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SAFETY AND EFFECTIVENESS OF SUBCUTANEOUS METHYLNALTREXONE FOR THE TREATMENT OF ACUTE COLONIC PSEUDO-OBSTRUCTION: A 9 YEAR-PERIOD STUDY

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Abstract

Introduction: Acute colonic pseudo-obstruction (ACPO) or Ogilvie syndrome is a condition characterized by acute atonic dilation of the colon in the absence of mechanical obstruction. The underlying etiology for the development of ACPO is unclear. Short-acting cholinesterase inhibitor, neostigmine is frequently used for treating ACPO. Due to the possible deleterious adverse effect of neostigmine including cardiovascular suppression, it is usually administered under controlled settings in a critical care unit. Methylnaltrexone, a peripherally acting μ-opioid receptor agonist, is indicated for use in treating constipation secondary to systemic opioid use. In this study, we looked into the efficacy and safety of the use of subcutaneous methylnaltrexone in treating patients with ACPO. **Materials & methods:** This is a single-centered retrospective study assessing the efficacy and safety of utilizing subcutaneous methylnaltrexone in the treatment of ACPO. The search period was conducted over a period of 9 years. Radiological findings of large bowel ileus without obstruction was the search criterion for allocating ACPO patients. Exclusion criteria included mechanical large bowel obstruction, intervention by fluoroscopic decompression, and patients who received neostigmine but not subcutaneous methylnaltrexone. Patients received a standard dose of methylnaltrexone 12 mg every 24 hours until a bowel movement (BM) was achieved. **Results:** A total of 39 patients who received at least one dose of subcutaneous methylnaltrexone for the treatment of ACPO were identified. 97.44% of studied patients had received systemic opioids for pain control within 30 days prior to the diagnosis of ACPO. Twenty-two (56.4%) patients had pain improvement after receiving the drug. A total of 35/39 (89.74%) had a BM following methylnaltrexone administration (p-value= 0.01246). Among the responders, an average dose of 1.17 doses (range of 1-2) was administered to achieve the result. The average time of first BM occurrence after receiving methylnaltrexone was 12.85 hours ± 12.29. Pain associated with ACPO measured by difference in pain scale 1-10/10, improved 5.47 hours ± 7.43 following first dose of methylnaltrexone administration (p-value= 0.02265). No adverse events were reported in patients who received methylnaltrexone. **Conclusion:** In setting of reported increase in ACPO incidence worldwide, non-invasive and effective medical management with safe medication profile is called for. Our study delineated objective clinical resolution of symptoms and signs of ACPO through the use of subcutaneous methylnaltrexone with a significant safety profile. Further studies are required to better differentiate the overall efficacy of subcutaneous methylnaltrexone for treatment of ACPO overall and, more specifically, in setting of recent systemic opioid treatment.

Keywords: Ogilvie, Methylnaltrexone, Constipation, Neostigmine

Introduction:

Acute colonic pseudo-obstruction (ACPO) or Ogilvie's syndrome is a condition characterized by acute atonic dilation of the colon in the absence of mechanical obstruction due to colonic autonomic dysregulation commonly occurring in hospitalized patients [1, 2]. The underlying etiology for the development of ACPO is unclear, but some reports have indicated risk factors such as major surgeries, severe acute medical conditions, electrolyte and metabolic dysfunction, and anesthesia could precipitate ACPO [2]. Short-acting cholinesterase inhibitor neostigmine is frequently used intravenously for treating ACPO with reported success rate of 60-90% [3]. In case of IV neostigmine failure to resolve ACPO, endoscopic decompression is resorted for with reported efficacy of 80% [3]. Due to the possible deleterious adverse effect associated with the use of IV neostigmine, including decreased heart rate, nausea and vomiting, hypersalivation, and abdominal discomfort; intravenous (IV) neostigmine is usually

administered under controlled settings in an intensive care unit [4]. Other reports mentioned decreased neostigmine cardiovascular side effects when given in an infusion fashion as opposed to bolus administration [5]. Methylnaltrexone, a peripherally acting μ-opioid receptor antagonist, is indicated for use in treating constipation secondary to systemic opioid use. The use of methylnaltrexone was first described to treat ACPO in a case report by Weinstock, LB, et-al with good safety profile. In our case series, we studied the effect of subcutaneous (SC) methylnaltrexone in patients with ACPO in various clinical settings given its reported safe adverse effect profile when compared to IV neostigmine [6].

