



1392 . 11 . 15 14129

ISFAHAN UNIVERSITY OF MEDICAL SCIENCES
SCHOOL OF MEDICINE
ANESTHESIOLOGY & INTENSIVE CARE DEPARTMENT

Thesis For Obtaining The Subspeciality Degree In Anesthesiology & Intensive Care

Title:

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

NUMBER: 391451

Author :

Dr. Mohammadreza Habibzadeh

Supervisors:

Dr. Saeed Abbasi

(Associate Professor of Anaesthesiology)

Dr. Parviz Kashefi

(Associate Professor of Anaesthesiology)

July 2013



دانشکده پزشکی

تایید

جلسه دفاع از پایان نامه تحقیقی دکتر محمدرضا حبیب زاده

تحت عنوان : تعیین تأثیر نئوستیگمین وریدی بر روی تحمل گاوژ در بیماران بستری در بخش مراقبتهای ویژه که دچار عدم تحمل گاوژ شده اند و مقایسه آن با گروه کنترل
برای دریافت درجه دکتری تخصصی رشته بیهوشی و مراقبتهای ویژه در تاریخ ۹۲/۴/۳۱

با حضور امضاء کنندگان زیر تشکیل و پس از ارائه پایان نامه و بحث و بررسی با درجه عالی مورد تصویب قرار گرفت.

استاد راهنما : دکتر سعید عباسی - دکتر پرویز کاشفی

دیگر اعضای هیئت داوران :

دکتر محمدرضا حبیب زاده
تخصص بیهوشی و مراقبتهای ویژه
دانشیار دانشکده پزشکی ۳۷۷۲۶

دکتر جلال جاشمی
تخصص بیهوشی و مراقبتهای ویژه
۳۱۲۶۴

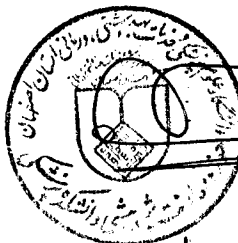
دکتر سعید عباسی
تخصص بیهوشی و مراقبتهای ویژه
۷۱۷۷

دکتر غلامرضا خلیلی
تخصص بیهوشی و مراقبتهای ویژه
دانشیار دانشکده پزشکی
ن.ب.د ۲۷۲۱

مدیر گروه : دکتر پرویز کاشفی

معاون پژوهشی دانشکده پزشکی : دکتر طالب آرزو

معاون آموزشی / تخصصی دانشکده پزشکی : دکتر سید مجتبی ابطی



Dear Dr. Kazemi,

We are pleased to inform that your manuscript "Evaluation of effects of IV neostigmine on tolerance of gavage in ICU patients" is provisionally accepted. You would receive an edited version of article in about 2-3 weeks from now for a final check and correction.

The journal does not charge for submission, processing or publication of manuscripts and except for color reproduction of photographs.

We thank you for submitting your valuable research work to Journal of Research in Medical Sciences.
With warm personal regards,

Yours sincerely,

Nastaran Eizadi-Mood

Journal of Research in Medical Sciences

انظر
نسترن عیادی-مود

مجله پژوهش در علوم پزشکی
Journal of Research in Medical Sciences

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

1. Mohammadreza Habibzade,
Anaesthesiologist , Flow sheep of Critical Care Medicine , Department of
Anaesthesiology and Intensive Care Unit , School of Medicine, Isfahan University
of Medical Sciences, Isfahan, IRAN.
2. Saeed Abbasi,
Associate Professor, Anaesthesiologist , Flow sheep of Critical Care Medicine,
Department of Anesthesiology and Intensive Care Unit , School of Medicine,
Isfahan University of Medical Sciences, Isfahan, IRAN.
3. Parviz Kashefi,
Associate Professor , Anesthesiologist , Department of Anesthesiology and
Intensive Care Unit , School of Medicine, Isfahan University of Medical Sciences,
Isfahan, IRAN.
4. Shadi Kazemi,

Internist , department of ICU , Shahid Montazeri Hospital , Najafabad , Isfahan,
IRAN.

Corresponding Author: Shadi Kazemi

E-mail: sh_kazemy@resident.mui.ac.ir

Tel:09133039771

Running title: neostigmine in tolerance of enteral feeding.

Abstract

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 patients .

Materials and Methods: A total of 60 patients hospitalized in Intensive Care Unit, entered the study . They were randomly assigned to one of two groups of case (who received intravenous neostigmine) or control (who received normal saline). They were compared with respect to incidence of constipation , diarrhea , vomiting , increasing of gastric lavage volume, that show the statement of enteral feeding tolerance , and also arrhythmia , bronchospasm , mean arterial blood pressure and heart rate at the time of 0 , 4 , 8 , 12 , 16 , 20 , and 24 hours after start of the study, for the evaluation of neostigmine adverse effects.

