Original articles

Does Neostigmine Increase Gastric Emptying in the Critically Ill? - Results of a Pilot Study

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ABSTRACT

Objective: *Based on the successful use of neostigmine for the treatment of acute colonic pseudo-obstruction, we hypothesised that neostigmine would increase gastric emptying and improve tolerance to enteral feeding in the critically ill patient.*

Methods: *: Eleven patients intolerant of enteral feeds due to high gastric aspirates, were randomised to receive a 'study infusion' consisting of either neostigmine (0.4 mg/hr) or 0.9% saline. If, after 12 hours the patient was deemed inolerant of the nasogastric feed, the rate of the 'study infusion' was doubled. Those who remained intolerant after 24 hours of the 'study infusion' were 'crossed-over' and continued on the other infusion for a further 24 hours. Gastric emptying was assessed in each group before and after the infusion by measuring the hourly rates of feed "absorption" [(delivery rate + returned aspirates) - total aspirates] and paracetamol absorption using the area under a time-concentration curve at 120 minutes (AUC_{120}). Differences within and between groups were analysed using Students t test and one-way analysis of variance.*

Results: *Six patients received neostigmine first and 5 received the placebo first. Four of the 6 patients receiving the neostigmine first compared with all of those receiving placebo first required to be 'crossed-over' to the other infusion. While the hourly rates of feed "absorption" were greater for patients receiving neostigmine than for placebo, these differences did not achieve statistical significance. The mean paracetamol AUC_{120} for all patients who received neostigmine was 3996 mg/min/L while that for placebo was 1929 mg/min/L ($p = 0.21$).*

Conclusions: *These data suggest that while neostigmine may have a positive effect on gastric emptying and enteral feed absorption in critically ill patients, the results did not reach statistical significance and an adequately powered study will be required to confirm this effect.* (**Critical Care and Resuscitation 2003; 5: 14-19**)

Key words: neostigmine, paracetamol absorption, enteral feed, gastric emptying, critically ill.

Enteral nutrition has a number of beneficial effects. It has a role in the maintenance of the normal gut mucosal barrier function, reducing bacterial and endotoxin translocation,[1] and has been associated with a reduced incidence of nosocomial infection.[2,3] Crucial to the clinical impact of enteral feeding are its early institution[4] and the ability to provide adequate nutritional intake.[5] These goals, however, are often difficult to achieve with gastrointestinal complications often limiting the use of enteral nutrition in critically ill patients. A recent multi-centre study found that up to 63% of patients suffered one or more gastrointestinal complications with enteral feeding; the most frequent being gastroparesis with high gastric residual volumes

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(39%), constipation (16%), diarrhoea (15%), abdominal distension (13%), vomiting (12%) and regurgitation (6%).[6]

Gastroparesis is multifactorial in origin and may be associated with recent gastrointestinal surgery, a primary gastrointestinal problem (e.g. mechanical obstruction) or a systemic problem such as sepsis, electrolyte abnormalities or autonomic nervous system dysfunction. The use of vasopressors and narcotics may also exacerbate gastric stasis. A number of prokinetic agents have been used to improve gastric motilty, including cisapride, metoclopramide and erythromycin; however, there is no definitive evidence for the benefit of one over another.[7]

Cisapride has a documented pro-arrhythmogenic effect and is no longer available in some countries. Erythromycin prolongs the QT_c interval and may precipitate cardiac arrhythmias whilst it's antibiotic effect may result in the selection of resistant microorganisms. Metoclopramide is a dopamine receptor antagonist and may cause extra-pyramidal reactions and the neuroleptic malignant syndrome.

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.[8] It is associated with a number of clinical conditions including trauma, major orthopaedic surgery, severe medical illness, retroperitoneal pathology, metabolic imbalance and regional anaesthesia. In 1999, Ponec *et al*, showed that neostigmine rapidly decompressed the colon in a group of patients with acute colonic pseudo-obstruction who had not responded to conservative treatment,[9] although in bolus doses of 2 mg neostigmine was associated with abdominal pain, vomiting and excess salivation as well as symptomatic bradycardia. Van der Spoell *et al*, investigated the influence of neostigmine on patients with critical illness-related colonic ileus and found that 0.4 to 0.8 mg/hr of neostigmine by continuous infusion, promoted defecation in critically ill patients without any appreciable adverse consequences.[10] We hypothesised that neostigmine may improve gastric emptying by a similar mechanism and thereby improve enteral feeding in the critically ill.

