ORIGINAL ARTICLE

Evaluation of intravenous neostigmine infusion on tolerance of enteral nutrition in Intensive Care Unit patients

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Background: Based on the dramatic response of acute colonic pseudo-obstruction to neostigmine, we designed this study to evaluate the effect of neostigmine on the tolerance of enteral feeding in Intensive Care Unit (ICU) patients. **Materials and Methods:** A total of 60 patients hospitalized in the ICU of Alzahra Hospital, Isfahan, Iran entered the study. They were randomly assigned to one of the two groups of case (who received intravenous neostigmine infusion) and control (normal saline). They were compared with respect to incidence of constipation, diarrhea, and vomiting. Arrhythmia, bronchospasm, mean arterial blood pressure (MAP), and heart rate (HR) were also evaluated at 0, 4, 8, 12, 16, 20, and 24 h. **Results:** The frequency distribution of constipation, diarrhea, vomiting, and increase in gastric lavage volume in the intervention group was 20%, 33.3%, 46.7% and 43.3%, while these indices in the control group were 40%, 30%, 43.3%, and 63.3% , respectively ($P > 0.05$). Arrhythmia was observed in 3% and 6% in the case and control groups, respectively. Bronchospasm was not detected in any of patients. **Conclusion:** There was no significance difference between neostigmine and normal saline with respect to tolerance of enteral nutrition in ICU patients.

Key words: Enteral feeding tolerance, Intensive Care Unit, neostigmine

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INTRODUCTION

One of the principal limiting factors to minimize hospitalization in Intensive Care Unit (ICU) after surgery or under any other condition is the tolerance of adequate enteral nutrition.

Enteral nutrition can decrease the incidence of infection in critically ill patients if started early in the course of critical illness. This has been demonstrated in many studies with different situations such as postsurgical or nonsurgical conditions.[1,2]

The mechanisms of decreasing infectious complications by enteral nutrition are unknown, but it has been proposed that enteral nutrition maintains the normal gut mucosal barrier function, reducing bacterial and endotoxin translocation,[1] and thus reduces the incidence of nosocomial infection.[2,3]

Furthermore, it has been demonstrated that early enteral nutrition can decrease the duration of hospital stay for patients after surgery.

Studies of large administrative databases show that on average, patients with a diagnosis of postoperative ileus stay 5 days longer in the hospital after abdominal surgery than the patients without postoperative ileus.[4]

However, gastrointestinal complications often limit the use of enteral nutrition in critically ill patients. A recent multi-center study found that up to 63% of patients suffered one or more gastrointestinal complications with enteral feeding; the most frequent complications were gastroparesis with high gastric residual volumes (39%), constipation (16%), diarrhea (15%), abdominal distension (13%), vomiting (12%), and regurgitation (6%).[5]

Over the last decade, substantial efforts have been made to minimize these complications and improve gastric tolerance in critically ill patients to achieve earlier discharge.

Prokinetic agents such as cisapride, metoclopramide, and erythromycin have been used to improve gastric motility, and there is no definitive evidence for the benefit of one over another.[6]

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Cisapride has a documented pro-arrhythmogenic effect. Its wide drug interactions are the most limiting factor of its use, and so, it is no longer available in some countries. Erythromycin prolongs the QT_c interval and may precipitate cardiac arrhythmias. Also, its antibiotic effect may result in the growth of resistant microorganisms. Metoclopramide is a dopamine receptor antagonist and may cause extra-pyramidal reactions and the neuroleptic malignant syndrome.

Neostigmine is an acetylcholinsterase inhibitor that causes an increase in cholinergic (parasympathetic) activity in the gut wall, which is thus believed to stimulate colonic motility. There are several studies that show this effect of neostigmine practically in patients with postoperative ileus,[7-9] intoxication with drugs which have ileus effect,[10] and colonic pseudo-obstruction.

The presence of massive dilatation of the colon in the absence of a mechanical obstruction is known as acute colonic pseudo-obstruction or Ogilvie's syndrome.[11] It may by caused by a number of clinical conditions including trauma, major orthopedic surgery, severe medical illness, retroperitoneal pathology, metabolic imbalance, and regional anesthesia.[11] There are several studies reporting that neostigmine rapidly decompressed the colon in a group of patients with acute colonic pseudo-obstruction who had not responded to conservative treatment.[11-16]

A bolus dose of 2 mg neostigmine is associated with bradycardia, abdominal pain, vomiting, and excess salivation.[12] In 2001, Van der Spoell *et al*. conducted an investigation on the influence of 0.4-0.8 mg/h of neostigmine by continuous infusion in patients with colonic ileus and found that this method of administration promoted defecation in these critically ill patients without any appreciable adverse effects.[17]

We hypothesized that neostigmine may improve gastric motility by a similar mechanism as in Ogilvie's syndrome and, thereby, improve enteral feeding in critically ill patients.

