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Subcutaneous Neostigmine is Effective and Safe in the Treatment of In-Hospital Colonic Ileus

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Abstract

The objective of this study is to compare the efficacy and safety of subcutaneous (SQ) neostigmine to intravenous (IV) neostigmine for the treatment of in-hospital colonic ileus on outcomes such as resolution of ileus, time to stooling, and total adverse events. This is a retrospective, cohort review study of inpatients diagnosed with colonic ileus and treated with either IV or SQ neostigmine. We found that no differences in ileus resolution post-neostigmine comparing the IV (37%; n=11) to the SQ (78%, n=7) (p=0.05) groups, time to first stooling in IV vs SQ (19.5 ± 32.4 hours vs. 5.3 ± 6.4 hours, p= 0.07), need for decompressive colonoscopy (30% vs 22%, p=1.0), and need for ICU admission (28% vs 6%, p= 0.07%) in the IV vs SQ groups respectively, or adverse events (p=0.11) in the IV versus SQ neostigmine groups; although the total neostigmine dose used in the SQ group was lower (p<0.001). There was no statistically significant difference in adverse events in the IV group vs the SQ group (14% vs 11%, p=0.11). Based on these results, SQ neostigmine appears to be effective and safe in resolving colonic ileus.

Keywords: Colonic ileus; Pseudo-Obstruction; Ogilvie's Syndrome; Neostigmine

Introduction

Acute colonic pseudo-obstruction, or colonic ileus presents with signs and symptoms of mechanical obstruction of the large bowel without exhibiting a mechanical origin. Patients often present with abdominal pain, nausea, vomiting, and constipation, and the hallmark feature which is abdominal distension [1]. Risk factors for developing colonic ileus include a history of multiple chronic medical conditions, prolonged hospitalizations, metabolic imbalance, and recent surgery. Colonic ileus can result in severe complications such as perforation and intestinal ischemia, especially in patients with greater than 12 cm cecal dilation on abdominal imaging [1]. The condition affects around 1.2% of hospitalized patients and is associated with substantial hospital costs, mortality and morbidity [2]. The exact pathophysiology is unknown, although current proposed mechanisms suggest disruption of the parasympathetic function of the bowel [1].

Uncomplicated colonic ileus is managed conservatively with bowel rest, discontinuing antimotility drugs such as opiates, nasogastric tube decompression, correction of fluid and electrolyte abnormalities, and patient ambulation. The reported success of using conservative measure to manage ileus varies, but has been described to be effective in up to 80% of patients [3]. Persistent ileus, defined as symptoms lasting for more than

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72 hours despite conservative management, often requires more aggressive pharmacological therapy or decompressive endoscopy. Although there is substantial variability in clinical practice, neostigmine, a pro-cholinergic medication that stimulates colonic contractility, is usually administered intravenously (IV) as a bolus and has been used with good success in treating refractory non-mechanical colonic ileus [4-8]. Interestingly, multiple studies have shown up to 90% resolution of colonic ileus cases with passage of stool or flatus after administering neostigmine [1,4,6,9]. Despite the current available literature showing that neostigmine is a safe and effective option for treating colonic ileus, reported and perceived adverse events has led to some hesitation in practice prescribing this medication [10]. The cholinergic adverse events of neostigmine that have been widely reported are abdominal pain, nausea, vomiting, sialorrhea, bronchospasm and most significantly - bradycardia [10]. One metanalysis has identified several randomized control trials comparing the benefits and adverse events of neostigmine, however, the power of these studies and number of patients enrolled are low [9]. Dosing protocols and regimens for neostigmine are currently unstandardized, likely further contributing to difficulty adopting neostigmine use for colonic ileus into clinical practice [9].

Although neostigmine is most frequently prescribed as an IV bolus, previous data has included treatment with continuous drips and other formulations such as subcutaneous (SQ) administration. Recently, SQ neostigmine was found to be very safe in the treatment of colonic ileus, with adverse events observed in only 1.6% of patients [5]. Given the concern for need for life-threatening bradyarrhythmia and the need for cardiac monitoring when using the IV formulation, SQ neostigmine might provide a safer option with lower adverse event rate in the treatment of ileus. However, there has been little data comparing the IV and SQ forms of neostigmine to evaluate efficacy in the inpatient setting. In this retrospective, single-center, cohort review study, we analyzed a group of hospitalized patients treated with either IV or SQ neostigmine to see if there were any differences in efficacy or adverse event profiles of the two formulations in treatment of non-mechanical colonic ileus.