Materials & Methods

We performed a single-centered retrospective study assessing the efficacy and safety of utilizing subcutaneous methylnaltrexone in the treatment of ACPO. After obtaining a local institutional review board (IRB) approval, the electronic medical records (EMR) data base was queried to identify appropriate research candidates. We used the following International Classification of Diseases 10th Revision (ICD 10) codes to find appropriate study candidates: other functional disorders of intestine, other intestinal obstruction, large bowel obstruction, ileus, Ogilvie syndrome, and other specified intestinal obstruction. Patients meeting the above desired ICD 10 codes were included if clinical services were provided during emergency department visits or patients admitted to inpatient or observation setting. The search period was conducted for the abovementioned ICD 10 diagnoses from January 1st of 2011 to September 30th of 2019. This resulted in a total of 2,107 target-appropriate ICD 10 code diagnoses. From the resulted 2,107 ICD 10 codes, the n-sample was formulated from patients who received at least one dose of SC methylnaltrexone and had radiological work-up including X-ray abdomen or CT abdomen and pelvis with findings consistent with ACPO diagnosis with radiological findings with statement “large bowel ileus without transition point” or similar radiological descriptions as key indicators for ACPO radiological diagnosis. Exclusion criteria included similar ICD 10 code diagnoses which required intervention by fluoroscopic decompression by interventional radiology (**diagram 1)**.

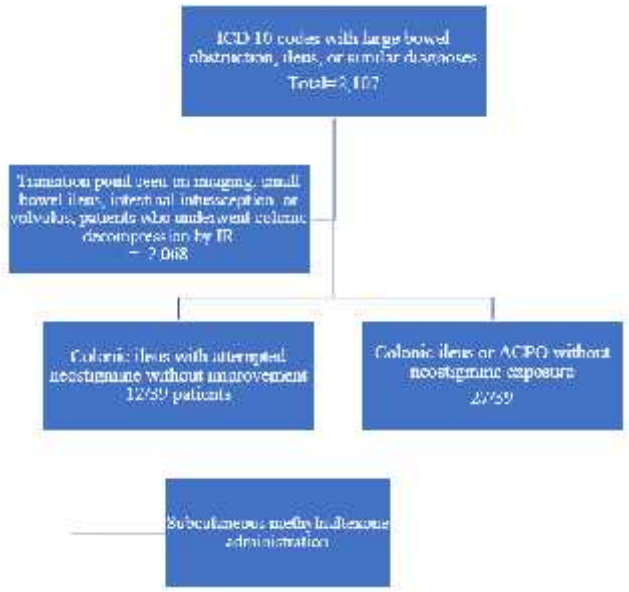

Diagram 1*: Study flowchart.*

To study the effectiveness of SC methylnaltrexone in patients meeting clinical criteria of ACPO, we looked at the following variables: total number of doses of methylnaltrexone received, achieving the desired target of having a bowel movement after methylnaltrexone administration, timing of first bowel movement after first dose of methylnaltrexone administered to correlate cause and effect, doses of SC methylnaltrexone needed to produce studied outcome, the occurrence of pain improvement with administration of SC methylnaltrexone, and 1-10/10 change in pain improvement following administration of SC methylnaltrexone. We also studied patients who received IV neostigmine prior to receiving SC methylnaltrexone. previous received prior IV opioids or IV neostigmine during same hospital stay, rates of cardiovascular complications occurring as result of SC methylnaltrexone administration, or endoscopic or surgical intervention as result of failure to have a BM in patients receiving one or more doses of SC methylnaltrexone. Given the lack of reported cardiovascular adverse events with SC methylnaltrexone administration in our hospital, generally and in cardiovascular patients, no protocols instating cardiac unit or critical unit observation were in place during SC methylnaltrexone administration during the period of the study. We utilized epiDisplay in R studio to measure the linear regression between the variables in the collected data.

