

# Measurement of Gastric Residual Volume via Ultrasound after Receiving Intravenous Ondansetron, Metoclopramide, and Neostigmine in Critically Ill Patients: A Double-Blind Clinical Trial

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**Background:** Gastric residual volume (GRV) is considered an important parameter for gastric emptying and nutrition tolerance. This volume is measured before any nutrition and has a direct effect on the volume and timing of the next nutrition. The present study aimed to examine the GRV via ultrasound after receiving intravenous ondansetron, metoclopramide, and neostigmine.

**Materials and Methods:** In the present study, 40 patients were included in the study, 10 patients were excluded from the study due to death during treatment, and 30 patients were divided into three groups of 10 (10 patients in each group). The first, second, and third groups received 2.5, 10, and 8 mg neostigmine, metoclopramide, and ondansetron every 8 h, respectively. The drugs were infused as a micro set in 100 ml normal saline into patients within 30 min. The patients underwent ultrasound imaging and GRV measurement by an intensive care unit (ICU) subspecialty fellow, who was not aware of the drugs received by the patients, in the 1<sup>st</sup> h of hospitalization, 6 h after drug injection, and once daily for 4 days.

**Results:** A total of 40 patients entered the study based on inclusion and exclusion criteria. The effect of neostigmine on reducing GRV (Gastric residual volume) in ICU patients was better than those of the other two drugs, which was significant.

**Conclusion:** The results of this study showed that neostigmine has a better and significant effect on reducing GRV in ICU patients, compared to those of ondansetron and metoclopramide.

**Key words:** Ondansetron; Metoclopramide; Neostigmine; Gastric residual volume

## INTRODUCTION

Proper nutritional support is crucial for all hospitalized patients, especially intensive care unit (ICU) patients who cannot maintain their nutritional status due to their clinical condition (1). Proper nutrition is vital for hospitalized

patients, especially critically ill patients hospitalized in ICUs. Enteral nutrition (EN) has numerous benefits and advantages over parenteral nutrition, such as maintaining intestine integrity and reducing mortality (2). Therefore,

early EN is a care principle in patients hospitalized in ICUs.

A major problem in ICU patients undergoing mechanical ventilation is delayed gastric emptying. Gastrointestinal disorders are common problems in patients hospitalized in ICUs (3). Studies have shown that a gastrointestinal disorder is an independent factor for predicting mortality rate in patients (4). In clinics, gastrointestinal disorders are examined by measuring gastric residual volume (GRV). Gavage intolerance and EN in critically ill patients increase mortality (5).

The measurement of GRV via ultrasound is a simple and accurate method (6). Therefore, this study aimed to compare the effects of different drugs used to prevent EN intolerance. This study examined three drugs the effects of which on gastric emptying have been shown in various studies. The first drug is ondansetron that is a drug of the HT35 receptor antagonist class, the effect of which on reducing residual gastric volume has been proven in various studies (7). The second drug is metoclopramide, which is the standard drug used for increasing gastrointestinal motility according to its prokinetic properties (8). The third drug is neostigmine with the effect on the reduction of GRV based on new studies (9).

## MATERIALS AND METHODS

The present double-blind clinical trial was conducted on patients hospitalized in an ICU. The study was conducted as a pilot study on 40 patients. The inclusion criteria of the study were the written informed consent of the patient's family, undergoing mechanical ventilation, nutrition through the gastric tube, and GRV of higher than 120 cc. The exclusion criteria of the study also were diabetes, heart rate of < 60 beats per minute, cardiac and arrhythmic blocks, systolic blood pressure of < 90 mmHg, hypothermia, kidney failure, use of prokinetic agents for 8 h before the intervention, known sensitivity to neostigmine and metoclopramide, and gastrointestinal bleeding.

The patients' demographic information, including gender, age, and disease diagnosis, were first collected,

and the severity of their disease was measured based on Acute Physiology And Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment score(SOFA). The patients were included in the study if they met the inclusion criteria of the study. The day to start EN, the amount of energy, and the type of EN given to the patients were calculated. Furthermore, the patients were daily examined, and the symptoms, such as abdominal distension and a reduction in bowel sounds, were noted. Blood electrolytes (e.g., sodium, potassium, calcium, and magnesium), infection factors (i.e., white blood cells and C-reactive protein), and patients' albumin levels were measured.