Methods

Patient Selection:

This is a retrospective, cohort review study conducted at a tertiary care, level one trauma hospital in Houston, Texas (TX), USA. Institutional Review Board approval was granted by the University of Texas Health Science Center at Houston, Houston, TX, USA. Patient information was obtained from an electronic medical record system. Patients were included if they were ≥18 years of age and were diagnosed with colonic ileus as defined by ICD-9 codes 564.89, 560.89, and 560.1 or -10 codes K59.39, K56.7, K56.50, and K56.0 (Table 1; Supplemental Figure 1). In our hospital the gastroenterology (GI) service is consulted for management of colonic ileus. The patients who were selected were hospitalized between 01/01/2015 to 12/31/2020 and were treated for non-mechanical colonic ileus with at least one dose of IV or SQ neostigmine and were seen by the GI service (Supplemental Figure 1). All patients who were included in the study were adults >18 years of age and met the radiographic imaging definition of colonic ileus which was determined by the reviewing radiologist as dilated colonic bowel loops in the absence of a mechanical cause. Radiological imaging specifically included plain film abdominal x-ray and computed tomography (CT) scan of the abdomen in all patients. Patients were diagnosed with colonic ileus as defined by ICD-9 and ICD-10 codes listed previously, received at least one dose of IV or SQ neostigmine, and were evaluated by the GI service.

Patients were excluded if they did not receive neostigmine, neostigmine was given for alternative reasons such as anesthesia, if they received both IV and SQ neostigmine, an incorrect diagnosis was made, no records were available for review or a concurrent diagnosis of mechanical bowel obstruction existed, or if they had pre-existing bradycardia or if they underwent a colonoscopic decompression prior to neostigmine administration.

Institutional Treatment Protocol:

The management protocol for colonic ileus at our institution begins with conservative measures for at least 48 hours which include bowel rest, nasogastric tube decompression, correction of fluid and electrolyte disturbances, ambulation and discontinuing opiates. After failing conservative measures and identifying reversible causes of colonic ileus, neostigmine is considered next at dosing and routes determined by the consultant gastroenterologist. Neostigmine

Table 1: ICD 9 and ICD 10 codes used by hospital EMR system to capture patients diagnosed with colonic ileus

ICD-10-Code	Description
K56.7	Ileus, unspecified
K56.0	Paralytic ileus
K56.51	Intestinal adhesions [bands], with partial
K56.50	Intestinal adhesions [bands], unspecified as to partial versus complete obstruction
K59.39	Other megacolon
K59.81	Ogilvie syndrome
ICD-9-Code	**Description**
560.1	Adynamic ileus or intestine (see also Ileus)
560.89	1. Ogilvie's (sympathicotonic colon obstruction) 2. Pseudo-obstruction, acute
564.89	Pseudo-obstruction, intestine (chronic) (idiopathic) (intermittent secondary) (primary)

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is typically dosed at our institution in 1 mg increments when administered IV and is most frequently prescribed as 2 mg IV once followed by a second dose of 2 mg to 5 mg administered every 6 hours if there is partial or non-response, as described by current practice guidelines [10]. SQ neostigmine is administered in 0.25 mg once followed by 0.25 mg every 6 hours to a maximum dose of 1 mg daily.

Per hospital protocol, patients treated with neostigmine were monitored in locations with cardiac monitoring and telemetry capabilities, namely in the intermediate monitoring units and intensive care units.

Statistical Analysis

Data was recorded using the computer program Microsoft Excel (Redmond, WA, USA). The computer program R (5), accompanying R-studio (6) (version 1.2.5033, Orange Blossom) and GraphPad (La Jolla, CA, USA, www.graphpad.com) Prism version 8 software program for Mac OS Catalina were used for statistical computations. For continuous variables, a Welch's One-Way test or Mann-Whitney-U test were used to make comparisons. For categorical data, a Fisher-exact test was used to make comparisons. For all analyses, a p-value<0.05 was considered statistically significant. The code and raw data are available for analysis upon reasonable request.

Clinical Outcomes

The primary outcome was resolution of ileus after administration of neostigmine defined by the passage of stools or flatus in 24 hours. Secondary outcomes included need for intensive care unit ICU stay (if patient was not already in the ICU), length of ICU stay, number of doses of neostigmine received, total dose of neostigmine received, time to first stooling, need for decompressive colonoscopy post-neostigmine administration, and total adverse event rate during hospitalization. Adverse events outcomes include the following: need for transcutaneous pacing, need for atropine administration and the development of minor adverse events which are defined as the development of nausea, vomiting, bronchospasm or abdominal pain post-neostigmine administration.