Results : Incidence of constipation , diarrhea , vomiting , increasing of gastric lavage volume in the intervention group was 20% , 33.3% , 46.7% and 43.3% , respectively , while these indices in the control group was 40% , 30% , 43.3% , 63.3% , respectively. Incidence of arrhythmia were 3% and 6% in case and control groups , respectively. Bronchospasm was not detected in any of patients.

Conclusion : There were no statistical significant difference in the field of indices of constipation($p=0.09$) , diarrhea($p=0.78$) , vomiting($p=0.08$) , increasing of gastric lavage volume($p=0.12$) and

also arrhythmia($p=0.99$) and bronchospasm($p=1$) between two groups.

Key words: neostigmine , enteral feeding tolerance , Intensive Care Unit (ICU)

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 incidence of nosocomial infection.^{2,3}

Furthermore it has been demonstrated that early enteral nutrition can decrease duration of staying in hospital in patients after surgery .

Studies of large administrative databases show that , on average , patients with a diagnosis of post-operative ileus stay 5 days longer in hospital after abdominal surgery than patients without post-operative 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

Intolerance of enteral feeding is multifactorial in origin and may be associated with a systemic problem such as sepsis, electrolyte abnormalities, autonomic nervous system dysfunction, recent gastrointestinal surgery or a primary gastrointestinal problem such as mechanical obstruction. Of course the use of vasopressors and narcotics may also exacerbate gastric stasis.

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

Cisapride has a documented pro-arrhythmogenic effect and 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 and also its antibiotic effect may result in growth of resistant microorganisms. Metoclopramide is a dopamine receptor antagonist and may cause extra-pyramidal reactions and the neuroleptic malignant syndrome.

Neostigmine is an acetylcholinesterase inhibitor that causes an increase in cholinergic (parasympathetic) activity in the gut wall, which is believed to thereby stimulate colonic motility.

There are several studies that show this effect of neostigmine practically in patients with post-operative ileus^{7,8,9}, intoxication with drugs which have ileus effect¹⁰, 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.¹² It may cause from a number of clinical conditions including trauma, major orthopedic surgery, severe medical illness, retroperitoneal pathology, metabolic imbalance and regional anesthesia¹². There are several studies show that neostigmine rapidly decompressed the colon in a group of patients with acute colonic pseudo-obstruction who had not responded to conservative treatment.^{12,13,14,15,16,17}

A bolus dose of 2 mg neostigmine is associated with bradycardia, abdominal pain, vomiting and excess salivation¹³. In 2001 Van der Spoell et al, had an investigation on the influence of 0.4 to 0.8 mg/hr. of neostigmine by continuous infusion on patients with colonic ileus and found that this method of administration promoted defecation in these critically ill patients without any appreciable adverse effects.¹⁸

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 is reviewed and approved by the Institutional Ethics Committee of the Faculty of Isfahan University of Medical Sciences (391451). Written, informed consent was obtained prior to inclusion in the study from 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 to 65 years old who were prescribed feeding via a naso- or oro-gastric tube in the intensive care unit (ICU) of Alzahra Hospital, Isfahan, Iran. Patients didn't include to the study were those with :

- Atrioventricular blocks
- Heart rate <60/min
- Base of systolic blood pressure<90mmHg
- 1st 10 days after gut surgery
- Clinical appearance of gastrointestinal obstruction
- Bronchospasm
- Pregnancy
- Breast feeding
- Administration of prokinetic agents in the last 24 hours
- Sensitivity to Neostigmin

Patients were randomly assigned to one of two groups of case or control (1st patient in case and 2nd one in 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 didn't 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 with dose of 1 mg in 100 ml normal saline, intravenous infusion in 30 min , and then 0.5 mg in 50 ml normal saline , intravenous infusion in 15 min every 4 hours to 24 hours . In the control group normal saline used alone at the same time with the same rate of infusion instead of neostigmine.

The enteral feeding protocol required Nutrition Standard to be infused initially at 30 mL/hr and increased at 4 hours to 60 mL/hr.¹⁹ Aspiration of the gastric tube was performed 4-hourly. Increasing of gastric lavage was defined as an aspiration volume of > 120 mL (>50% of gavage volume) at the end of a 4 hour period.¹⁹

Demographic and clinical data of 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 level of hypotension ^{20,21}) were collected by a written questionnaire at beginning of the study.

