

ORIGINAL RESEARCH

INTENSIVE CARE

The effect of different doses of neostigmine plus metoclopramide on the gastric residual volume in patients under enteral nutrition in intensive care unit

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ABSTRACT

Background & Objective: Gastric motility disorder is common in patients admitted to an intensive care unit (ICU), leading to increased morbidity and mortality. We investigated the effects of different doses of neostigmine in combination with metoclopramide on gastric residual volume (GRV) in ICU patients on enteral feeding.

Methods: In this double-blind clinical trial, 144 patients hospitalized in the ICU who were under enteral nutrition through nasogastric (NGT) or orogastric (OG) tube were randomly allocated to four groups. In all four groups, 20 mg of metoclopramide was prescribed IV slowly within one minute. In groups A, B, and C, 1, 1.5, and 2 mg of neostigmine were injected IV, respectively. Group D received only 20 mg of metoclopramide. All patients were gavaged every 4 h with 300 ml. The patient's head was kept at a 45° angle. To determine GRV, aspiration was done through NG tube or OG tube before the start of infusion and then at 3, 6, 9, and 12 h after the end of infusion.

Results: There was no significant difference between the studied groups in terms of demographic variables such as age, blood pressure, heart rate and BMI ($P > 0.05$). The average difference of SOFA and APACHE and laboratory factors between the groups was not significant. The results of the comparison of the marginal averages of the residual volume of the stomach at different hours of the day showed that the amount of the residual volume at all hours had a significant average difference with each other. The addition of different doses of neostigmine had a significant effect on the residual volume of the stomach after 3 and 6 h ($P < 0.05$). Meanwhile, a dose of 2.0 mg of neostigmine had the most of the change 3 h after administration.

Conclusion: Administration of neostigmine in combination with metoclopramide in ICU patients on enteral feeding significantly reduces the residual volume of the stomach within 12 hours after the treatment.

Abbreviations: APACHE- Acute Physiology And Chronic Health Evaluation; GRV - Gastric Residual Volume; NG – Nasogastric; OG - Orogastric; SOFA- Sequential Organ Failure Assessment; VAP - ventilator-associated pneumonia

Key words: APACHE; Enteral Nutrition; ICU; Metoclopramide; Neostigmine; SOFA

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1. INTRODUCTION

One of the major problems in intensive care unit (ICU) patients under mechanical ventilation is delayed gastric emptying.¹⁻³ Evidence shows that more than 50% of patients in the ICU have gastric motility disorder, which leads to slow gastric emptying and high gastric residual volume (GRV) which is associated with increased mortality in these patients.⁴⁻⁷ Delayed gastric emptying can lead to several problems, including insufficient caloric intake. In addition, nausea, regurgitation, and aspiration can increase the risk of ventilator-associated pneumonia (VAP) and thus increase the length of hospital stay.⁸⁻¹² Therefore, monitoring of GRV is recommended to reduce the incidence of these complications.

Until now, there have been surgical methods and pharmacological methods to facilitate gastric emptying and reduce GRV in patients, but each of them has its limitations.^{13,14} A variety of drugs have been used, including metoclopramide, erythromycin, and cisapride; however, there is no conclusive evidence for any of these to have superior effects over one another.¹⁵ One of the recently used drugs in this field is neostigmine.¹⁸ Studies have reported mixed results regarding the effectiveness of neostigmine on enteral feeding tolerance, especially in patients admitted to the ICU.^{16,17} While the effect of neostigmine on postoperative ileus has been evaluated in several studies, very few studies have evaluated the effect of neostigmine on GRV in ICU patients.¹⁹⁻²¹ In addition, complications such as dysrhythmias and extrapyramidal side effects limit the use of these drugs.²²⁻²⁴ Considering the above information and the high potential risk of GRV in mortality in ICU patients and few studies to compare the effect of neostigmine and metoclopramide on gastrointestinal feeding tolerance in critically ill patients, this study was conducted with the aim of comparing the effects of neostigmine and metoclopramide on gastric residual volume of patient under enteral nutrition in ICU.

2. METHODOLOGY

The present study was a double-blind clinical trial which was performed with the approval of the Ethics Committee in Biomedical Research, on patients admitted to ICU of Aiatolla Taleghani Hospital, who were candidate of enteral nutrition through nasogastric (NG) tube or orogastric (OG) tube.

Inclusion criteria included patients aged 20 to 60 y, feeding through a NG or OG tube, gastric residual volume > 120 ml, absence of previous underlying diseases, such as diabetes, arrhythmia and heart block, renal failure, asthma etc., HR > 60 beats/min and SBP > 90 mmHg, absence of known allergy to neostigmine and metoclopramide.