Results

In total, 449 patients were diagnosed with colonic ileus. Thirty-nine patients (9%) met inclusion criteria (Supplemental Figure 2). Patients who did not receive neostigmine and achieved resolution with conservative management were excluded from the study criteria (79%, n=324). In total, 77% (n=30) patients received IV and 23% (n=9) received SQ neostigmine (Table 2). The average age of the total population was 55.9 15.1 years, average BMI was 29.1 6.5 kg/m^2 and median Charlson Co-morbidity index [10] was 4 (Interquartile range, IQR: 3-5). Most of the patients were male in the combined groups (87%, n=34). Both the IV and SQ neostigmine cohorts presented with other chronic comorbidities including diabetes and hypertension, which were the most common concurrent medical conditions. There were no differences between both groups in the length of stay, BMI, age, gender or Charlson co-morbidity index.

Table 2: Demographic data comparing IV to SQ neostigmine administration for ileus treatment

	All Study Patients	Type of Neostigmine Used		P-value
		IV	SQ	
Demographics				
Population, count (%)	39 (100)	30 (77)	9 (23)	--
Age, years	55.9±15.1	54.4±14.6	61.1±16.7	0.29
BMI, kg/m^2	29.1±6.5	29.2±6.5	28.5±6.9	0.78
LOS, days	27.5±21.9	29.0±23.7	22.4±14.3	0.32
Charlson co-morbidity index, IQR	4 (3-5)	4 (2-5)	4 (3-5)	0.91*
Male, count (%)	34 (87)	26 (87)	8 (89)	1
Co-morbidity Present, count (%)				
Diabetes	12 (31)	8 (27)	4 (44)	0.41
Hypertension	23 (59)	17 (57)	6 (66)	0.71
Congestive Heart Failure	8 (20)	6 (20)	2 (22)	1
Liver disease	3 (8)	3 (10)	0 (0)	1
Chronic Kidney Disease	6 (15)	5 (17)	1 (11)	1
Chronic Obstructive Pulmonary Disease	3 (8)	2 (7)	1 (11)	0.55

Legend: Unless otherwise stated, data listed as mean ⍰ standard deviation or count (% of column total). Column total listed next to data point if different than main column header. *=Mann-Whitney U test was used to calculate significance

Abbreviations: BMI=Body Mass Index; IQR=Interquartile Range; IV=Intravenous; LOS=Length of stay; SQ=Subcutaneous

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There was no statistically significant difference between the number of patients who had resolution of ileus post-neostigmine comparing the IV (37%; n=11) to the SQ (78%, n=7); (p=0.05) groups (Table 3). Additionally, there were no differences in the IV vs SQ groups respectively in time to first stooling (19.5 ± 32.4 hours vs. 5.3 ± 6.4 hours, p= 0.07), need for decompressive colonoscopy (30% vs 22%, p=1.0), and need for ICU admission (28% vs 6%, p= 0.07%) in the IV vs SQ groups respectively. Patients who were admitted for colonic ileus had an average length of hospital stay of 27.5 ± 21.9 days.

Patients who received SQ neostigmine received more doses (median 3 doses, IQR 1.5-4.5 doses), but a lower total dose (median 1mg, IQR 0.37-1.25mg) relative to the those who received IV neostigmine (number of doses: median 1 dose, IQR 1-2doses, p=0.003; total median dose 2mg, IQR 1-4mg, p<0.001) (Table 3). Surgical management of colonic

Table 3: Clinical outcomes comparing IV to SQ neostigmine administration for ileus treatment

	All Study Patients	Type of Neostigmine Used		P-value
		IV	SQ	
Population Size, count	--	30	9	--
Number of doses received, median (IQR), doses	1 (1-3)	1 (1-2)	3 (1.5-4.5)	0.003*
Total dose of neostigmine received, median (IQR), mg	2 (1-4)	2 (2-4)	1 (0.37-1.25)	<0.001*
Resolution of ileus after any dose of neostigmine, count (%)	18 (46)	11 (37)	7 (78)	0.05
Resolution of ileus after first dose, count (%)	10 (26)	7 (23)	3 (33)	0.67
Resolution of ileus after second dose, count (%)	5 (33), n=15	3 (30), n=10	2 (40), n=5	1
Resolution of ileus after third dose, count (%)	3 (8), n=5	1 (50), n=2	2 (67), n=3	1
Time to first stool, hours	16.8±29.7, n=26	19.5±32.4, n=21	5.3±6.4, n=5	0.07
Need for decompressive colonoscopy, count (%)	11 (28)	9 (30)	2 (22)	1
Need for surgical management	3 (8)	3 (10)	0 (0)	1
Need ICU admission, count (%)	34 (87)	28 (93)	6 (67)	0.07
Average ICU LOS, days	16.9±19.7	18.5±20.9	11.4±14.5	0.26
Need intubation during hospital stay, count (%)	27 (69)	23 (77)	4 (44)	0.1
Need vasopressors during hospital stay, count (%)	19 (49)	16 (53)	3 (33)	0.45
RRT needed during hospital stay, count (%)	11 (28)	9 (30)	2 (22)	1
In-hospital mortality, count (%)	8 (20)	8 (20)	0 (0)	0.16

