A Double-Blind Randomized Clinical Trial Comparing the Effect of Neostigmine and Metoclopramide on Gastric Residual Volume of Mechanically Ventilated ICU Patients

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doi: 10.5455/aim.2016.24.385-389
ACTA INFORM MED. 2016 DEC; 24(6): 385-389
Received: SEP 21, 2016 • Accepted: NOV 18, 2016

ABSTRACT

Background: In critically ill patients, enteral feeding through the nasogastric tube is the method of choice for nutritional support. Gastrointestinal feeding intolerance and disturbed gastric emptying are common challenges in these patients. The aim of this study was to compare the effect of Neostigmine and Metoclopramide on gastric residual volume (GRV) in mechanically ventilated ICU patients. **Methods**: In a double blind, randomized clinical trial, a total of 60 mechanically ventilated ICU patients with GRV >120 mL (3 hours after the last gavage), were randomly assigned into two groups A and B. At baseline and 6 hours later, patients in group A and B received intravenous infusion of neostigmine in a dose of 2.5 mg and metoclopramide in a dose of 10 mg in 100 ml of normal saline, within 30 minutes. Patients' gastric residual volumes were evaluated before the beginning of the intervention, and 3, 6, 9 and 12 hours after the intervention. **Results:** After adjusting of other variables (Sex, BMI and ICU stay period) generalized estimating equation (GEE) model revealed that neostigmine treatment increased odds of GRV improvement compare to metoclopramide group (Estimate: 1.291, OR= 0.3.64, 95% CI: 1.07-12.34). However there is a statistically significant time trend (within-subject differences or time effect) regardless of treatment groups (P<0.001). The median time from intervention to GRV improvement was 6 hours (95% CI: 3.75-8.25) and 9 hours (95% CI: 7.38-10.17) in neostigmine and metoclopramide groups, respectively. This difference was statistically significant (P<0.05). **Conclusion:** It seems that neostigmine is more effective than metoclopramide in reducing GRV and improving gastric emptying in mechanically ventilated ICU patients without significant complication and this protocol may be effective on the tolerance of enteral feeding in ICU patients. Further well-designed randomized clinical trials are needed.

Key words: Neostigmine, Metoclopramide, Gastric Residual Volume, ICU.

1. INTRODUCTION

Proper nutrition is a fundamental for all hospital patients, especially for patients with severely critical situation that for various reasons are not able to maintain their nutritional status (1-3). In addition, nutritional support and proper nutrition will reduce mortality and morbidity and improve the clinical situation in patients who are severely ill (2, 4, 5).

Oral feeding is the most effective method of feeding in patients. But when patients are not able to oral feeding, such as critically ill patients, nutritional support using nasao-gastric tube is the best alternative method (6). The benefits of this method is to permit the stomach acts as a natural reservoir and regulate the quantities and types of food released into the intestine and since receiving food ingestion takes place without depending on appetite or power, to reduce the catabolism related to damage, maintain the integrity of the intestinal mucosa, reduction of intestinal bacteria translocation and helps wound healing progress and reduce the incidence of morbidity and mortality and length of stay in intensive care and financial burden it gets (4-7). Therefore, early enteral nutrition is one of the principles of intensive care (8). One big problem in mechanically ventilated ICU patients is delayed gastric emptying (5, 9).

Delayed gastric emptying in these patients, causes intolerance and high gastric residual volume (GRV) that can lead to abdominal distention, vomiting, increased aspiration risk and consequently increased the length of hospital stay (10, 11). It has been shown that delayed gastric emptying and high GRV,

which approximately affect fifty percent of patients admitted to the ICUs, is associated with increased mortality in these patients (5, 12, 13). In order to facilitate the GRV, different kinds of drugs including metoclopramide, erythromycin and cisapride are used, but none of them had conclusive evidence of better effects on each other (14).

Moreover, complications such as dysrhythmia, and extrapyramidal side effects limit the use of these drugs (15). Another drug that can be used to increase gastric emptying in critically ill patients is neostigmine (15). Although several studies have evaluated the efficacy of neostigmine on postoperative ileus (16-20), very few studies have evaluated the effect of this drug on GRV in ICU patients (15, 21).

Based on the foregoing information and the potential consequence of high GRV on mortality and morbidity in ICU patients and few studies to compare the efficacy of neostigmine and metoclopramide in improving the gastrointestinal feeding intolerance in critically ill patients, this study aimed to compare the effects of neostigmine and metoclopramide on GRV in mechanically ventilated ICU patients.

2. METHODS

Approval from the Mazandaran University of Medical Sciences ethics committee, as well as informed consents from patients' family members was obtained. A total of 60 mechanically ventilated ICU patients of both sexes, aged 20-70 years, with nasogastric tube feeding and GRV >120 mL (3 hours after the last gavage) were enrolled in this prospective, double-blind, randomized, clinical trial. The study was carried out between March 2014 and February 2015 and registered in the Iranian Registry of Clinical Trials Database (IRCT201412044365N18).

