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Effects of combined prokinetic administration on gastric emptying in critically ill patients

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ABSTRACT

Background and study aims: Combination of prokinetic drugs with different mechanisms of action is frequently used when feeding intolerance is not improved with a single agent. In this study, we evaluated the effect of combined infusion of neostigmine and metoclopramide on gastric passage in critically ill patients in the intensive care unit (ICU).

Patients and methods: This study is a randomized double-blind controlled trial in 90 patients between 20 and 60 years of age who were under mechanical ventilation and had gastric residual volumes (GRVs) >120 mL 3 h after the last lavage. Patients were randomly assigned to one of the following three groups: intravenous neostigmine 2.5 mg, intravenous metoclopramide 20 mg, and combination of both agents at the mentioned doses. Gastric volume aspiration was first performed before starting the study and then at 3, 6, 9, and 12 h after the infusion of study drugs was finished. Increase in gastric lavage was defined as an aspiration volume of >120 mL.

Results: In total, 86 cases in the three groups completed the treatment (all 90 patients included in the study were analysed according to an intention-to-treat approach). There was no significant difference detected at baseline in age, intubation duration, albumin, haemoglobin, haematocrit, total leucocytic count (WBC), Na, K, Mg, and sequential organ failure assessment score between the study groups. In the combination group, 96.7% of patients showed GRV improvement (GRV < 120 cc), whereas in the metoclopramide and neostigmine groups, 50% and 43.3% of the patients, respectively, showed improvement ($p < 0.001$). The frequency of overall adverse effects in the metoclopramide, neostigmine, and combination groups were 3.3%, 16.7%, and 10%, respectively ($p = 0.28$).

Conclusions: The present results suggested that combination therapy with metoclopramide and neostigmine decreases GRV in critically ill patients with a higher efficacy than monotherapies.

Introduction

Evidence suggests that intensive nutritional support in critically ill patients can improve survival and reduce the duration of recovery, thereby leading to a reduced length of hospital stay and reduced overall hospital costs [1–2]. Gastric motility dysfunction with high gastric residual volumes (GRVs) in mechanically ventilated patients reduces gastric passage, limits enteral nutrition, and increases the risk of aspiration pneumonia [3]. The prevalence of feeding intolerance in critically ill patients, mainly characterised by large GRVs, has been reported to be approximately 30% in a large cohort of ICU patients [4], although the values range substantially between 2% and 75% [5].

During the last decade, substantial efforts have been made to improve gastric tolerance in critically ill patients to achieve earlier discharge [6]. Prokinetic agents such as cisapride, metoclopramide, and erythromycin have been used to improve gastric motility, increase the rate of luminal transit, and increase the force of contraction and are used commonly in the intensive care unit (ICU) [7].

The gastroprokinetic activity of metoclopramide is mediated by muscarinic effects that lead to increased gastric passage [8–9]. Neostigmine is a cholinesterase inhibitor that increases

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acetylcholine concentrations at the neuromuscular junction, thereby enhancing the intestinal transit time. In several studies, a trend toward accelerated gastric emptying and improved feed tolerance has been observed in critically ill patients following neostigmine treatment [10]. However, an adequately powered study is required to confirm these effects.

Prokinetic drugs with different mechanism of action are often used in combination if feeding intolerance is not improved with a single agent [11]. In a previous study, a higher efficacy of neostigmine compared with metoclopramide was reported [12]. In this study, we hypothesised that neostigmine in combination with metoclopramide may improve gastric motility and, thereby, improve enteral feeding in critically ill patients. The aim of this study was to investigate the effect of combination of neostigmine and metoclopramide administered through intravenous infusion, compared with the effect of each agent alone, on the tolerance to enteral feeding in critically ill patients in ICU.

Patients and methods

The protocol of this study was reviewed and approved by the Institutional Ethics Committee of the Mazandaran University of Medical Sciences and registered in the Iranian Registry of Clinical Trials website (ID: 201408104365N16). Written informed consent was obtained prior to inclusion in the study from the patient or their family. This study was designed as a randomized double-blind controlled trial, and study population consisted of 90 patients between 20 and 60 years of age who were prescribed feeding through a naso- or orogastric tube in the ICU of the Imam Khomeini General Hospital, Sari, Iran.

Included subjects were critically ill patients who were under mechanical ventilation and had GRVs >120 mL and in whom 3 h were passed after the last gavage.