The aim of this study was to investigate the effect of neostigmine by intravenous infusion compared with placebo on tolerance to enteral feeding in critically ill patients in ICU.

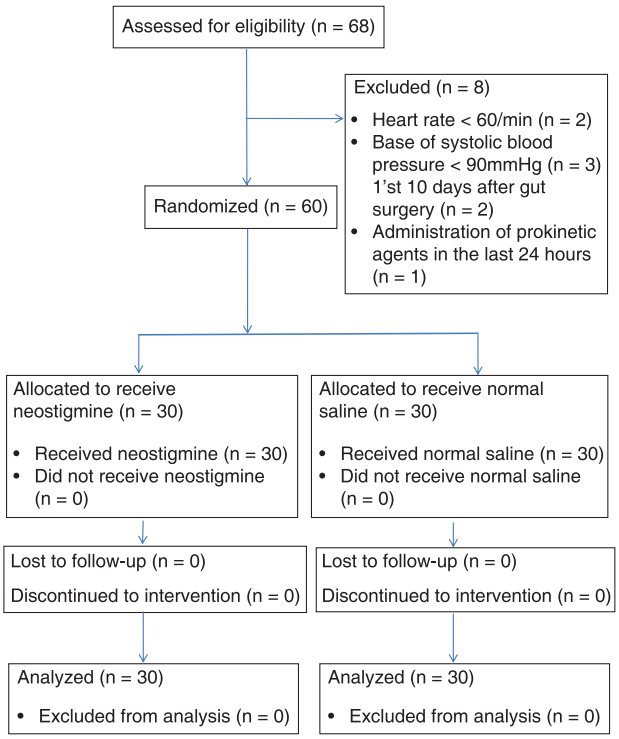
MATERIALS AND METHODS

The protocol of this work was reviewed and approved by the Institutional Ethics Committee of the Faculty of Isfahan University of Medical Sciences (Research Project Number 391451). Written, informed consent was obtained prior to inclusion in the study from the patients or from the nominated person responsible for the patient.

This work was a double-blind randomized controlled trial study undertaken on 60 patients between 18 and 65 years old, who were prescribed feeding via a naso- or oro-gastric tube in the ICU of Alzahra Hospital, Isfahan, Iran. The patients who were excluded from the study were those with the following:

- Atrioventricular blocks
- Heart rate <60/min
- Base of systolic blood pressure <90 mm Hg
- First 10 days after gut surgery
- Clinical appearance of gastrointestinal obstruction
- Bronchospasm
- Pregnancy
- Breast feeding
- Administration of prokinetic agents in the last 24 h
- Sensitivity to neostigmine

Patients were randomly allocated to one of the two groups of case and control (first patient to case group, second one to control group, and so on) without telling them in which group they were. Neostigmine and normal saline were prepared by a person who had information about the drug and group of patients, but infusion of the drugs and filling the written forms were done by another person or persons who did not have information about the drug and group of patients. In the case group, neostigmine (neostigmine methylsulfate 0.5 mg/ml; IPDIC, Rasht, Iran, batch no. 015) was administered



Graph 1: Data flow diagram

in a dose of 1 mg in 100 ml normal saline by intravenous infusion for 30 min, and then 0.5 mg in 50 ml normal saline was administered by intravenous infusion for 15 min every 4 h to 24 h. In the control group, normal saline alone was used at the same time with the same rate of infusion.

The enteral feeding protocol required the nutrition standard to be infused initially at 30 ml/h, which is increased to 60 ml/h at 4 h.[18] Aspiration of the gastric tube was performed 4-hourly. Increase in gastric lavage was defined as an aspiration volume of >120 ml (>50% of gavage volume) at the end of a 4-h period.[18]

Demographic and clinical data of the participants[age, gender, Sequential Organ Failure Assessment (SOFA) score(which predicts ICU mortality based on PaO2 FiO2, platelet count, Glasgow Coma Score, total bilirubin, serum creatinine or urine output, and the level of hypotension[19,20] were collected using a written questionnaire at the beginning of the study.

Incidence of constipation (fewer than three defecations per week),[21] diarrhea (three or more loose or watery stools per day),[22] vomiting (the forceful expulsion of gastric contents),[23] increase in gastric lavage (as defined previously),[18] all of which show the status of enteral feeding tolerance; arrhythmia, bronchospasm, mean arterial blood pressure and heart rate at 0, 4, 8, 12, 16, 20, and 24 h after the start of the study for the evaluation of neostigmine adverse effects; and also duration of hospitalization in the ICU and death during the study were compared in the two groups.