Patients with history diabetes, heart block, bradycardia (heart rate <60/min), using beta-blockers, systolic blood pressure less than 90 mm Hg, hypothermia (core temperature below 35 ° C), renal insufficiency (serum creatinine level greater than 1.5 in two consecutive tests), using any prokinetic agents such as erythromycin or cisapride within 8 hours prior to study initiation, recent surgery (10 days or less) on the stomach or digestive system, signs and symptoms of intestinal obstruction, pregnancy and lactation, active bronchospasm, occurrence of extrapyramidal side effects, known hypersensitivity to neostigmine or metoclopramide, and active gastrointestinal (GI) bleeding, were excluded from the study.

Patients who meet the inclusion criteria were randomly assigned into two groups A and B by a nurse who was blind to the study groups, using sealed envelope technique and computer generated random numbers. At baseline and 6 hours later, patients in group A and B received intravenous infusion of neostigmine in a dose of 2.5 mg and metoclopramide in a dose of 10 mg in 100 ml of normal saline, within 30 minutes, respectively. Patients' GRVs were evaluated before intervention, and 3, 6, 9 and 12 hours after the intervention using gavage syringe by an expert nurse who had been unaware of the groups under study. Enteral feeding intolerance was defined as GRV> 120 mL.

Type and rate of enteral feeding nutrition was same for all patients (180ml/3h). All patients have 30 degrees head up position. Demographic and clinical data of the participants, age, gender, Sequential Organ Failure Assessment (SOFA) score and intubation duration were recorded using a written questionnaire at the beginning of the study. Moreover, 5 cc of blood were taken to assess levels of Na, K, Mg potassium, magnesium as well as patients' WBC, hemoglobin and hematocrit levels. In order to assess the nutritional status, patients' blood albumin level was evaluated.

Statistical analysis

We used the Shapiro-Wilk test to test whether data were normally distributed. Descriptive baseline characteristics for two groups (neostigmine and metoclopramide) comparisons were tabulated as mean (standard deviation, SD), median (inter-quartile range) or as percentages. Comparing between two groups for categorical data were statistically analyzed using chi- square or Fisher-exact test and for continuous data were statistically analyzed using Student's t test or mann-whitney U test if necessary. The primary efficacy data on GRV were examined using intention-to-treat analysis. Gastric residual volume data was collected every three hours for 12 hours once the treatment began. Mean blood pressure (MBP) and heart rate (HR) were examined in that same times after treatment. Gastric residual volume (primary endpoint) lesser than or equal to 120 cc were coded as 1 (GRV improvement) and MBP and HR considered as continuous variables. We used a generalized estimating equation (GEE) model to estimate the differences in values of GRV state (binary variable), MBP and HR at each time point between the two groups and also the time trend after treatment. We used survival analysis (Kaplan-Meier and log-rank test) for evaluation of treatment effect on time of GRV improvement. A p value of 0.05 or less was considered statistically significant and p value of less than 0.1 considered marginally statistically significant. Data were analyzed using IBM SPSS statistics version 16 and stata version 10.

3. RESULTS

Baseline characteristics of study participants

The enrollment flow chart of patients is displayed in Figure 1. Twenty nine out of 30 cases and 28 out of 30 cases, respectively, in the neostigmine and metoclopramide groups completed the study.

Demographic and baseline clinical characteristics of patients were evaluated (Table 1). As indicated in Table 1, there

Variables		Group of study		P value
		Neostigmine (N=29)	Metoclopramide (N=28)	
Age, years		48.86±13.77	46.5±17.24	0.57a
Sex, female/male		12/17	3/25	0.015b
BMI		24.69 (24.04-26.15)	25.95 (24.97-27.68)	0.039c
Etiology of admission	Surgical	18 (62.1)	16 (57.1)	0.79
	Non-surgical	11 (37.9)	12 (42.9)	
ICU stay period, days		20 (16-20)	17.5 (13-20)	0.072 c
Intubation duration, days		12 (6.5-15)	11.5 (7-13)	0.58 c
Albumin		4.14±0.27	4.08±0.24	0.59 a
Hemoglobin		11.29±1.28	11.06±1.93	0.59 a
Hematocrit		34.52±2.17	33.04±4.87	0.14 a
WBC		7000 (6000-8100)	7300 (6075-9225)	0.512
Na		138.52±2.65	139.71±3.76	0.17 a
K		4.07±0.44	4.28±0.84	0.25 a
Mg		2.2 (2.2-2.5)	2.2 (2.2-2.48)	0.44 c
SOFA		8 (7-9)	8 (7.25-9)	0.22 c

