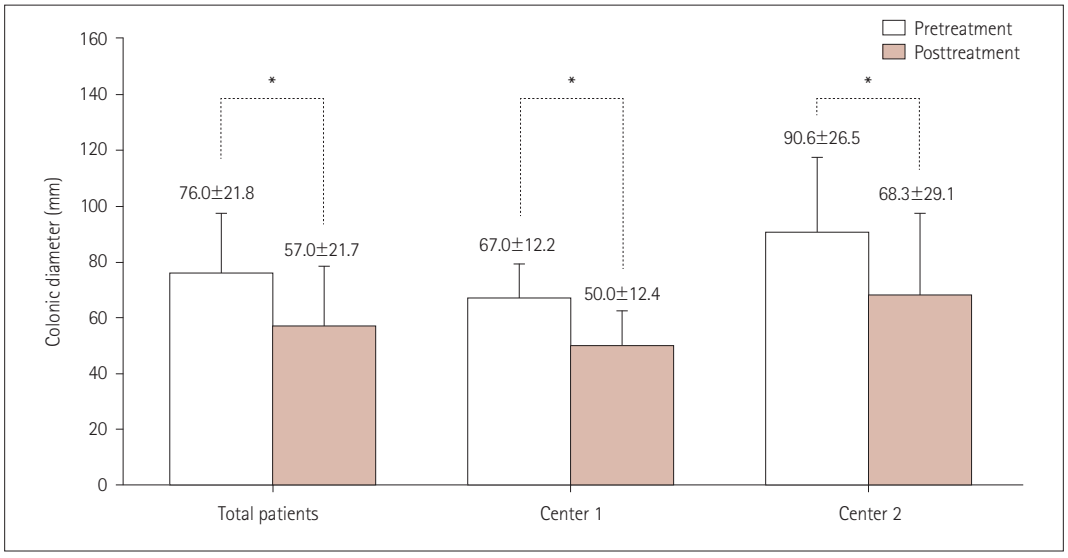

Fig. 2. Effect of neostigmine on colon diameter. Neostigmine treatment induced significant reductions in the colon diameter at the two centers. Data are mean±standard deviation values. *$p<0.001$.

DISCUSSION

This study found that the IV or SC injection of neostigmine facilitated bowel movements and reduced the colon diameter on radiographic imaging in neurocritically ill patients with ACPO that were refractory to conventional medical management. The effect was consistent regardless of the route of injection and the treatment center. Moreover, adverse effects were transient and minor, and hence did not raise significant clinical concerns.

While the exact pathophysiology of ACPO remains to be elucidated, it is regarded as a dysfunctional colonic motility disorder caused by an imbalance in the gastrointestinal autonomic nervous system.[1,6,8,9] Neurocritically ill patients are at high risk of ACPO because they are frequently treated using drugs that have anticholinergic effects, such as barbiturates or opioids. In addition, most of these patients have a serious brain injury such as severe stroke, status epilepticus, traumatic brain injury, or encephalitis, which often leads to excessive parasympathetic suppression, sympathetic stimulation, and impairment of colonic autonomic regulation.[1,11-14,17,18] Together these factors could disturb gastrointestinal motility and result in the development of ACPO.

The traditional management of ACPO includes bowel rest with the placement of a nasogastric tube or the use of prokinetics.[1,3] Colonoscopic decompression can be attempted if conventional treatment fails. Our study suggests that neostigmine can be a safe and effective option for medical treatment. Neostigmine is a parasympathomimetic agent that reversibly inhibits acetylcholinesterase activity and thereby increases the concentration of acetylcholine at synapses. Moreover, neostigmine indirectly stimulates nicotinic and muscarinic receptors, which help contract colonic smooth muscles and increase colonic motility.[6,7,9,10] In the present study, the administration of neostigmine via either IV or SC injection rapidly resolved colonic dilatation in all patients with ACPO who had failed to respond to multiple prokinetics or laxatives. In addition, 20 patients (71.6%) responded to the first round of treatment, regardless of age, dosage, route, or treatment center, despite neostigmine having a short elimination half-life (about 80 minutes), which is consistent with previous reports.[7,9,10] However, another round of treatment was required when the dose was lower than 2 mg. We also found a low rate of significant adverse events. Only one patient (3.2%) experienced an episode of bradycardia, which was successfully managed by the IV injection of atropine. The percentage of patients with adverse events was similar or even lower than in previous studies.[5-10]