Exclusion criteria was new-onset arrhythmias and heart blocks, SBP < 60 mmHg during study, hypothermia, renal failure (serum creatinine greater than 1.5 in two consecutive tests), use of prokinetic drugs within 8 h before intervention, gastric or digestive system surgery within the past 10 days, clinical evidence of obstruction of the digestive system, pregnancy and breastfeeding, occurrence of extrapyramidal complications, active bronchospasm requiring medication, hypokalemia (potassium level less than 3 meq/L) and active gastrointestinal bleeding.

The clinical caregiver and the patient were kept blind to the drug grouping. After the patients signed the written consent form, 144 eligible patients were randomly divided into 4 groups via sealed envelopes (Figure 1). In all 4 groups, 20 mg of metoclopramide was prescribed IV slowly within one minute. In groups A, B, and C, 1 mg, 1.5 mg, and 2 mg of neostigmine were administered intravenously, respectively. Group D received placebo instead. Thereafter all patients were fed with the same formula every 3 h in the amount of 300 ml via NG or OG tube, while the patients were head-up at a 45-degree angle. To determine GRV, aspiration was done through NG or OG tube before the next enteral feeding. During the

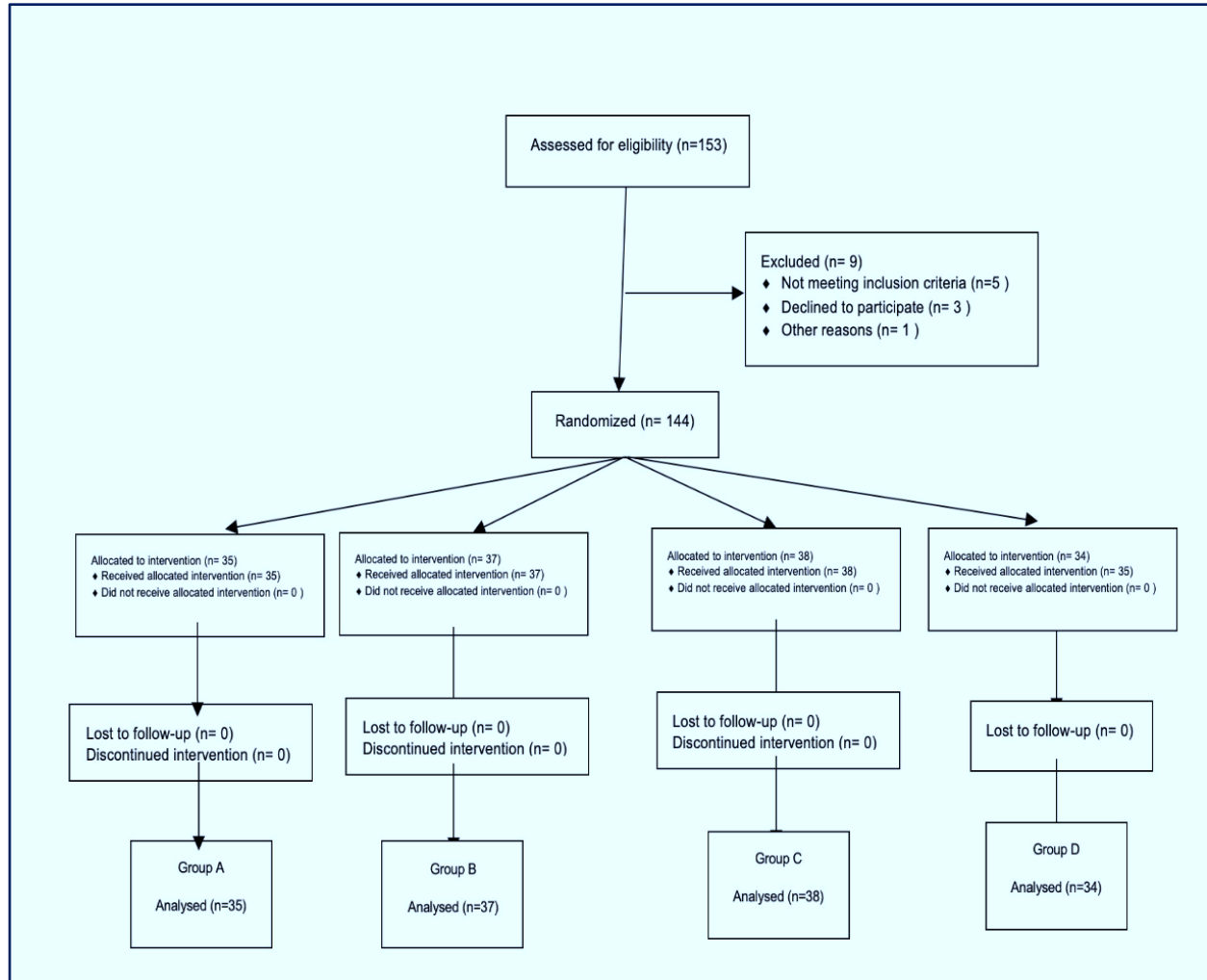


Figure 1: Flowchart of patient's collection

study, clinical and para-clinical NG parameters of the patients were recorded in a pre-designed questionnaire and analyzed using SPSS 25 software.