Table 2. Basic demographic and clinical characteristics of patients in two groups. a two sample t-test, bchi-squre test, c mann-whitney U test

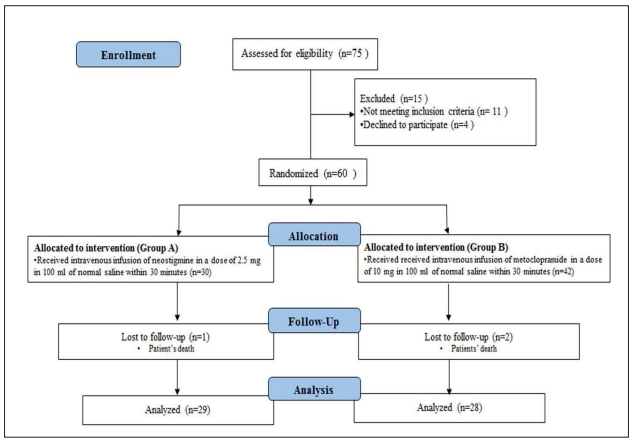

Figure 1. Flow chart of study population selection

Side effects	Study group		Total
	Neostigmine	Metoclopramide	
Without side effect	23 (79.3%)	26 (92.8%)	49 (85.9%)
Sweating	1 (3.4%)	2 (7.2%)	3 (5.3%)
Salivation	2 (6.8%)	0	2 (3.5%)
Bradycardia	1 (3.4%)	0	1(1.8)
Diarrhea	2 (6.8 %)	0	2 (3.5%)

Table 3. Frequency of complication in two groups

mide group respectively and this difference was statistically significant (P=0.014) (Figure 2).

Adverse events

Mean of blood pressure and HR at any time after treatment were evaluated too (Table 2). After adjusting of other variables (sex, BMI and ICU stay period) generalized estimating equation (GEE) model revealed that there was no statistically

		Time trend					P-value [a]	P-value [b]
		Baseline	3 h	6 h	9 h	12 h		
GRV	Neostigmine	0 (0)	11 (37.9)	16 (55.2)	27 (93.1)	29 (100)	<0.0001	0.039
	Metoclopramide	0 (0)	5 (17.9)	8 (28.6)	20 (71.4)	28 (100)		
MBP	Neostigmine	74.1±10.07	72.69±9.26	76.38±8.16	74.86±11	75.69±8.68	0.256	0.459
	Metoclopramide	73.04±9.43	75.79±9.55	75.68±8.14	74.71±9.87	74.96±8.29		
HR	Neostigmine	77.69±8.23	77.76±8.61	76.55±7.28	77.55±8.34	77.14±9	0.604	0.361
	Metoclopramide	78.86±8.94	78.5±8.32	77.89±8.58	76.82±8.94	78.25±9.28		

Table 2. Gastric residual volume (GRV) improvement, mean of blood pressure (MBP) and Heart rate (HR) at 3, 6, 9 and 12 hours follow-up in both groups. a repeated measurement of time trend in the GEE model. b comparison of change from respective baseline between the neostigmine and metoclopramide groups using the generalized estimating equation (GEE) model to control for time effect and sex, BMI and ICU stay period in the repeated measurement

were no significant differences detected at baseline in age, intubation duration, albumin, hemoglobin, hematocrit, WBC, Na, K, Mg and SOFA but there were statistically significance difference between two groups in sex, BMI and ICU stay period.

The efficacy of neostigmine on GRV

GRV improvement state (<120 cc) at any time after treatment were evaluated (Table 2). After adjusting of other variables (sex, BMI and ICU stay period) generalized estimating equation (GEE) model revealed that neostigmine treatment increased odds of GRV improvement compare to metoclopramide group (Estimate: 1.291, OR= 0.3.64, 95% CI: 1.07-12.34). However there is a statistically significant time trend (within-subject differences or time effect) regardless of treatment groups (P<0.001). The median time from intervention to GRV improvement was 6 hours (95% CI: 3.75-8.25) and 9 hours (95% CI: 7.38-10.17) in neostigmine and metoclopramide groups respectively and this difference was statistically significant (P=0.014) (Figure 2).