Patients who met the following criteria were excluded: Diabetes, atrioventricular blocks, heart rate (HR) <60/min, systolic blood pressure <90 mmHg, ⩽10 days after gut surgery, history of bronchospasm or asthma, clinical appearance of gastrointestinal obstruction, administration of prokinetic agents in the past 24 h, hypersensitivity to neostigmine or metoclopramide, renal failure or creatinine >2 mg/dL, and hypokalaemia.

Eligible patients were randomly, using a computer random number generator, assigned to three groups. The study drugs were prepared by a nurse unaware of the objectives of the study as follows:

(1) Neostigmine group: neostigmine methyl sulfate (250 mg) was infused in 100-ml normal saline intravenously for 60 min.
(2) Metoclopramide group: 20 mg was infused in 100-mL normal saline intravenously for 60 min.
(3) Combination group: neostigmine (250 mg) and metoclopramide (20 mg) was infused in 100-mL normal saline intravenously for 60 min.

The head of the bed, elevated 35°, and the enteral feeding standard nutrition was similar for all patients and was gavaged at 250 mL/4 h.

Aspiration of the gastric tube was performed every 3 h, first before starting the study and then at 3, 6, 9, and 12 h after the study drug infusions were finished. Increase in gastric lavage was defined as an aspiration volume of >120 mL (>50% of lavage volume) at the end of a 3-h period

Demographic and clinical data of the participants including age, gender, sequential organ failure assessment (SOFA) score (which predicts ICU mortality based on PaO_2/FiO_2), intubation duration, albumin, haemoglobin, haematocrit, WBC, Na, K, and Mg were collected at the beginning of the study. GRV data were collected every 3 h for 12 h once the treatment was started. Mean blood pressure (MBP) and HR were examined in the same manner as GRV after treatment initiation.

Statistical analysis

Data were analysed using IBM SPSS statistics version 16 and Stata version 12 software. Shapiro–Wilk test was used to assess the normal distribution of data. Baseline characteristics for the three groups (neostigmine vs. metoclopramide vs. combination groups) were tabulated as mean (standard deviation; SD), median (inter-quartile range), or as percentages. Comparisons among the three groups for categorical data were performed using Chi-square or Fisher's exact test, and for continuous data, ANOVA (in case of normal distribution) or Kruscal–Wallis test (in case of nonnormal distribution) was used. The primary efficacy data (GRV) were examined using intention-to-treat (ITT) analysis. GRV (primary endpoint) ⩽120 cc was coded as 1 (GRV improvement), and MBP and HR were considered as continuous variables. We used a generalised estimating equation (GEE) model to estimate the differences in values of GRV state (binary variable), MBP, and HR at each time point between the three groups and also the time trend after treatment. We used survival analysis (Kaplan–Meier and log-rank test) for the evaluation of treatment effect on the time of GRV improvement. A p-value of ⩽0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

The enrolment flowchart of patients is displayed in Fig. 1. A total of 86 cases in the three groups (neostigmine, metoclopramide, and combination groups) completed the treatment. The randomization codes of cases were not broken, and unblinding did not occur in any case until the conclusion of the study.

Demographic and baseline clinical characteristics of patients are shown in Table 1. As indicated in Table 1, there were no significant differences detected at baseline in age, gender, BMI, intubation duration, ICU stay period, albumin, haemoglobin, haematocrit, WBC, Na, K, Mg, and SOFA score.

Effects on GRV

Number of patients with GRV improvement (GRV < 120 cc) at any time after treatment was compared among the study groups (Table 2). The GEE model revealed that neostigmine and metoclopramide combination treatment increases the odds of GRV improvement compared with the metoclopramide treatment (Estimate: 0.63, OR = 1.87, 95% CI: 1.49–2.36). Again, using the GEE method, the difference in the serial percentage changes of GRV from the corresponding baselines failed to show any statistical significance between the neostigmine and metoclopramide groups ($p = 0.22$). However, there was a statistically significant time trend (within-subject differences or time effect) regardless of treatment group ($p < 0.001$). The median time from intervention to GRV improvement was 6 h (95% CI: 4.83–7.17) and 3 h (95% CI: 2.9–4.99) in the metoclopramide and neostigmine groups, respectively, and this difference was not statistically significant ($p = 0.13$) (Fig. 2). The median time in the combination group was 3 h (95% CI: 2.01–3.3), and this confidence interval does not overlap with the median confidence interval of the metoclopramide group, indicating that the difference is statistically significant ($p < 0.001$) (Fig. 2).