3. RESULTS

In this double-blind clinical trial, the average age of the patients was 59 ± 19.8 y (range 21-96 y). No significant

difference was observed between demographic indicators and prognostic indicators of patients admitted to the ICU (Table 1).

The results of Table 2 show that there is no significant difference between the laboratory indicators in the four studied groups.

Table 1: Comparative study of demographic indicators and prognostic indicators of the patients

Index	Group A	Group B	Group C	Group D	P-value
Age	59.5 ± 20.8	58.2 ± 21.4	57.8 ± 17.00	60.7 ± 20.3	0.903
BMI	25.3 ± 4.87	24.6 ± 4.22	24.5 ± 3.87	24.7 ± 3.9	0.920
BP	77.1 ± 14.2	81.9 ± 14.8	82.00 ± 14.5	79.5 ± 12	0.330
HR	90.70 ± 15.00	82.20 ± 18.90	83.90 ± 17.30	87.00 ± 15.00	0.111
SOFA score	4.31 ± 3.6	4.78 ± 3.4	4.92 ± 3.24	4.68 ± 3.58	0.613
APACHE score	15.600 ± 5.75	15.6 ± 4.77	16.7 ± 5.47	15.3 ± 5.00	0.681

Data presented as mean ± SD; P < 0.05 considered as significant

The results of Table 3 show the results of the four drug groups on the residual stomach volume, which has a significance level of 0.0001. As a result, it can be stated that the present model has a significant mean difference.

The results of Lon's test show (Table 4) that the residual volume of the stomach immediately after drug injection and after 6 h had a significance level of less than 0.05. As a result, the assumption of equal variance of the groups in these two dependent variables is not confirmed. While the significance level of other times is higher than 0.05, which confirms the assumption of equal variance of the groups in the other three dependent times.

The results of the marginal averages of the effect of drugs on the residual volume of the stomach show that metoclopramide drug alone did not cause an average difference in the residual volume of the stomach at different hours because the averages are almost the same. But with the addition of different doses of neostigmine had a significant effect on the residual volume of the stomach. The average volume of the residual volume immediately after the injection with metoclopramide and neostigmine (1 mg) became 62.286 and 3 h after the injection it was 42.571. But 6 h after injection, the average residual volume of the stomach increased by 55.714 units, and after 9 and 12 h, the residual volume of the stomach also increased (Figure 2).

4. DISCUSSION

The purpose of this study was to investigate the effect of different doses of neostigmine in combination with metoclopramide on the gastric residual volume of ICU patients under enteral nutrition. Based on the results obtained from this study, there was no significant difference between the studied groups in terms of demographic variables such as age, blood pressure, heart rate, and BMI. Also, the average difference of SOFA and APACHE scores and laboratory factors between groups was not significant.

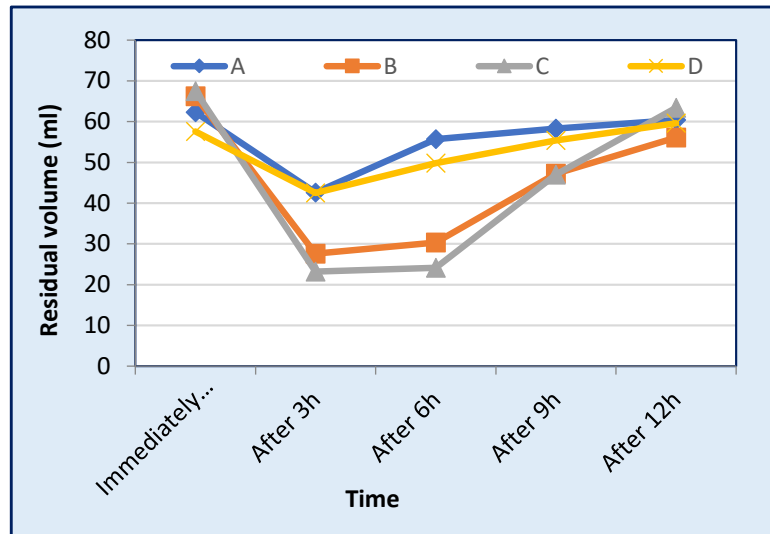


Figure 2: Changes in the residual gastric volume

Previously, Rahat-Dahmardeh et al. investigated the effect of neostigmine and metoclopramide on the residual volume of the stomach of mechanically ventilated patients in the ICU. These researchers showed that the effect of treatment with neostigmine by adjusting the effect of age, sex, and SOFA increases the chance of improving GRV compared to the metoclopramide group.²⁵

In the present study, the comparison of the marginal averages of the residual volume of the stomach in different hours of the day in each group separately shows that the amount of the residual volume of the stomach in all hours has a significant average difference with each other. This is expected due to the prokinetic properties of metoclopramide and neostigmine.