Our study was subject to several limitations. First, it had a retrospective design, and so there was a risk of unmeasured bias. Second, we did not include control groups with which to compare the effect of neostigmine on ACPO. However, a bowel movement occurred in all patients and their colon diameter decreased by 25% (from 76.0 mm before treatment to 57.0 mm after treatment). Given that none of the patients responded to conventional medical treatment, we consider this effect of neostigmine on ACPO to be noteworthy. Third, this study included a relatively small number of patients, although the number is comparable to those in previous studies.[5-10] Fourth, abdominal CT scans were performed in 15 patients (48.4%) to rule out mechanical causes of bowel obstruction. ACPO was diagnosed in the remaining patients based on clinical presentations and serial abdominal plain radiographs based on previous studies.[6-10,16] Fifth, 11 patients (35.5%) were being treated using opioids or anticholinergics prior to neostigmine administration. However, the effect of neostigmine on APCO was similar regardless of the presence or absence of other drugs. Sixth, neostigmine was administered at the discretion of the neurointensivists in charge according to the treatment protocols at each center. Notably, the effect of neostigmine on bowel movements was similar in the two centers. In addition, the relationship between neostigmine and improvement of ACPO remained significant after adjusting for the center effect.

In conclusion, neostigmine may be a safe and effective treatment option for neurocritically ill patients with ACPO who fail to respond to conventional medical management. Monitoring of adverse events should be considered despite their low probability. Future clinical trials and larger studies are needed to validate the use of neostigmine and identify the optimal dose and route of administration in neurocritically ill patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.4.563.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Sang-Bae Ko, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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REFERENCES

1. De Giorgio R, Knowles CH. Acute colonic pseudo-obstruction. *Br J Surg* 2009;96:229-239.
2. Antonucci A, Fronzoni L, Cogliandro L, Cogliandro RF, Caputo C, De Giorgio R, et al. Chronic intestinal pseudo-obstruction. *World J Gastroenterol* 2008;14:2953-2961.
3. Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome). An analysis of 400 cases. *Dis Colon Rectum* 1986;29:203-210.
4. Ritz MA, Fraser R, Tam W, Dent J. Impacts and patterns of disturbed gastrointestinal function in critically ill patients. *Am J Gastroenterol* 2000;95:3044-3052.
5. Kram B, Greenland M, Grant M, Campbell ME, Wells C, Sommer C. Efficacy and safety of subcutaneous neostigmine for ileus, acute colonic pseudo-obstruction, or refractory constipation. *Ann Pharmacother* 2018;52:505-512.
6. Valle RG, Godoy FL. Neostigmine for acute colonic pseudo-obstruction: a meta-analysis. *Ann Med Surg (Lond)* 2014;3:60-64.
7. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure--a prospective, double-blind, placebo-controlled trial. *Intensive Care Med* 2001;27:822-827.
8. Elsner JL, Smith JM, Ensor CR. Intravenous neostigmine for postoperative acute colonic pseudo-obstruction. *Ann Pharmacother* 2012;46:430-435.
9. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999;341:137-141.
10. Lee JW, Bang KW, Jang PS, Chung NG, Cho B, Jeong DC, et al. Neostigmine for the treatment of acute colonic pseudo-obstruction (ACPO) in pediatric hematologic malignancies. *Korean J Hematol* 2010;45:62-65.
11. Lee SJ, Na IH, Choi ES, Jung SH, Yoon JS. Occurrence of intestinal pseudo-obstruction in a brainstem hemorrhage patient. *Ann Rehabil Med* 2012;36:278-281.
12. Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. *Nat Clin Pract Neurol* 2007;3:291-296.
13. Madl C, Druml W. Gastrointestinal disorders of the critically ill. Systemic consequences of ileus. *Best Pract Res Clin Gastroenterol* 2003;17:445-456.
14. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011;134:2802-2818.
15. Vogel JD, Feingold DL, Stewart DB, Turner JS, Boutros M, Chun J, et al. Clinical practice guidelines for colon volvulus and acute colonic pseudo-obstruction. *Dis Colon Rectum* 2016;59:589-600.
16. Naveed M, Jamil LH, Fujii-Lau LL, Al-Haddad M, Buxbaum JL, Fishman DS, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. *Gastrointest Endosc* 2020;91:228-235.
17. Kieninger M, Sinner B, Graf B, Grassold A, Bele S, Seemann M, et al. Standardized application of laxatives and physical measures in neurosurgical intensive care patients improves defecation pattern but is not associated with lower intracranial pressure. *Crit Care Res Pract* 2014;2014:367251.
18. Bansal V, Costantini T, Kroll L, Peterson C, Loomis W, Eliceiri B, et al. Traumatic brain injury and intestinal dysfunction: uncovering the neuro-enteric axis. *J Neurotrauma* 2009;26:1353-1359.