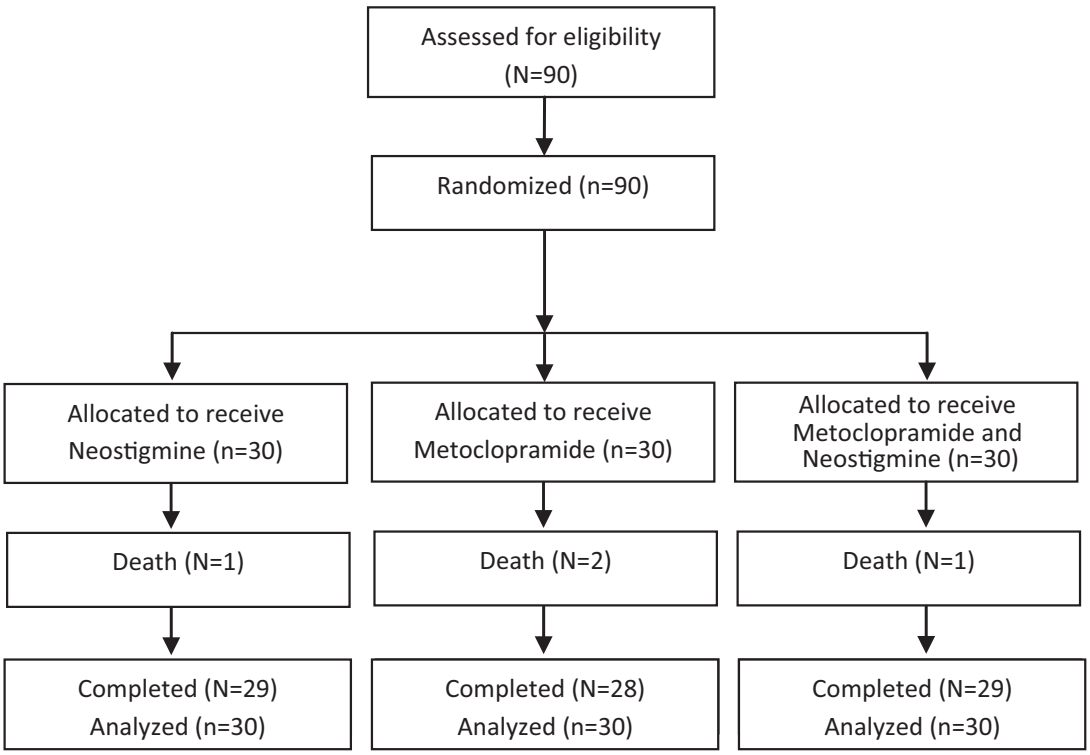

Fig. 1. The enrolment flowchart of patients.

Table 1
Basic demographic and clinical characteristics of patients in the study groups.

Variable		Group of study			p value
		Neostigmine (N = 30)	Metoclopramide (N = 30)	Neostigmine and metoclopramide (N = 30)	
Age (years)		42.83 ± 11.14	39.27 ± 2.6	39.9 ± 11.31	0.49[a]
Female/male		13/17	10/20	14/16	0.55[b]
BMI (kg/m^2)		25.12 ± 4.6	25.65 ± 3.6	25.67 ± 3.37	0.80[a]
ICU stay period (days)		18.97 ± 6.25	16.8 ± 6.27	18.27 ± 6.3	0.40[a]
Intubation duration (days)		12.17 ± 4.56	11.13 ± 3.84	11.8 ± 5.91	0.71[a]
Albumin (g/dL)		4 (4–4)	3.9 (3.9–4.1)	4 (3.85–4.1)	0.31[c]
Haemoglobin (g/dL)		11.28 ± 1.26	11.28 ± 2.21	11.54 ± 2.5	0.85[a]
Haematocrit (%)		35 (33–36)	36 (30–36)	36 (30–36)	0.97[c]
WBC ($\times 10^9$/L)		6.7 ± 1.1	6.7 ± 2.4	7.1 ± 1.8	0.56[a]
Na (mEq/L)		139 (137–140.25)	139 (138–142)	139 (137–140.25)	0.39[c]
K (mEq/L)		4.02 ± 0.43	3.89 ± 0.71	3.95 ± 0.49	0.65[a]
Mg (mEq/L)		2.2 (2.2–2.5)	2.2 (2.18–2.4)	2.3 (2.1–2.6)	0.75[c]
SOFA		7.8 ± 1.81	8.07 ± 1.41	7.9 ± 1.73	0.82[a]
Reason for hospitalisation	Multiple trauma	12	15	12	0.94[b]
	Surgical interventions	9	8	10	
	Respiratory disorders	4	3	3	
	Cardiovascular disorders	3	2	1	
	Others	2	2	4	

[a] ANOVA test.
[b] Chi-square test.
[c] Kruscal–Wallis test.