Results

A total of 39 patients who received at least one dose of SC methylnaltrexone for the treatment of ACPO were identified. Patient demographics is provided in **table I.** The average age of patients was 59.1 years and consisted of 64.1% (25/39) males and 35.9% (14/39) females. 97.44% of studied patients had received systemic opioids for pain control within 30 days prior to the diagnosis of ACPO.

Table I. Patients demographics.

	Sample n=39	(%)
Male	*25*	*64.10*
Female	*14*	*35.90*
Age 25 Less	*2*	*5.13*
Age 26-45	*5*	*12.82*
Age 46-65	*19*	*48.72*
Age 66 and greater	*13*	*33.33*
Presence of comorbid diseases e.g. HTN, CAD, CHF, CKD, CVA, or DM.	*37*	*94.87*

HTN=hypertension, CAD=coronary artery disease, CHF-congestive heart failure, CKD=chronic kidney disease, CVA=cerebrovascular accident, or DM=diabetes mellitus.

Twenty-two patients (56.4%) had pain improvement after receiving subcutaneous methylnaltrexone. Patients received a standard dose of methylnaltrexone 12 mg every 24 hours until a bowel movement (BM) was achieved. A total of 35/39 (89.74%) had a BM following methylnaltrexone administration (p-value= 0.01246). Among the responders, an average dose of 1.17 doses (average range of 1-2) was administered to achieve the result. The average time of first BM occurrence after receiving methylnaltrexone was 12.85 hours ± 12.29 (**Figure 1**).

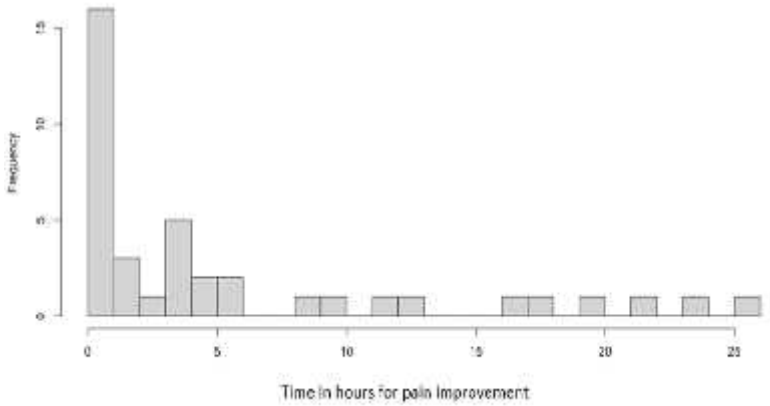

Figure 1. *Y-axis is number of patients achieving bowel movement (BM) over X-axis hours from receiving first dose of methylnaltrexone and having a bowel movement.*

Pain associated with ACPO measured by difference in pain scale 0-10/10, showed statistically significant improvement (p-value= 0.00323) in total pain reduction with average duration of response at 5.47 hours ± 7.43 (p-value= 0.02265) following first dose of methylnaltrexone administration (**Figure 2**).

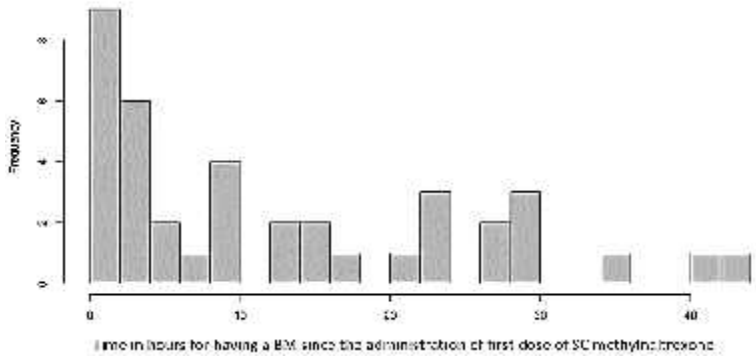

Figure 2*. Y-axis number of patients with clinical pain improvement plotted against X-axis of hours duration since first dose of receiving methylnaltrexone for treatment of ACPO.*

Furthermore, patients who received methylnaltrexone for treatment of ACPO upfront had an earlier pain improvement response compared to patients who had neostigmine upfront followed by subcutaneous methylnaltrexone for ACPO treatment at 5.47 ± 7.43 hours and 7.2 ± 9.54 hours, respectively (**Table II**).