Statistical analysis

The values were expressed as mean ± standard deviation (SD). The differences between demographic and clinical data and also study outcomes of the two groups were analyzed using Student's *t*-test and chi-square test. The level of significance was set at $P < 0.05$. Repeated measure analysis of variance was used to evaluate changes in mean arterial blood pressure and heart rate. Statistical analysis was performed using SPSS software version 18 for Windows.

RESULTS

Sixty patients were included in our study. They were randomized to receive either neostigmine ($n = 30$) or normal saline ($n = 30$). Flow diagram of the randomized patients is shown in Figure 1. Mean age in the case and control groups were 40.1 ± 14.7 and 37.6 ± 13.7 years, respectively ($P = 0.47$). In the intervention group, there were 16 males (53.3%) and 14 females (46.7%), whereas in the control group, there were 17 males (56.7%) and 13 females (43.3%) ($P = 0.8$). Mean of SOFA index was not significantly different between the two groups ($P > 0.05$) [Table 1].

With regard to enteral feeding tolerance indices (constipation, diarrhea, vomiting, increasing of lavage volume), adverse effects of neostigmine (arrhythmia, bronchospasm), duration of hospitalization in the ICU, and mortality rate, there were no statically differences between the two groups [Table 2].

Mean of heart rate and mean arterial blood pressure changes (which are related to the adverse effects of neostigmine) were balanced in the two groups until 24 h ($P = 0.12$ and 0.1, respectively) (repeated measure analysis of variance) [Table 3, Figures 1 and 2].

Table 1: Demographic data in case and control groups

Variables	Case	Control	*P* value
Age(years)	40.1±14.7	37.6±13.7	0.47
Gender			
Male	53.3%	56.7%	0.8
Female	46.7%	43.3%	
SOFA	5/75±2/47	6/4±3/21	0.27

SOFA=Sequential Organ Failure Assessment

Table 2: Frequency of variables in case and control groups. (Study outcomes of two groups were analyzed using Student's *t* test and Chi-square test. The level of significance was set at *P*<0.05.)

variables	Groups	Case (%)	Control (%)	*P* value
Constipation	Yes	6 (20)	12 (40)	0.09
	no	24 (80)	18 (60)	
Diarrhea	Yes	10 (33/3)	9 (30)	0.78
	no	20 (66/7)	21 (70)	
Increasing in lavage volume	Yes	13 (43/3)	19 (63/3)	0.12
	no	17 (56/7)	11 (63/7)	
Vomiting	Yes	14 (46/7)	13 (43/3)	0.8
	no	16 (53/3)	17 (56/7)	
Arrhythmia	Yes	1 (3/3)	2 (6/7)	0.99
	no	29 (96/7)	28 (93/3)	
Bronchospasm	Yes	0 (0)	0 (0)	1
	no	30 (100)	30 (100)	
Death	Yes	0 (0)	0 (0)	1
	no	30 (100)	30 (100)	
Hospitalization in ICU	days	11/13±6/5	14/3±8/7	0.1

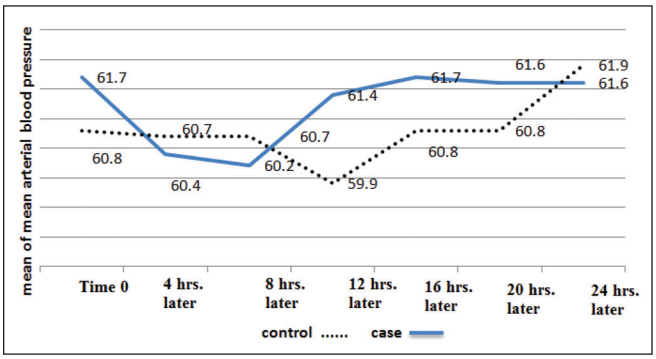


Figure 1: Mean arterial blood pressure at defined time intervals during the study in the two groups

Table 3: Mean of heart rate and mean arterial blood pressure at the definite times during the study in two groups. (Study outcomes of two groups were analyzed using Student's *t* test and Chi-square test. The level of significance was set at *P*<0.05.)