Adverse events

MBP and HR at the assessed time points (3, 6, 9, and 12 h) after treatment were evaluated (Table 2). The GEE model revealed no statistically significant difference between the treatment groups and no time trend (within-subject differences or time effect) ($p > 0.05$).

Proportions of other adverse effects were also assessed as summarised in Table 3. Four deaths occurred in this study: One in the neostigmine group and one in the metoclopramide group due to multiple organ dysfunction, one in the metoclopramide group due to acute cardiac arrest, and one in the combination group due to sepsis. Occurrence of death was not found to be significantly different among the study groups ($p = 0.77$). As shown in Table 3, the proportion of overall adverse effects in the metoclopramide, neostigmine, and combination groups were 3.3%, 16.7%, and 10%, respectively ($p = 0.28$).

Discussion

The results of this study showed that the combination of neostigmine and metoclopramide by intravenous infusion decreases GRV in 96% of critically ill patients in the early hours after administration without significant complications. However,

Table 2
Percentage of patients with gastric residual volume (GRV) improvement (GRV < 120 cc), mean blood pressure (MBP), and heart rate (HR) at 3, 6, 9, and 12 h of follow-up in the three groups.

Variable	Study group	Time trend					p value[a]	p value[b]	p value[c]
		Baseline	3 h	6 h	9 h	12 h			
GRV < 120 cc N (%)	Neostigmine	0	43.3	80	96.7	100	<0.0001	0.22	<0.001
	Metoclopramide	0	50	93.3	100	100			
	Neostigmine and metoclopramide	0	96.7	100	100	100			
MBP mm/Hg	Neostigmine	47 ± 9.91	72.53 ± 9.14	76.43 ± 8.02	75.07 ± 10.88	75.43 ± 8.64	0.87	0.89	0.68
	Metoclopramide	72.03 ± 15.82	75.97 ± 9.74	75.67 ± 8.26	75.37 ± 10.8	75.73 ± 8.72			
	Neostigmine and metoclopramide	70.33 ± 15.4	74.7 ± 9.57	74.93 ± 7.87	74.33 ± 9.65	76.33 ± 7.46			
HR B/Min	Neostigmine	77.63 ± 8.1	77.7 ± 8.47	76.3 ± 7.3	77.23 ± 8.38	77.03 ± 8.85	0.5	0.39	0.89
	Metoclopramide	78.8 ± 8.83	78.5 ± 9.1	78.43 ± 8.2	76.53 ± 8.75	78.13 ± 9.13			
	Neostigmine and metoclopramide	76.27 ± 8.01	77.83 ± 8.66	77.4 ± 8.75	76.83 ± 9.5	76.97 ± 9.32			

[a] Repeated measurement of time trend in the generalised estimating equation (GEE) model.
[b] Comparison of change from respective baselines between the metoclopramide group and neostigmine group using the GEE model in the repeated measurement.
[c] Comparison of change from respective baselines between the metoclopramide group and combination of metoclopramide and neostigmine group using the GEE model in the repeated measurement.

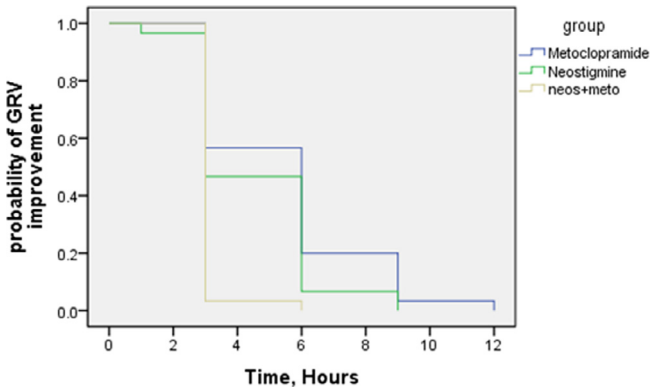

Fig. 2. Cumulative gastric residual volume improvement curves of 90 patients in the metoclopramide, neostigmine, and combination of metoclopramide and neostigmine groups.

only 43% of patients in the neostigmine group and 50% of patients in the metoclopramide group had improvement in gastric passage. In this study, four deaths occurred, but the frequency of deaths was not found to be significantly different among the study groups. However, because this study was not originally designed to assess mortality, additional investigations may be required to confirm if neostigmine, metoclopramide, and their combination differentially affect the survival of critically ill patients in ICU.