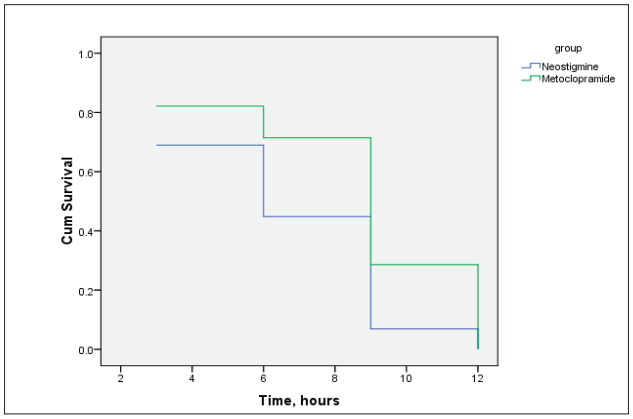

Figure 2. Cumulative gastric residual volume improvement survival curves of 57 patients in neostigmine and metoclopramide groups

Adverse events

Mean of blood pressure and HR at any time after treatment were evaluated too (Table 2). After adjusting of other variables (sex, BMI and ICU stay period) generalized estimating equation (GEE) model revealed that there was no statistically significant difference between treatment groups and time trend (within-subject differences or time effect) regardless of treatment groups (P>0.05). As shown in Table 3, the proportion of overall adverse effects in metoclopramide and neostigmine groups were 20.4% and 7.2% respectively (P=0.02).

4. DISCUSSION

In the present study we compared the effects of neostigmine and metoclopramide on GRV of ICU patients. In this study, neostigmine treatment significantly increased odds of GRV improvement compare to metoclopramide group. This statistically significant difference between two groups indicates the better efficacy of neostigmine in reducing GRV in critically ill patients. Neostigmine is a peripheral cholinesterase inhibitor with a plasma half-life of 20-60 minutes after intravenous (IV) administration. It induces smooth muscle contraction that causes an increase in cholinergic activity in the gut wall, which is thus believed to stimulate colonic motility. It was practically used in patients with postoperative ileus, intoxication with drugs which have ileus effect, and colonic pseudo-obstruction (18-19). Application of neostigmine in upper part of gastrointestinal segment like stomach is under investigation. Imai et al, demonstrated increased amplitude on electrogastrography clearly after administration of neostigmine (22). Lucey et al. evaluate the effect of neostigmine to increase gastric emptying in critically ill patients. In this study paracetamol absorption test was used for gastric emptying evaluation. The results of this study showed that neostigmine can increase the patients' gastric emptying and intestinal absorption, although the difference was not statistically significant (15). Parthasarathy et al. evaluate the efficacy of 1 mg IV neostigmine on gastro-duodenal motor activity

in patients with a suspected gastrointestinal motility disorder. The results of this study indicate that in patients with hypomotility, neostigmine can improve antral and intestinal motor activity (23). However, in another study aiming to assess the efficacy of neostigmine on enteral feeding tolerance in ICU patients, it has been shown that although the incidence of high GRV in patients who received neostigmine infusion was lower than control group (43.3% versus 63.3%), but this differences was not statistically significant (21).

Metoclopramide is a centrally acting antiemetic, which increases gastric motility via muscarinic receptors. Intravenous metoclopramide is usually used to manage delayed gastric emptying and to facilitate early enteral feeding. Occasionally tachyphylaxis to metoclopramide occurs after a few days of treatment. The etiology of tachyphylaxis is unknown but desensitization, down-regulation and endocytosis of neurohumoral receptors have been proposed as mechanisms underlying the occurrence of tachyphylaxis (24).

Although in this study only one patient who received neostigmine developed bradycardia, it is important to note that treatment with neostigmine is not without risk. Especially in patients with bradycardia, arrhythmias or patients with using beta-adrenergic antagonists there is the risk of severe bradycardia. Metoclopramide can also cause side effects such as extrapyramidal side effects, akatesia, tardive dyskinesia and sweating (25, 26). In this regards, in our study two patients who received metoclopramide had sweating. In this study, length of ICU stay and duration of mechanical ventilation in the neostigmine group were slightly higher than in the group receiving metoclopramide, however the differences was not statistically significant. In a study that was conducted by Aghadavoudi et al. has been shown that neostigmine reduces the time of hospitalization in ICU (21).

There are different ways to assess the rate of gastric emptying. Classical methods can be used to aspirate gastric contents (27, 28). Some studies did not consider food aspiration of gastric contents as an appropriate method for evaluation of enteral feeding tolerance (29). Other methods for measuring gastric emptying and absorption of food, including scintigraphy, breathe test, MRI, epigastric impedance, ultrasound, blood tracker drugs such as paracetamol which each have their own limitations (27). In this study, aspirations of patients' gastric content were used to evaluate enteral feeding intolerance, which may be a potential limitation of this study. We recommend further studies to evaluate patients' gastric residual volume using more accurate and precise methods.

5. CONCLUSION

According to the results of the present study it seems that administration of neostigmine may have a positive and meaningful effect on gastric emptying in mechanically ventilated ICU patients without significant complication and this protocol may be effective on the tolerance of enteral feeding in ICU patients. However further well-designed randomized clinical trials are needed.

• Conflict of interest: none declared.

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