Time group	Mean arterial blood pressure		Heart rate	
	case	control	case	control
Time of 0	61/7±4/8	60/8±3/8	79/9±5/8	80/9±2/5
4 hours	60/4±5/6	60/7±4/3	79/6±5	79/7±2/5
8 hours	60/2±6/1	60/7±4/7	80/4±5	80/9±3/1
12 hours	61/4±6/8	59/9±3	80/5±5/1	79/7±5/1
16 hours	61/7±4/8	60/8±3/8	80/8±1/4	79/3±3
20 hours	61/6±6/3	60/8±4/3	78/3±4/6	79/3±2/5
24 hours	61/6±5	61/9±5/3	80/1±4/5	80/5±4/5
P value	0.1		0.12	

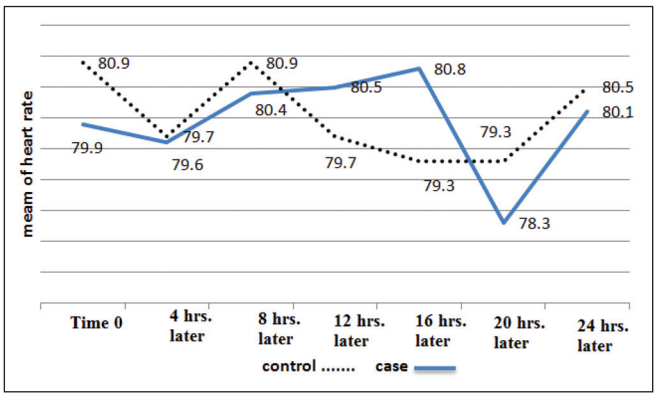


Figure 2: Heart rate at defined time intervals during the study in the two groups

DISCUSSION

Early beginning of enteral feeding is a scientific rule in the ICU. Tolerance of enteral feeding is very important and is reported immediately after vital signs of the patient in daily visits of ICU. It is because of the important effect of enteral feeding on the one of the greatest complications of hospitalization, which is "infection,"[1-3] and also, its noticeable effect on the duration of hospitalization,[4] which is very important economically and also a great healthy index.

Till now, there have been surgical procedures and pharmacological methods to facilitate this process and increase the tolerance of enteral feeding in patients, but each of them has their limitations.[6-9]

One of the drugs that have been used in this field recently is neostigmine. Studies have reported different results about the effectiveness of neostigmine on the tolerance of enteral feeding, especially in patients in ICU.[7-10] Increased amplitude on electrogastrography was clearly demonstrated after administration of neostigmine.[24] But the most important effect of neostigmine that makes it the first choice for investigation in this field is its dramatic effect on recovering from pseudo-obstruction syndrome that is called Ogilvie's syndrome.[11-16]

In the present study, we investigated the direct effect of neostigmine on the tolerance of enteral feeding in patients in ICU by the evaluation of related factors such as constipation, diarrhea, vomiting, and volume of gastric lavage. Earlier, Lucey *et al.* investigated if neostigmine increases gastric emptying in critically ill patients, by the evaluation of gastric paracetamol absorption. In that study, it was shown that while neostigmine might have a positive effect on gastric emptying and enteral feed absorption, the results did not reach statistical significance.[25]

Our study had a similar outcome. In our investigation, the groups matched well because there were no significant differences in the demographic data and SOFA index between them. With regard to the indices of enteral feeding tolerance, there were no significant differences between the two groups. By comparing these two studies with those on Ogilvie's syndrome, we can conclude that probably the pathophysiological mechanisms of these two settings are a little different. In other words, the gastric emptying may not be the only pathophysiological cause of gastrointestinal tolerance. On the other hand, the other effective factors on enteral tolerance, such as the last clinical underlying condition of the patient, history of underlying diseases, especially gut diseases or those affecting the gastrointestinal tract, duration and cause of being nil per os (NPO; nothing by mouth) before the beginning of gavage, and any other unknown conditions, may have affected our study outcome.

Moreover, it is important to notice that two of the chief indicators of enteral intolerance, constipation and return of materials in gastric lavage, had noticeably lower incidence in the group that received neostigmine, which also had lower duration of hospitalization in the ICU, while not being statistically significant. We cannot omit this outcome simply, especially when we see that the dangerous adverse effects of neostigmine were not seen in any of the patients in the case group by this manner of administration.

One of the imitations of our study was inability to omit the effect of other drugs such as opiates and other confounding factors such as hypokalemia, which have noticeable role in gastrointestinal intolerance, especially in ICU patients. The other one was the limitation in increasing the dose of neostigmine. Maybe if our cases were younger, or more stable, they would have responded better to neostigmine, or we could have increased the dose

of the drug without serious adverse effect. Matching of patients in the areas of the first diagnosis, intubation, and also ventilation state of them needs further studies to be conducted.

Of course, further evaluation of the effect of neostigmine on the tolerance of enteral feeding is a high potential subject for investigation and practical usage.

It is concluded that although neostigmine has high potential cholinergic effects, it was not significantly effective on the tolerance of enteral feeding in ICU patients.

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