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

MATERIALS and METHODS

Institutional ethics committee approval was obtained prior to commencement of the study. Written, informed consent was obtained prior to inclusion in the study from patients or from the nominated person responsible for the patient.

All patients prescribed feeding via a naso- or oro-gastric tube were eligible for inclusion in the study if they were deemed intolerant of an enteral feeding protocol within 48 hours of commencement of feeds. Exclusion criteria are listed in Table 1.

Table 1. Study exclusion criteria

- Atrioventricular block on ECG or baseline heart rate less than 60
- Baseline systolic blood pressure less than 90
- Less than 10 days following surgery to the stomach or gastrointestinal tract
- Clinical evidence of mechanical gastrointestinal obstruction
- Active bronchospasm requiring medication
- Pregnancy or lactation
- Prescription of any prokinetic agent in previous 24 hours
- Known hypersensitivity to neostigmine or paracetamol

The enteral feeding protocol required Nutrison Standard® to be infused initially at 30 mL/hr and increased at 4 hours to 60 mL/hr and again after 24 hours (unless they were intolerant of enteral feeding) to the target volume (in mL/hr) determined by the equation: (body weight in kg x 32)/24.[11] Aspiration of the gastric tube was performed 4-hourly. Intolerance of enteral feeding was defined as an aspiration volume of > 120 mL at the end of a 4 hour period. Where there were excessive gastric aspirates the feed volume was not increased.

Patients were randomised (by random number allocation) to receive either neostigmine (diluted in 0.9% sodium chloride solution and infused at a rate to deliver 0.4 mg/hr i.e. 4 mL/hr) or placebo (0.9% sodium chloride solution infused at an equivalent rate).

Prior to commencement of the infusion, enteral feeds were discontinued and all gastric contents aspirated. Baseline (time 0) arterial bloods were collected and 1.5 g of paracetamol elixir (31 mL) was administered via the gastric tube. Arterial blood samples were collected at 15, 30, 45, 60, 90 and 120 minutes and measured for paracetamol levels. The enteral feeds were then recommenced at the previous rate whilst the 'study infusion' was simultaneously commenced. Gastric aspiration was repeated 4 hours after any rate increase or after any aspirate greater than 120 mL; thereafter gastric

aspiration was performed 12-hourly. If, after 12 hours of the 'study infusion', the feed rate could not be increased, the 'study infusion' rate was doubled. For the neostigmine group this equated to 0.8 mg/hr. Paracetamol absorption testing (over 2 hours) was then repeated at 24 hours. At this time, (i.e. 26 hours), any patient deemed still intolerant of enteral feeds due to high gastric aspirates was 'crossed-over' to the other group and continued on the new infusion for a further 24 hours after which paracetamol absorption tests were again repeated. If, after the initial 26 hours, the patient was tolerating their feed, the 'study infusion' was discontinued and the subject continued to be fed according to the protocol.

Enteral feed volume data were collected 48 hours prior to commencing the 'study infusion', during the infusion and 48 hours after the infusion. Hourly volumes of feed "absorbed" were calculated from the formula [(delivery rate + returned aspirates) - total aspirates]. Paracetamol levels (except baseline) on arterial blood samples taken during the 'study infusion' and were measured using a fluorescent polymerisation immunoassay (Abbott Laboratories, Illinois USA). Feeding volumes in each period were normalised to hourly rates to permit comparison and statistical analysis.

Statistical Analysis

Gastric emptying before and after infusion was evaluated, in each group, by paracetamol absorption using the area under a time-concentration curve[12] and differences within and between groups were analysed using Student's *t* test and one-way analysis of variance.

RESULTS

Eleven patients were randomised to receive either neostigmine (n = 6) or placebo (n = 5) first during a 12 month study period. Group demographics are shown in table 2. Four of the six patients who received neostigmine first were 'crossed-over' to the other infusion after the first 24 hours, whilst all of the patients who received placebo first were 'crossed-over' to the neostigmine infusion. Figure 1 shows hourly volumes of feed "absorbed" in patients receiving neostigmine first and placebo first. Although neostigmine treatment was associated with greater feed "absorption" (i.e. less aspirate volumes), the differences failed to reach statistical significance.