The patients who met the inclusion criteria of the study were randomly assigned into three groups through computer and random numbers. The first, second, and third groups received 2.5, 10, and 8 mg neostigmine, metoclopramide, and ondansetron every 8 h, respectively. The drugs were infused as a micro set in 100 ml normal saline into patients within 30 min. The patients underwent ultrasound imaging and GRV measurement by an ICU subspecialty fellow who was not aware of the drugs received by the patients in the 1<sup>st</sup> h of hospitalization, 6 h after drug injection, and once daily for 4 days. Finally, the ultrasound image and the amount of GRV were confirmed by the sonographer. For GRV calculation, the diameter of the gastric antrum was measured based on the shape of the ultrasound and inserted in the following formula:

$$\text{Area} = 3.142 \times (\text{Average anteroposterior diameter} \times \text{Average craniocaudal diameter}) / 4$$

The data were analyzed using SPSS software (version 16), and a p-value of less than 0.5 was considered statistically significant.

This study was registered at the Iranian Registry of Clinical Trials (IRCT registration No.: IRCT20190215042716N1).

## RESULTS

40 patients were included in the study, 10 patients were excluded from the study due to death during treatment,

and 30 patients were divided into three groups of 10(10 patients in each group).

The mean difference of factors, such as age, gender, and tolerance level, among the drug groups was examined using the Kruskal-Wallis nonparametric test, the results of which are summarized in Table 1. The results of Table 1 show that there is no significant difference among the three groups regarding age, gender, and tolerance level variables. The mean GRV difference among the three groups was examined using the Kruskal-Wallis nonparametric test, the results of which are summarized in Table 2. According to Table 2 results, there was a significant difference among the three groups regarding the GRV variable on all days. The GRV mean differences in all the three groups showed a decreasing trend. This trend was better in the neostigmine group than those reported for the other two groups.

Table 1. Investigating the mean difference among drug groups in terms of age, gender and tolerance level factors

Variable		Ondansetron	Metoclopramide	Neostigmine	P value
Gender	Male	5	5	5	1.000
	Female	5	5	5	
Age		68	64.10	74.10	0.156
Tolerance	Non-tolerance	2	1	0	1.000
	Normal	8	9	10	

Table 2. Investigating disease severity differences among drug groups in terms of APACHI Score I

APACHI Score I	Ondansetron	Metoclopramide	Neostigmine	P value
First hour	18	18.10	17.60	0.601
Day 1	563.90	523.90	389.30	0.044
Day 2	438.20	433.10	320.90	0.004
Day 3	438.20	418.70	306.30	0.003
Day 4	387.50	426.90	294.90	0.012
Mean	453.95	450.65	327.85	0.003

Pairwise comparison of drug groups in terms of GRV mean differences and disease severity was performed based on APACHE II score and using the Mann-Whitney U nonparametric test, the results of which are shown in tables 3, 4, and 5. According to the results of Table 3, no significant difference was observed between the two groups of ondansetron and metoclopramide. Based on the results of Table 4, a significant difference was observed between the two groups of ondansetron and neostigmine. According to the results of Table 5, a significant statistical difference was observed between the two groups of metoclopramide and neostigmine on all days, except for the first day.

Table 3. Investigating disease severity differences between two groups of ondansetron and metoclopramide in terms of APACHI Score I

APACHI Score I	Ondansetron	Metoclopramide	P value
Day 1	563.90	523.90	0.472
Day 2	438.20	433.10	0.545
Day 3	438.20	418.70	0.570
Day 4	387.50	426.90	0.623
Mean	456.95	450.65	0.940

Table 4. Investigating disease severity differences between two groups of ondansetron and neostigmine in terms of APACHI Score I

APACHI Score I	Ondansetron	Neostigmine	P value
Day 1	563.90	389.30	0.023
Day 2	438.20	320.90	0.010
Day 3	438.20	306.30	0.008
Day 4	387.50	294.90	0.034
Mean	456.95	237.85	0.008

Table 5. Investigating disease severity differences between two groups of metoclopramide and neostigmine in terms of APACHI Score I

APACHI Score I	Metoclopramide	Neostigmine	P value
Day 1	523.90	389.30	0.059
Day 2	433.10	320.90	0.002
Day 3	418.70	306.30	0.002
Day 4	426.90	294.90	0.004
Mean	450.65	327.85	0.001

The mean GRV difference among the groups in 4 days was obtained using the generalized linear model in repeated measures, the results of which are summarized in

Table 6. The results of Table 6 show that the differences between the two groups of ondansetron and neostigmine and the two groups of metoclopramide and neostigmine were statistically significant. These results showed that a decrease in GRV was evident in all three groups. The effect of neostigmine was better than those of the other two drugs, which was significant. Figure 1 also shows the significant effect of neostigmine, compared to those of the other two drugs, in reducing GRV levels.