Legend: Unless otherwise stated, data listed as mean ± standard deviation or count (% of column total). Fisher test, t-test and Mann Whitney U-test (*) used for statistical computation. Column total listed next to data point if different than main column header.

Abbreviations: ICU=Intensive Care Unit; IV=intravenous; LOS=Length of Stay; SQ=Subcutaneous; IQR = Interquartile Range; RRT=Renal Replacement Therapy

Table 4: Adverse events during hospitalization comparing IV to SQ neostigmine administration for ileus treatment

	All Study Patients, count (%)	Type of Neostigmine Used, count (%)		P-value
		IV	SQ	
Population Size	39	30	9	--
Any adverse event	5 (13)	4 (14)	1 (11)	1
Developed Bradyarrhythmia	1 (2)	1 (3)	0 (0)	1
Need for pacing	0 (0)	0 (0)	0 (0)	--
Need for atropine	0 (0)	0 (0)	0 (0)	--
Developed nausea	3 (8)	2 (7)	1 (11)	1
Developed vomiting	0 (0)	0 (0)	0 (0)	--
Developed abdominal pain	2 (5)	2 (7)	0 (0)	1
Developed bronchospasm	3 (8)	3 (10)	0 (0)	1

Legend: Data listed as count (% of column total). Fisher test used to make statistical comparisons. Column total listed next to data point if different than main column header.

Individual adverse events may have occurred more than once in the same patient.

Abbreviations: RRT=Renal Replacement Therapy; IV=intravenous; SQ=Subcutaneous

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ileus was needed in 3 patients in the IV neostigmine group and no patients in the SQ neostigmine groups. Interestingly, the all-cause in-hospital mortality rate was higher at 20% (n=8) in the IV neostigmine cohort. Causes of in-hospital mortality were unrelated to ileus and included 3 patients with septic shock, 2 patients with obstructive and cardiogenic shock, 2 patients with respiratory failure, and one patient with decompensated cirrhosis.

Interestingly, few patients (n=5, 13%) developed adverse events post-neostigmine administration such as nausea, vomiting, abdominal pain, bronchospasm, and bradycardia (Table 4). One patient who developed bronchospasm had a history of COPD and needed scheduled nebulizers after receiving neostigmine. New onset bradyarrhythmia occurred in only 1 patient in the IV neostigmine group and no patients in the SQ neostigmine groups. The patient who developed bradycardia did not require pacing or atropine administration. There were 3 patients in the IV neostigmine group and no patients in the SQ neostigmine group who developed bronchospasm with wheezing and/or chest tightness with new oxygen requirements. There was no statistically significant difference in adverse events in the IV group vs the SQ group (14% vs 11%, p=0.11).

Discussion

Neostigmine is an integral component on management of refractory in-hospital ileus however very few evidence-based guidelines exist clarifying administration route and dosage [1,4,6,10]. The use of neostigmine is currently not commonplace when managing ileus, and most studies to date using SQ neostigmine have only followed small patient cohorts. To our knowledge, this is the first study to retrospectively compare the efficacy of IV and SQ neostigmine in the inpatient setting. We find that there is little difference in clinical outcomes between the two formulations. Importantly, there was no significant difference in ileus resolution, time to first stooling, need for ICU admission or adverse events post-administration, although, the SQ group may have performed better. Additionally, there was no difference in the need for decompressive colonoscopy post IV versus SQ neostigmine. Thus, this data provides supporting evidence that IV and SQ neostigmine share comparable outcomes in safety profile and resolution of colonic ileus.

Interestingly, we found that the total dose of neostigmine used is lower in the SQ group. At our institution, IV and SQ neostigmine are used in 1mg and 0.25 mg increments, respectively. Although there was a clinical difference in adverse events between the IV and SQ neostigmine groups, this was not statistically significant likely due to the low sample size of the study. It is possible that more adverse events were observed in the IV group relative to the SQ group due to the higher total dose of neostigmine administered. Future studies should include larger, prospective clinical trials and controlling for dosage when comparing the two formulations. In addition, an underlying confounding variable might be that the patients in the IV neostigmine group were more ill than the SQ group given that there was a higher mortality rate (although there was no significant difference in the Charlson comorbidity index) and IV medications are more frequently prescribed in ICU level patients. However, it is alarming that 20% of patients receiving IV neostigmine ultimately died, relative to 0% in the SQ group. Due to limited sample size and frequency of this event, it is difficult to draw conclusions regarding this outcome.