The change in pain assessment out of 10 after receiving methylnaltrexone for ACPO is charted on (**Figure 3**) with a mean of 2.85 ± 2.94 pain difference improvement on the 0-10/10 standardized pain scale.

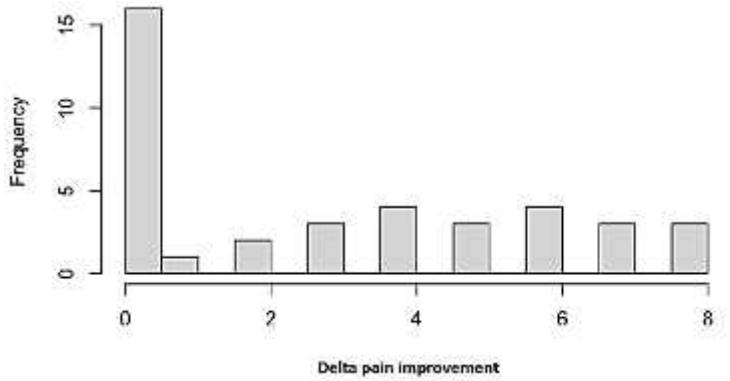

Figure 3. *Y-axis is number of patients plotted against X-axis representing delta pain improvement on 1-10/10 scale after receiving subcutaneous methylnaltrexone.*

In the studied patients who underwent initial treatment with IV neostigmine, 7 patients (20%) failed to attain a BM after receiving one or more doses of IV neostigmine for ACPO. All 7 patients who failed treatment with IV neostigmine upfront managed to have a BM following methylnaltrexone administration. Noteworthy, patients who received subcutaneous methylnaltrexone following single or multiple dose(s) of IV neostigmine were able to attain a BM occurrence compared to patients who received methylnaltrexone upfront at 16.8 ± 14.75 compared to 12.85 hours ± 12.29, (**Table II**).

Table II. *Response to subcutaneous methylnaltrexone in pain level compared to pain level improvement for patients who did and did not receive IV neostigmine.*

	Prior IV neostigmine administration	***No prior IV neostigmine administration***
	Total = 12	*Total = 27*
Age	*60 ±13*	*59 ±17*
Time of first BM in hours from 1st methylnaltrexone dose	*16.8 ±14.75*	*12.85 ±12.29*
Delta pain improvement 1-10/10	*3.4 ±3.04*	*2.85 ±2.94*
Duration in hours until pain improvement after 1st methylnaltrexone dose administration	*7.2 ±9.54*	*5.47 ±7.43*

A total of 4/39 patients (10.26%) required endoscopic decompression and 2/39 patients (5.13%) required surgical intervention for the management of ACPO after having an incomplete or lack of response to subcutaneously administered methylnaltrexone. No adverse events were recorded after endoscopic or surgical management of ACPO in patients who received methylnaltrexone previously. A total of 15/39 patients were in the range group of less than 25 and greater than 65 (total of 38.46%) had no adverse effects with the administration of subcutaneous methylnaltrexone. No significant adverse events or symptoms/signs of opioid withdrawal were reported in the subjects who received methylnaltrexone for ACPO. This is in spite the high rate of reported comorbid medical illness of 94.87% in patients who received methylnaltrexone for ACPO.

Discussion

In our study, we identified a total of 39 patients who received at least one dose of SC methylnaltrexone for the treatment of ACPO. Nearly all (97.44%) of studied patients had received systemic opioids for pain control within 30 days prior to the diagnosis of ACPO. This observation aids in understanding the relationship of opioid receptor blockade by systemic opioids on autonomic nerve receptors and development of ACPO, at least partially, and the basis for pharmacological efficacy of systemic methylnaltrexone in the treatment of ACPO [7].