Incidence of constipation(fewer than three defecations per week)²² , diarrhea(three or more loose or watery stools per day)²³ , vomiting(the forceful expulsion of gastric contents)²⁴ , increasing of gastric lavage (as defined previously)¹⁹ , that show the statement of enteral feeding tolerance , arrhythmia , bronchospasm , mean arterial

blood pressure and heart rate at the time of 0 , 4 , 8 , 12 ,16 , 20 , and 24 hours after start of the study, for the evaluation of neostigmine adverse effects , and also duration of hospitalization in ICU , and death during the study were compared in two groups .

Statistical analysis

The values were expressed as the mean \pm SD(standard deviation). The differences between demographic and clinical data and also study outcomes of two groups were analyzed using Student's *t* test and Chi-square test. The level of significance was set at $p < 0.05$. Repeated measure analysis of variance was used to evaluate changes of 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). Mean of age in the case and control group was 40.1 ± 14.7 and 37.6 ± 13.7 respectively. There were no significant difference between two groups based on t-test ($p=0.47$). In the intervention group there were 16 male (53.3%) and 14 female (46.7%) whereas in the control group there were 17 male (56.7%) and 13 female (43.3%). Based on Chi-square test this difference was not significant too ($p=0.8$). Also, mean of SOFA index was not significantly different between two groups ($p>0.05$). These are shown in table 1.

In the field of enteral feeding tolerance indices (constipation, diarrhea, vomiting, increasing of lavage volume), adverse effects of neostigmine (arrhythmia, bronchospasm), duration of hospitalization in ICU, and mortality rate, there were no statically difference between two groups. ($p=0.09, 0.78, 0.8, 0.12, 0.99, 1, 0.1, 1$, respectively). These are shown in table 2.

Mean of heart rate and mean arterial blood pressure changes (which are related to the adverse effects of neostigmine) were balanced in two groups until 24 hours (p value = 0.12 and 0.1, respectively) (Repeated measure analysis of variance). It is shown in table 3.

Discussion

Early beginning of enteral feeding is a scientific rule in ICU and successfulness of patient in tolerance of it is as important that is often reported even immediately after vital signs of the patient in daily visits of ICU. It is because of important effect of enteral feeding on the one of the greatest complications of hospitalization which is "infection"^{1,2,3} and also its noticeable effect on duration of hospitalization⁴ which is very important economically and also a great healthy index.

Till now there were surgical procedures and pharmacological methods to facilitate this process and increase tolerance of enteral feeding in patients but each of them had their limitations.^{6,7,8,9}

One of these drugs which has been noticed in this field in the last years, is neostigmine. Studies had different results about effectiveness of neostigmine on the tolerance of enteral feeding especially in patients in ICU.^{7,8,9,10} Increase amplitude on ElectroGastroGraphy was clearly demonstrated after administration of neostigmine¹¹. But the most important effect of neostigmine that makes it the first choice for investigation in this field, is its dramatically effect on recovering of pseudo-obstruction syndrome that calls Ogilvie's syndrome.^{12,13,14,15,16,17}

In present study we investigate the direct effect of neostigmine on the tolerance of enteral feeding in patients in ICU by evaluation of related factors such as constipation, diarrhea, vomiting, volume of gastric lavage. Formerly, Lucey et al investigated that if neostigmine

increase 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 matching was performed well because there were no significant difference in the demographic data and SOFA index between two groups .In the field of indices of enteral feeding tolerance there were no significant difference between two groups ; By the comparement of these two studies with those on Ogilvie's syndrome we can conclude that maybe the pathophysiological mechanisms of these two settings are a little different ; In other words , maybe the gastric emptying is not the only pathophysiological cause of gastrointestinal tolerance . On the other way , the other effective factors on the enteral tolerance such as the last clinical underlying condition of the patient , history of underlying diseases especially gut diseases or those affect gastrointestinal tract , duration and cause of being NPO(nil per os (nothing by mouth)) before beginning of gavage , and any other unknown conditions , may affect our study outcomes .

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 group received neostigmine , who had also lower duration of hospitalization in ICU , while not statistically significant . We cannot omit this outcome simply especially when we see that danger adverse effects of

neostigmine was not seen in any of patients in case group , by this manner of administration .

One of the greatest limitations 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 limitation in increasing dose of neostigmine . Maybe if our cases were younger , or more stable , they would responded better to neostigmine or we could increase dose of the drug without serious adverse effect . Matching of patients in the field of the first diagnosis , intubation and also ventilation state of them needs greater studies in the future.

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

Acknowledgment

We are grateful for the dedication of all the research assistants especially Mr.Mehrabi and also patients who agreed to coordinate with us.