The mean AUC_{120} ($\pm$ SD) of the serum paracetamol was 3996 $\pm$ 3573 mg/min/L for the neostigmine group and 1929 $\pm$ 1476 mg/min/L for the placebo group (figure 2), indicating a greater paracetamol absorption with neostigmine, although this did not reach statistical significance (p = 0.21).

Table 2. Demographic data in patients randomised to receive neostigmine or placebo

	Neostigmine (n = 6)	Placebo (n = 5)
Age in years (range)	55 (18 - 73)	59 (40 - 66)
Male:female	6:0	4:1
APACHE II (mean, range)	18 (15 -22)	25 (21 -28)
Diagnosis	Multitrauma (2) Hepatic failure Sepsis with shock Ruptured abdominal aortic aneurysm Bacterial pneumonia	Cardiogenic shock (2) Sepsis with shock Dissecting aortic aneurysm Pneumonia and shock

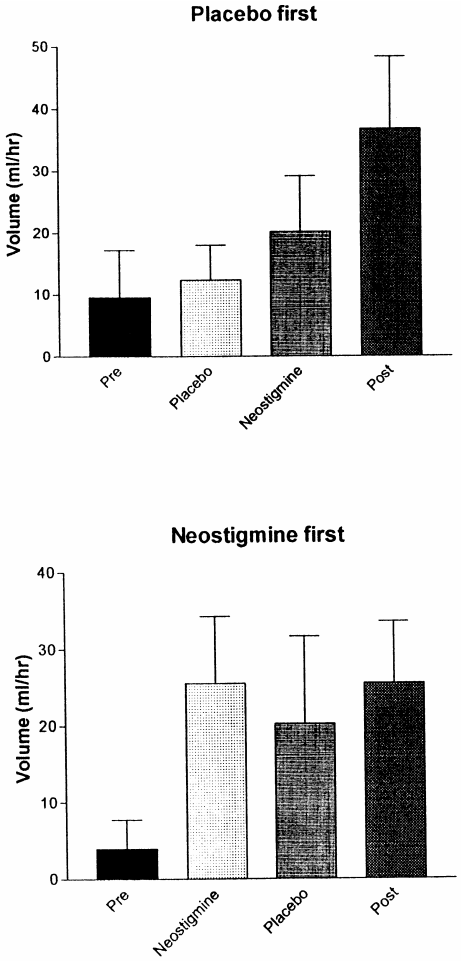

Figure 1. Graphs illustrating hourly volumes in mL/ hr of feed "absorbed" [(delivery rate +returned aspirates) – total aspirates] in patients receiving placebo first and neostigmine first. The columns represent the phases of the experiment, Pre = 48 hour period pre-randomisation, neostigmine and placebo = 26 hour infusion periods, Post = 48 hour period following cessation of infusion.

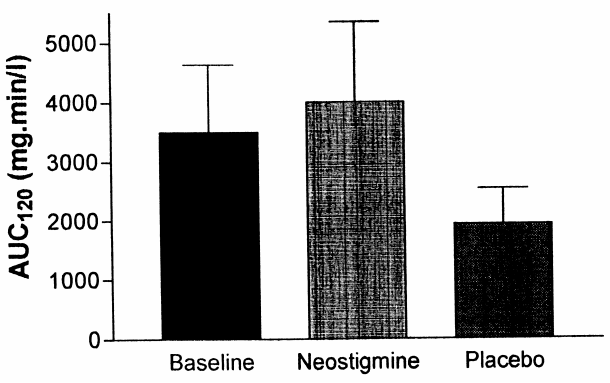

Figure 2. Graph illustrating the mean area under the curve at 120 minutes (AUC_{120} in mg.min/L) for serum paracetamol following a 1.5 g nasogastric bolus in patients prior to the study infusion (Baseline), following 24 hours neostigmine infusion (Neostigmine) and following 24 hours placebo infusion (Placebo).

When feed volumes were analysed in terms of infusion received (i.e. all patients receiving neostigmine combined and all patients receiving placebo combined) the quantities of feed received during neostigmine infusion were greater than during placebo infusion, a difference that was not significantly significant. When all eleven patients were analysed together (figure 3), the post-infusion quantity of feed absorbed was greater than pre-infusion ($p < 0.05$).