Table 6. GRV mean difference in drug groups in 4 days

GRV		Mean difference	P value
Ondansetron	Metoclopramide	6.3000	0.980
Ondansetron	Neostigmine	129.1000*	0.002
Metoclopramide	Neostigmine	122.8000*	0.003

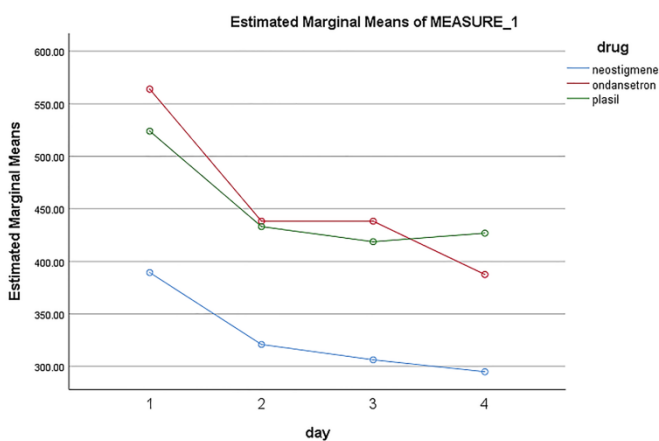


Figure 1. Decreasing trend of GRV in three drug groups

## DISCUSSION

Disability in EN is common in ICU patients and generally multifactorial. Gastric empties due to postoperative ileus in patients undergoing major gastric and intestinal surgery, use of opioid and adrenergic drugs, the effect of low-flow states and consequently intestinal ischemia, sepsis and endotoxemia, high level of nitric oxide, or a combination of these factors are involved in this regard. This study aimed to investigate the effect of three different drugs on GRV in patients undergoing mechanical ventilation in an ICU.

There are several methods for the assessment of gastric emptying. Classical methods can be used for aspirating stomach contents (10, 11). Some studies have not considered the aspiration of food from the stomach contents as a suitable method for assessing the tolerance of EN (12). Other methods for the assessment of gastric emptying and absorption of food include spirometry, magnetic resonance imaging, epigastric impedance, and blood tracking drugs (e.g., paracetamol), each of which has its limitations (11). In the current study, ultrasound was used for assessment.

The proposed hypotheses and the results of each of them are discussed in this section. According to the results of this study, ondansetron had a greater effect on reducing GRV levels than metoclopramide, although the observed difference between the two groups was not significant. The decreasing trend of GRV levels in the ondansetron group had a steeper slope, compared to that of the metoclopramide group. Neostigmine was more effective in reducing GRV levels than metoclopramide, and the observed differences between the two groups were significant in this regard. The decreasing trend in GRV levels in the neostigmine group had a steeper slope than that of the metoclopramide group.

Neostigmine was more effective in reducing GRV levels than ondansetron. Additionally, the decreasing trend in GRV in the neostigmine group had a steeper slope than that of the ondansetron group, and the difference between the two groups was statistically significant in this regard. This significant difference between the groups indicated a better effect of neostigmine on reducing GRV in patients.

Neostigmine is a peripheral cholinesterase inhibitor with a plasma half-life of 20-60 min after intravenous (IV) administration. It causes the contraction of smooth muscles, which increases cholinergic activity in the intestinal wall; therefore, it is believed that neostigmine stimulates colonic motility. Neostigmine has been used in patients with postoperative ileus, poisoning caused by drugs with ileus, and intestinal obstruction effects (13, 14).

The use of neostigmine in the upper gastrointestinal tract, such as the stomach, has been investigated. Imai et al. showed an increased range of electrogastrography after neostigmine administration (15). Jacques et al. assessed the effect of neostigmine on increasing gastric emptying in patients hospitalized in ICUs. In the aforementioned study, the paracetamol absorption test was used to assess gastric emptying. The results of the aforementioned study showed that neostigmine could increase gastric emptying and intestinal absorption in patients, although this difference was not statistically significant (16).