Our results showed that infrequent dosing of standardized 12 mg per day (average administered methylnaltrexone dose of 1.17) was adequate to treat ACPO [6]. ACPO treatment failure to subcutaneous methylnaltrexone was observed in 4/39 (23.18%). All 4/39 patients had received systemic opioids in the last 30 days suggesting that systemic opioid inhibition of the colon does not solely explain the complete picture of ACPO pathogenesis, herein supporting a multifactorial causality to ACPO [8,9]. A hypothesis can be inferred from this observation that the role of methylnaltrexone in the treatment of ACPO may or may not be contingent only on patients who have received exogenous systemic opioid treatment. Although statistically insignificant, one of the patients in our study had good response to a single dose of SC methylnaltrexone without documented exogenous systemic opioids administration within the last 30 day from ACPO diagnosis. Thus, when considering SC methylnaltrexone treatment in patients with ACPO, the efficacy of SC methylnaltrexone might be explained by the antagonistic effect expressed through blocking colonic μ-opioid receptors of endogenously secreted opioid hormones resulting from physiologic response to acute pain during acute illness [10]. The effect of systemic exogenous opioid analgesics on the colon is through decreasing peristaltic motor waves and colonic secretion resulting in decreased colonic motility, colonic dilation, and constipation; which is exhibited in patients with ACPO [11,12]. Similar effects are seen in post-operative ileus affecting the small intestine resulting from perioperative exogenous opioid administration [13].

89.74% of patients who received SC methylnaltrexone for ACPO had a favorable response in the form of having a BM following methylnaltrexone administration (p-value= 0.01246). One metanalysis study reported a response rate of 89.2% in patients who received IV neostigmine for ACPO treatment, which is comparable to our cohort with a response rate of 89.74% through the use of SC methylnaltrexone [14]. This being said, methylnaltrexone lends itself as both safe and efficacious when compared to IV neostigmine. The aforementioned meta-analysis study found a significant side effect profile with the use of IV neostigmine in the treatment of ACPO including abdominal discomfort and pain greater than 50% of patients, sialorrhea, greater than 30% of patients, and nausea and vomiting greater than 15%. The most feared side effect which necessitates ICU admission for IV neostigmine observation during administration was bradycardia, reported to occur at ~6.5% in the same meta-analysis study [14]. In our study, no adverse events or side effects were reported with using methylnaltrexone for ACPO treatment. Quite the contrary, administering methylnaltrexone was associated with decrease in abdominal pain explained by resolution of colonic distention and atony and

eventual passage of a BM. Additionally, minimal dosing of methylnaltrexone (average of 1.17 doses) was required for the resolution of ACPO signs and symptoms and, thus, theoretically decreasing healthcare cost through decreasing hospital stay duration and morbidity atop of obviating ICU transfer/admission for cardiac monitoring during IV neostigmine administration. The average time of first BM occurrence after receiving methylnaltrexone was 12.85 hours ± 12.29 (p-value less than 0.05). Prompt response following methylnaltrexone administration was similarly documented in the first case report of describing the use of methylnaltrexone in ACPO [15]. In our center, we recommend daily dosing of 12 mg subcutaneous methylnaltrexone. The recommendation was based on pharmacokinetics of this drug with an average half-life of 8-9 hours and high bioavailability on subcutaneous administration of this medication. Moreover, subcutaneous administration of methylnaltrexone has a safe drug-drug interaction with minimal systemic metabolism [16, 17]. The pharmacokinetics of subcutaneous methylnaltrexone, thus, came hand in hand with the observation of attaining a BM 12.85 hours ± 12.29 from medication administration. Notably, the safety profile of subcutaneous methylnaltrexone presents an efficacious pharmacological option in patients with ACPO who tend to be hospitalized under significant metabolic and pharmacological burden in which administration of neostigmine might complicate the overall co-morbid clinical status and prolong hospital stay [18-20]. Pain associated with ACPO was seen to significantly improve with subcutaneous methylnaltrexone measured by difference in pain scale 1-10/10 at an average of 5.47 hours ± 7.43 following methylnaltrexone administration (p-value less than 0.05). This notion elucidates the strict peripheral opioid receptor antagonistic action of methylnaltrexone while sparing the central analgesic opioid receptor activation as evident by pain improvement [21, 22]. The pain improvement, again, was attributed to effective resolution of ACPO by methylnaltrexone administration.