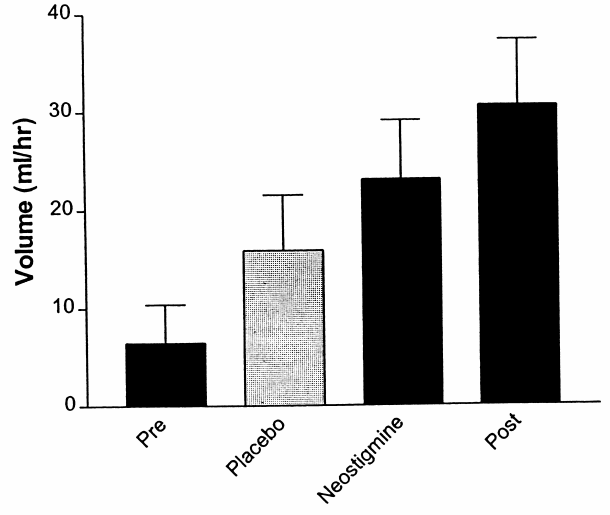

Figure 3. Graph illustrating hourly volumes in mL/hr of feed "absorbed" [(delivery rate +returned aspirates) – total aspirates] in patients according to infusion received (i.e. all patients receiving placebo combined and all patients receiving neostigmine combined). The columns represent the phases of the experiment, Pre = 48 hour period pre-randomisation, Neostigmine and Placebo = 26 hour infusion periods, Post = 48 hour period following cessation of infusion.

Diarrhoea occurred in 33% of those who received neostigmine first and in 20% of those who received placebo first. After cross-over, no patient developed diarrhoea who crossed-over into the placebo group, while one further patient developed diarrhoea after crossing-over to the neostigmine group.

DISCUSSION

Inability to establish enteral feeding is common in the intensive care population and is generally multifactorial in origin. Impaired gastric emptying due to post-operative ileus in patients undergoing primary gastro-intestinal surgery, the use of opiate narcotics and adrenergic agents,[13-15] the effect of low flow states resulting in intestinal ischaemia,[16] sepsis and endotoxaemia,[17] elevated levels of nitric oxide[18] or a combination of these factors often appear to be responsible.

There are a number of methods available for the assessment of gastric emptying. Classically gastric aspirates are measured.[19,20] However, a number of authors have shown that an abnormally high residual volume is not necessarily a reliable indicator of gastric emptying or absorption of feed.[21] For the purpose of this study, we decided to use the formula [(delivery rate + returned aspirates) - total aspirates] hourly, as indicative of gastric emptying as we contend that this is the most clinically relevant volume and accordingly the amount of feed "absorbed". Alternative methods of measuring gastric emptying and feed "absorption" include scintigraphy (the current gold standard),[19] breath tests,[22] magnetic resonance imaging,[23] epigastric impedance,[24] ultrasonography[25] and pharmacological tracers in blood, such as paracetamol,[26] although each have their limitations.

Paracetamol in solution is rapidly and almost exclusively absorbed from the small intestine with the rate of absorption indicating a functional gastric emptying rate. Van Wyk *et al*, showed it to be a reliable method for investigating liquid gastric emptying in diabetic patients and in assessing the effects of a number of prokinetic agents on diabetic gastroparesis.[27] Willems *et al*, in a systematic review, evaluated the validity of this test compared with scintigraphy for gastric emptying assessment and concluded that the paracetamol absorption test correlated well with the accepted "gold standard".[28] The limitations of the test relate primarily to pharmacokinetic issues such as individual differences in first-pass metabolism and elimination.[29] To overcome these shortcomings, and in an effort to make the technique more reliable, Sanaka *et al* recommended a 'cross-over' design[30] as employed in our study.

We found that the volumes of feed absorbed were greater in those patients who received neostigmine first

compared with placebo first, although the effect did not reach statistical significance. We also found that the volume of gastric aspirate in those patients who 'crossed-over' to the neostigmine group was less than with the placebo group but again this failed to achieve statistical significance. The area under the time-concentration curve for paracetamol over 120 minutes was used as a measure of the effect of neostigmine on liquid gastric emptying and while it was higher in those who received neostigmine as opposed to those who received placebo, this difference was not statistically significant. In the 11 patients recruited, no adverse events potentially attributable to the neostigmine infusion were reported.

This study demonstrated non-significant increases in rates of feed "absorption" and liquid gastric emptying during a low-dose neostigmine infusion in critically ill patients. However, while neostigmine may improve gastric emptying and hence tolerance of enteral feeding in the critically ill, an adequately powered trial needs to be undertaken to confirm the impression generated by this small study.

Received: 28 November 2002
Accepted: 8 January 2003

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