This study is limited by its retrospective nature, the smaller sample size and the single center design that limits generalizability. A large percentage of ileus cases resolve with conservative measures, and only refractory cases of ileus necessitated the use of neostigmine. In this study, 79% of patients improved with conservative measures, which falls within the expected range outlined in the literature and likely contributed to low sample size. To date, most retrospective and prospective trials evaluating neostigmine have had small sample sizes likely attributable to provider unfamiliarity in prescribing this cholinergic medication and small patient population with refractory colonic ileus [9]. Current guidelines do not include standardized algorithms for the management of refractory colonic ileus using neostigmine and more research in the field is needed. In contrast to other reviews with average patient population ages of 60-70 years old, our study population involved a younger cohort of patients with a median age of 50 years. It is important to note that this study took place in a level-1 trauma center and tertiary care referral center, and thus, likely included sicker patients relative to other smaller hospital centers. In addition, data was collected prior to the COVID-19 pandemic and may not reflect the impact that the pandemic has had.

In summary, there is no difference between the SQ and IV formulation of neostigmine comparing multiple clinical outcomes of efficacy and safety. However, the SQ group may have performed better in primary and secondary outcomes and may have had fewer adverse events with a larger sample size. Conservative management, such as neostigmine administration, remains the mainstay of therapy of colonic ileus to achieve decompression, per current guidelines [1,6]. This study proposes a change in practice in considering SQ neostigmine as an equally efficacious treatment measure in the management of colonic ileus compared with IV neostigmine.

Conflict of Interest: None declared

Guarantor of the article: Dr. Asmeen Bhatt

Specific author contributions: Jason Wagner, Yllen Hernandez-Blanco, Maneera Chopra, Joseph Young, Colin

Goodman, and Asmeen Bhatt were involved in planning the study. Jason Wagner, Maneera Chopra, Joseph Young, and Colin Goodman collected data. Jason Wagner performed data analysis. Jason Wagner, Maneera Chopra, Yllen Hernandez Blanco, Joseph Young, Colin Goodman, Nirav Thosani, and Asmeen Bhatt wrote the manuscript. All authors have seen and approve of the manuscript in its current form.

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Potential Competing Interests: Jason Wagner, Yllen Hernandez-Blanco, Maneera Chopra, Joseph Young, Colin Goodman, Nirav Thosani, and Asmeen Bhatt have no competing interests involved with this study.

Data Availability: Data is available per reasonable request from the corresponding author

Patient Consent for Publication: None necessary given the retrospective nature of the study

Institutional Review Board Statement: This study involves human participants, no animal participants, and was approved by the UT Health Science Center at Houston McGovern Medical School IRB, approval number 210286, protocol number: HSC-MS-21-0008.

References

1. Harrison, M. Edwyn, et al. "The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction." Gastrointestinal endoscopy 71.4 (2010): 669-679.
2. Solanki S, Chakinala RC, Haq KF, et al. Paralytic ileus in the United States: A cross-sectional study from the national inpatient sample. SAGE Open Med 8 (2020): 2050312120962636.
3. Vilz, Tim O et al. "Ileus in Adults." Deutsches Arzteblatt international 114 (2017): 508-518.
4. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 341 (1999): 137-141.
5. Kram B, Greenland M, Grant M, et al. Efficacy and Safety of Subcutaneous Neostigmine for Ileus, Acute Colonic Pseudo-obstruction, or Refractory Constipation. Ann Pharmacother 52 (2018): 505-512.
6. Saunders MD. Acute colonic pseudoobstruction. Curr Gastroenterol Rep 6 (2004): 410-416.
7. Naveed M, Jamil LH, Fujii-Lau LL, 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 91 (2020): 228-235.
8. Vogel JD, Feingold DL, Stewart DB, et al. Clinical Practice Guidelines for Colon Volvulus and Acute Colonic Pseudo-Obstruction. Dis Colon Rectum 59 (2016): 589-600.
9. Valle RG, Godoy FL. Neostigmine for acute colonic pseudo-obstruction: A meta-analysis. Ann Med Surg (Lond) 3 (2014): 60-64.
10. Saunders, Michael D. "Acute colonic pseudo-obstruction." Best practice & research clinical gastroenterology 21.4 (2007): 671-687.
11. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40 (1987): 373-383.