Neostigmine is a peripheral cholinesterase inhibitor with a plasma half-life of 20–60 min following intravenous administration. The cholinesterase inhibitory activity of neostigmine increases acetylcholine levels that can then stimulate both nicotinic and muscarinic cholinergic receptors [10]. Neostigmine induces smooth muscle contraction that causes an increase in cholinergic activity in the gut wall, followed by the stimulation of colonic motility. Neostigmine has been used in patients with postoperative ileus, intoxication with drugs that have affect ileus, and colonic pseudo-obstruction [13–14]. Effect of neostigmine on the upper part of the gastrointestinal segments such as the stomach is under investigation. Imai et al. demonstrated increased amplitude in electrogastrography after the administration of neostigmine [15]. However, many studies have reported different results on the effectiveness of neostigmine as a prokinetic on the tolerance of enteral feeding in patients in ICU [16–17].

Aghadavoudi et al. investigated the direct effect of neostigmine on the tolerance of enteral feeding in patients in ICU by evaluating related factors such as constipation, diarrhea, vomiting, and the volume of gastric lavage. They concluded that there was no significant difference between neostigmine and normal saline with respect to the tolerance of enteral nutrition in ICU patients [18]. In another study, Lucey et al. investigated the effect of neostigmine on gastric emptying in critically ill patients by evaluating gastric paracetamol absorption and did not report a significant result [16].

Metoclopramide is a centrally acting antiemetic agent that increases gastric motility through muscarinic receptors. Antagonizes the presynaptic inhibition of muscarinic receptors, leading to increased acetylcholine release and increased tone of lower oesophageal sphincter and stomach. Moreover, metoclopramide exerts its prokinetic effects through antagonistic effects on dopamine D_2 receptors (at both pre- and postsynaptic levels) and agonistic effects on the histamine 5-HT_4 receptors (at the presynaptic level) [19]. Intravenous administration of metoclopramide is frequently used to manage delayed gastric emptying and facilitate early enteral feeding. Occasionally, tachyphylaxis to metoclopramide occurs after a few days of treatment. Although the exact aetiology of the aforementioned tachyphylaxis is still unclear, desensitization, downregulation, and endocytosis of neu-

Table 3
Frequency of complications in the study groups.

Variables	Group of study			Total (N = 90)
	Neostigmine: N = 30 [ITT analysis]; N = 29 [completers]	Metoclopramide: N = 30 [ITT analysis]; N = 28 [completers]	Neostigmine and metoclopramide: N = 30 [ITT analysis]; N = 29 [completers]	
No Complication	29 (96.67%)	25 (83.33%)	27 (90.00%)	81 (90.00%)
Sweating	0 (0.00%)	1 (3.33%)	1 (3.33%)	2 (2.22%)
Bradycardia	0 (0.00%)	2 (6.67%)	0 (0.00%)	2 (2.22%)
Salivation	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.11%)
Death	1 (3.33%)	2 (6.67%)	1 (3.33%)	4 (4.44%)

rohumoral receptors have been suggested as plausible mechanisms [20]. In such tachyphylactic cases of delayed gastric emptying, combination therapy with prokinetic agents may be more effective owing to the complementary mechanisms of actions.

Intravenous erythromycin may also be added to enhance the prokinetic effects and decrease tachyphylaxis. Early combination therapy of erythromycin and metoclopramide has been shown to be more effective than the single administration of either drug [21].

In conclusion, the present study revealed that combination therapy with metoclopramide and neostigmine decreases GRV in critically ill patients without significant complications. This combination may represent a novel approach, i.e., the application of two drugs with two different mechanisms of action on upper and lower gastrointestinal tract, to enhance the tolerance of enteral feeding in ICU patients.

Declaration of interest

The authors have no competing interests to disclose.

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