References

1. Alverdy J. The effect of nutrition on gastrointestinal barrier function. *Sem Respir Inf* 1994;9:248-255.
2. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces post-operative septic complications. The results of a meta-analysis. *Ann Surg* 1992;216:172-83.
3. Lowry SF, Fong Y. Determine whether 1 week of total parenteral nutrition in healthy subjects alters systemic responses to a subsequent dose of endotoxin. *Ann Surg* 1996;223:107-8.
4. Delaney C, Kehlet H, Senagore A, et al. Postoperative ileus: profiles, risk factors, and definitions—a framework for optimizing surgical outcomes in patients undergoing major abdominal colorectal surgery. In: Bosker G, editor. *Clinical consensus update in general surgery*. Roswell(GA): Pharmatecture, LLC; 2006. p.1-26.
Available: www.clinicalwebcasts.com/pdfs/GenSurg_WEB.pdf (accessed 2008 May 15).
5. McClave SA, Sexton LK, Spain DA et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Crit Care Med* 1999;27:1252-6.
6. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: A systematic review of the evidence. *Crit Care Med* 2002;30:1429-35.
7. Zeinali F, Stulberg JJ, Delaney CP. Pharmacological management of postoperative ileus. *Can J Surg*. 2009 Apr;52(2):153-7.
8. Emirleroglu M, Ekci B, Durgun V. The effect of neostigmine on postoperative ileus and the healing of colon anastomoses. *Bratisl Lek Listy* 2011;112(6):309-13.
9. Caliskan E, Turkoz A, Sener M, Bozdogan N, Gulcan O, Turkoz R. A prospective randomized double-blind study to determine the effect of thoracic epidural neostigmine on postoperative ileus after abdominal aortic surgery. *Anesth Analg* 2008 Mar;106(3):959-64.

10. Chan B, Whyte I, Dawson A, Downes M. Use of neostigmine for the management of drug induced ileus in severe poisonings. *J Med Toxicol* 2005 Dec;1(1):18-22.
11. Imai K, Kitakoji H, Chihara E, Sakita M. Effects of atropine sulfate and neostigmine on gastric electrical activity in human subjects--electrogastrographic study. *Hepatogastroenterology*. 2008 Jan-Feb;55(81):294-7.
12. Batke M, Cappell MS. Adynamic ileus and acute colonic pseudo-obstruction. *Med Clin North Am* 2008 May;92(3):649-70.
13. Ponc RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999;341:137-141.
14. Khosla A, Ponsky TA. Acute colonic pseudoobstruction in a child with sickle cell disease treated with neostigmine. *J Pediatr Surg* 2008 Dec;43(12):2281-4.
15. Ozkurt H, Yilmaz F, Bas N, Coskun H, Basak M. Acute colonic pseudo-obstruction (Ogilvie's syndrome): radiologic diagnosis and medical treatment with neostigmine. Report of 4 cases. *Am J Emerg Med* 2009 Jul;27(6):757.e1-4.
16. Robert McNamara, FAAEM and Michael J. Mihalakis .Acute colonic pseudo-obstruction: rapid correction with neostigmine in the emergency department . *J Emerg Med* 2008 ; 35(2), 167-70.
17. White L, Sandhu G. Continuous neostigmine infusion versus bolus neostigmine in refractory Ogilvie syndrome. *Am J Emerg Med* 2011 Jun;29(5):576.e1-3.
18. Van der Spoel JJ, Oudemans-van Straaten HM, Stoutenbeek CP, et al. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure - a prospective, double-blind, placebo-controlled trial. *Intensive Care Med* 2001;27:822-7.
19. Frost P, Bihari D. The route of nutritional support in the critically ill: physiological and economic considerations. *Nutrition* 1997;13:58S-63S.
20. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286:1754.

21. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; 26:1793.
22. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006; 130:1480.
23. American Gastroenterological Association medical position statement: guidelines for the evaluation and management of chronic diarrhea. *Gastroenterology* 1999; 116:1461.
24. American Gastroenterological Association. American Gastroenterological Association medical position statement: nausea and vomiting. *Gastroenterology* 2001; 120:261.
25. M.A.Lucey , V. Patil , K. Girling , T. Jacques , M. O'leary. Does Neostigmine Increase Gastric Emptying in the Critically Ill? - Results of a Pilot Study. *Critical Care and Resuscitation* 2003; 5: 14-19.

variables		Case	Control	P value
Age		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

Table 1-Demographic data in case and control groups. (The level of significance was set at $p < 0.05$.)

SOFA: Sequential Organ Failure Assessment

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

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 $p < 0.05$.)

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	

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 $p<0.05$.)