On the other hand, the comparison of the averages of the residual volume of the stomach as a two-by-two comparison of the groups without considering the time factor showed that there is no significant difference between the effects of drugs on the amount of the residual volume of the stomach. In other words, the average residual stomach volume of all 4 groups in 12 h was not significantly different from each other,

Table 2: Comparative laboratory results in different groups

Index	Group A	Group B	Group C	Group D	P value
Hb	10.1 ± 2.53	10.5 ± 2.48	10.4 ± 2.38	10.9 ± 2.44	0.527
Mg	1.89 ± 0.37	1.90 ± 0.30	1.88 ± 0.37	1.98 ± 0.22	0.351
k	4.00 ± 62.00	4.2 ± 0.72	4.2 ± 0.57	4.08 ± 0.63	0.289
Na	136.1 ± 3.17	137.5 ± 3.15	136.5 ± 3.9	137.7 ± 2.87	0.085

Data presented as mean ± SD; P < 0.05 considered as significant

Table 3: Multivariate tests and investigation of four drug groups on the remaining stomach volume

Indexes		Value	f	Hypothesis df	P.value
The rest of the stomach volume	Pillai's Trace	0.738	95.721	136	<.00001
	Wilks' Lambda	0.262	95.721	136	<.00001
	Hotelling's Trace	2.185	95.721	136	<.00001
	Roy's Largest Root	2.185	95.721	136	<.00001
The rest of the volume of the stomach and the group	Pillai's Trace	0.567	8.033	414	<.00001
	Wilks' Lambda	0.473	9.828	360.14	<.00001
	Hotelling's Trace	1.034	11.605	404	<.00001
	Roy's Largest Root	0.95	32.775	138	<.00001

P < 0.05 considered as significant

Table 4: Examination of the remaining volume in the stomach at different time periods

Times	Levene	Df1	Df2	P value
Immediately after injection	3.132	3	139	0.028
After 3 h	3.172	3	139	0.036
After 6 h	1.847	3	139	0.142
After 9 h	1.168	3	139	0.324
After 12 h	0.934	3	139	0.426

and a decrease in the average residual volume was observed in all groups within 12 h.

But the results of the marginal averages of the residual volume of the stomach at different hours of the day show that the amount of the residual volume of the stomach at all hours has a significant average difference from each other. The high difference is related to the residual volume of the stomach immediately after injection and 3 h after injection, and the lowest difference related to the residual volume of the stomach immediately after injection and 12 h after injection is 3.645.

The results of the marginal averages of the effect of drugs on the residual volume of the stomach show that metoclopramide drug alone did not cause an average difference in the residual volume of the stomach at different hours because the averages are almost the same. However, the addition of different doses of neostigmine had a significant effect on the amount of residual volume of the stomach, and a significant decrease, especially in the 3rd and 6th hours after the injection. This reduction has been more considerable and evident in 1.5 and 2 doses of neostigmine. It should be noted that during this study, the patients were under strict monitoring and fortunately, none of the patients showed significant drug side effects and were not excluded from the study. Previous studies have shown that although neostigmine

treatment significantly improved GRV in more patients within 12 h of treatment, all patients in both groups had a complete recovery. Considering that there was no significant difference between the two groups in terms of complications, it seems that both drugs are effective in improving the GRV of ICU patients. Gholipour et al aimed to compare the effect of neostigmine and metoclopramide and showed that neostigmine is effective in reducing GRV and improving gastric emptying in ICU patients under mechanical ventilation without significant complications compared to metoclopramide and this protocol can be effective in tolerating enteral feeding in ICU patients.²⁵⁻²⁷

5. CONCLUSION

In general, within 12 hours after the treatment with three different doses of neostigmine, the residual volume of the stomach of all patients in all 3 intervention groups significantly decreased compared with the control group. It was noted that higher dose of neostigmine had the most significant effect.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Ethical considerations

Formal approval of the Ethics Committee in Biomedical Research of Aiatolla Taleghani Hospital was obtained. Written consent of every patient or their next of kin was obtained. The study was conducted according to the World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects.

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

All the authors met the standard criteria of authorship based on recommendations of the international committee of medical journals editors.

MM: concept, study design

MD, MV: manuscript writing

SD, ST: revising and editing of the manuscript

FM: statistical analysis

MA, ZT: data collection

MK, ZT: conduction of study

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