Parthasarathy et al., examining the effect of 1 mg IV neostigmine on gastric and duodenal motility in patients with suspected gastrointestinal motility disorder, showed that neostigmine could improve antral motility in patients with an inactive lifestyle (17). However, another study conducted to assess the effectiveness of neostigmine in EN in ICU patients showed that although the prevalence of high GRV was lower in patients receiving neostigmine injections than that of the control group, this difference was not statistically significant. The current study showed better effectiveness of neostigmine, compared to that of metoclopramide. This result is consistent with the results of a study conducted by Gholipour Baradari et al. The recent study also showed the significant and better effectiveness of neostigmine, compared to that of metoclopramide (18).

Metoclopramide increases gastric motility through muscarinic receptors. It increases the secretion of acetylcholine and the sphincter sound of the lower abdomen and stomach. Moreover, metoclopramide applies its predictive effects by antagonistic effects on dopamine D2 receptors (at both pre- and post-synapse surfaces) and agonist effects on histamine HT45 receptors (at the pre-synaptic surface) (19). The IV administration of metoclopramide is often used to manage delayed gastric emptying and facilitate early EN. Metoclopramide stimulates gastric motility through muscarinic receptors. The IV metoclopramide is commonly used to manage delayed gastric emptying and facilitate early EN.

Sometimes tachyphylaxis to metoclopramide occurs a few days after treatment. The causes of tachyphylaxis are unknown; however, it has been suggested that desensitization, decreased regulation, and endocytosis of neurotransmitters are predisposing mechanisms to tachyphylaxis (20). Considering the side effects of metoclopramide and the results of the present study indicating that neostigmine has a better effect on improving GRV, compared to metoclopramide, it can be concluded that neostigmine is preferred to metoclopramide.

MacLaren et al. assessed the effect of erythromycin and metoclopramide in facilitating gastric emptying in ICU patients. The results of the aforementioned study showed that both drugs improved the gastric emptying process in these patients; nevertheless, erythromycin was more effective than metoclopramide in increasing gastric motility (21). The results of the aforementioned study are in line with the results of the present study regarding the lower effectiveness of metoclopramide than that of other drugs. The current study also showed that metoclopramide had a lower effect on the process of gastric emptying in ICU patients, compared to those of the other two drugs.

Netzer et al. examined the effect of IV ondansetron injection on GRV in healthy individuals and compared it to that of a placebo. The results of the aforementioned study revealed that ondansetron did not have a significant effect on gastric emptying from solids, gastric electrical frequency, or plasma concentration of gastrointestinal peptides, compared to that of the placebo (22). This result is inconsistent with the results of the current study and most similar studies. Similar studies have shown that ondansetron and other selective antagonists of selective HT3-5 receptor accelerate gastric emptying in baseline conditions and cause a delayed induction by drugs, such as cisplatin. Studies have shown that the effect of ondansetron on improving gastric emptying depends on species; accordingly, ondansetron has a better effect on some animals but less effect on some others. For example, in studies conducted by Costall et al. and Nagakura et al.,

better acceleration of gastric emptying with the use of ondansetron was proven in various species, such as pigs and dogs, compared to humans (23,24).

Lucey et al. showed that neostigmine might have a positive effect on accelerating gastric emptying in patients with severe disease. The aforementioned study was a pilot study; therefore, Lucey et al. stated that this effect was not statistically significant and needed sufficient investigation to confirm this effect. The present study performed on a larger statistical population showed a positive effect of this drug on accelerating gastric emptying in patients, which is in line with the results of the study conducted by Lucey et al. (25).

Aghadavoudi et al. investigated the effect of neostigmine on EN tolerance in ICU patients and showed that this drug did not have a significant effect on EN tolerance, compared to a placebo (i.e., normal saline) (26). Consequently, the results of Aghadavoudi et al.'s study are not consistent with the results of the current study. The observed difference can be attributed to a lower dose of the drug used in the aforementioned study.

Gholipour Baradari et al. investigated the effects of neostigmine and metoclopramide alone and in combination on GRV in ICU patients (18). Gholipour Baradari et al. indicated that in case of using a combination of neostigmine and metoclopramide, 96.7% of the patients showed better GRV; however, in case of using neostigmine and metoclopramide alone, the improvement rates were 50% and 43.3%, respectively (27). The aforementioned study, in line with the present study, showed that neostigmine was more effective in improving GRV than metoclopramide; however, the aforementioned study did not show a statistically significant difference between the two drugs.

## CONCLUSION

The results of the present study revealed that all three drugs, namely ondansetron, metoclopramide, and neostigmine, improved and accelerated gastric emptying in

ICU patients. In addition, the effect of neostigmine was significantly better than those of the other two drugs.

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