No adverse events were reported in patients who received methylnaltrexone for ACPO treatment including those who received more than one dose. The safety profile of subcutaneous methylnaltrexone was also seen in patients age greater than 65. The safety profile of subcutaneous methylnaltrexone is encouraging especially that 94.87% of our patient cohort had documented co-morbid medical illnesses. In light of the overall success rate of subcutaneous methylnaltrexone to treat ACPO by means of having a BM and decreased pain levels atop of significant safety profile, subcutaneous methylnaltrexone poses an appealing non-invasive pharmacological option against IV neostigmine in the management of ACPO whereas neostigmine has been reported to be inferior to endoscopic decompression in some studies [23, 24]. One previous case-report looking at the efficacy and safety of the use of methylnaltrexone for ACPO documented occurrence of a serious adverse event: colonic perforation. In this case report, a single dose of 12 mg of SC methylnaltrexone was administered without prior IV neostigmine administration. Similarly, colonic perforation has been documented in the literature with the use of methylnaltrexone for opioid-induced constipation (OIC) [25, 26]. Our cohort herein showcases the lack of similar serious complications in the form of colonic or other gastrointestinal perforation or any other adverse events. Furthermore, no adverse events were recorded in 7 patients (20%) who failed to attain a BM after receiving one or more doses of intravenous neostigmine when given subsequent methylnaltrexone. All of the 7 patients referred here successfully had a BM and significant pain improvement after receiving methylnaltrexone subcutaneously. Overall, our studied cohort evaluating the administration of methylnaltrexone subcutaneously after failing IV neostigmine was both efficacious and safe. Noteworthy, there was a delay in both having a BM and pain improvement when subcutaneous methylnaltrexone was given following IV neostigmine after lack of response with IV neostigmine. The etiology of the delay occurring in having a response with methylnaltrexone in patients who received neostigmine previously is unclear but could be attributed drug-drug interaction by neostigmine-induced enhancement of systemically administered opioids used for analgesia prior to ACPO development via side effect including constipation. This being said, majority of the synergistic effect described between neostigmine and opioid systemic enhancement was studied reported in intrathecal neostigmine administration [27]. A limitation to the use of subcutaneous methylnaltrexone in the management of ACPO in our cohort is that the majority of patients studied had received systemic opioids 30 days prior to receiving subcutaneous methylnaltrexone. Thus, other cohorts can be designed to study the efficacy of subcutaneous methylnaltrexone for the management of ACPO in non-opioid exposed patients. Regardless, in our cohort, patients with ACPO without recent opioid treatment were documented to have similar efficacy with resolution of ACPO through the administration of SC methylnaltrexone.

Moreover, SC methylnaltrexone showcases its efficacy and safety profile for which its inclusion into the conservative options for the management of ACPO should be considered. Another limitation to the study,

with the study being retrospective in design, includes lack of control study in which a IV neostigmine only cohort could be designed and outcomes such as efficacy, safety, and need for endoscopic or surgical intervention; studied in comparison to subcutaneous methylnaltrexone, in an effort to observe for head to head comparison.

Conclusion

In setting of reported increase in ACPO incidence worldwide [6], non-invasive and effective medical management with safe medication profile is called for. Our study delineated objective clinical resolution of symptoms and signs of ACPO through the use of subcutaneous methylnaltrexone with a significant safety profile. The administration of subcutaneous methylnaltrexone for the management of ACPO in a non-critical inpatient setting obviates the need for admission to high intensity clinical monitoring setting, such as the intensive care unit to administer IV neostigmine, and invasive measures such as surgical or endoscopic management; resulting in overall decreased health costs and length of hospital stay. We noticed a relationship between recent opioid use and development of ACPO, which could partially explain the pharmacological efficacy with administering methylnaltrexone. Further studies are required to better differentiate the overall efficacy of subcutaneous methylnaltrexone for treatment of ACPO overall and, more specifically, in setting of recent systemic opioid treatment.

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