Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure – a prospective, double-blind, placebo-controlled trial

Abstract  Objective: Critical illness-related colonic ileus (CIRCI) is characterized by the non-passage of stools in critically ill patients as a result of the absence of prokinetic movements of the colon, while the upper gastrointestinal tract functions properly and mechanical ileus is absent. We investigated whether neostigmine resulted in defecation in patients with CIRCI.  Design: Double-blinded, placebo-controlled prospective study.  Setting: Eighteen-bed intensive care unit.  Patients: Thirty ventilated patients with multiple organ failure with CIRCI for > 3 days.  Intervention: Continuous intravenous administration of neostigmine 0.4–0.8 mg/h over 24 h, or placebo.  Measurements and results: Time to first defecation and adverse reactions were recorded. Thirty patients were randomized, 24 could be evaluated. The mean pre-study time was 5 days, mean APACHE II score on admission was 23.2, and mean MOF score on the day of the study was 6.4. Of the 13 patients receiving neostigmine, 11 passed stools, whereas none of the placebo-treated patients passed stools \( (P < 0.001) \). After 24 h, the non-responders received in a cross-over fashion neostigmine or placebo respectively. Eight out of the 11 neostigmine patients now passed stools (mean 11.4 h), and none of the placebo patients. Overall, in none of the patients did passage of stools occur during placebo infusion, whereas 19 of the 24 neostigmine-treated patients had defecation (79\%). No acute serious adverse effects occurred, but three patients had ischemic colonic complications 7–10 days after treatment.  Conclusion: Continuous infusion of 0.4–0.8 mg/h of neostigmine promotes defecation in ICU patients with a colonic ileus without important adverse reactions.

Key words  Critical care · Ileus · Neostigmine · Prokinetics · Gastrointestinal motility · Selective decontamination of the digestive tract

Introduction

In critically ill patients, gastrointestinal motility is often disturbed [1]. Traditionally, most emphasis is placed on dysmotility of the upper digestive tract. However, the stomach and small intestines may function properly while at the same time an isolated paralysis of the colon exists. This critical illness-related colonic ileus (CIRCI) is found in critically ill medical as well as surgical patients, in the latter after both non-abdominal surgery and after laparotomy with or without opening of the gut. CIRCI is characterized by the non-passage of stools for prolonged periods without gastric retention and with normal findings during physical and radiological examination – in contrast to a dynamic ileus, in which abdominal distension and vomiting are found, and Ogilvie’s syndrome, in which a dilated colon is paramount. Proposed mechanisms for CIRCI are the administration of...
morphinomimetics and adrenergic agents [2, 3, 4], a low-flow state resulting in ischemia [5], endotoxemia [6], elevated levels of nitric oxide (NO) [7, 8], or a combination of these factors. An ileus in critically ill patients prohibits enteral feeding and promotes bacterial overgrowth and translocation of bacteria and absorption of endotoxins [9]. It further prohibits adequate selective decontamination of the digestive tract (SDD) because the non-absorbable antibiotics do not reach the rectum. Untreated ileus may ultimately lead to distension of the colon, increasing the risk of colonic wall ischemia and perforation [10, 11].

Neostigmine is a cholinesterase-inhibitor, which augments the concentration of acetylcholine (ACh) at the neuromuscular junction, thereby increasing contractions in the normal gut [8]. Since defecation might be beneficial for the patient, as it removes bacteria and endotoxins [12, 13], a double-blind, placebo-controlled trial was undertaken to investigate whether continuous intravenous administration of neostigmine results in defecation in critically ill patients with an ileus of the colon.

**Material and methods**

**Patients**

After approval by the hospital’s scientific and ethical committee, 30 consecutive patients were enrolled in the study, after written informed consent was obtained from their legal representatives. Inclusion criteria were: no production of stools in a mechanically ventilated patient with normal or diminished peristalsis, after more than 3 days of intensive care treatment including enteral feeding and electrolytes. Exclusion criteria were: expected death within 7 days, expected discharge from the ICU within 2 days, signs or symptoms of an acute abdomen, mechanical ileus or Ogilvie’s syndrome diagnosed by physical and radiological examination, gastrointestinal surgery less than 10 days prior to inclusion, atrial-ventricular conduction disturbances, and sinus bradycardia < 60 BPM or a nodal rhythm.

**Intensive care treatment**

Patients were treated according to our standard therapeutic protocols. Circulatory support consisted of dopamine and vasodilators (nitroglycerin, ketanserin, or a combination). Enoxime was added in case of persistent low cardiac output in spite of optimal filling pressures and titrated therapy with dopamine and vasodilators. An intra-aortic balloon pump was inserted in case of persistent cardiac failure. Selective decontamination of the digestive tract was accomplished by administration of q.i.d. the non-absorbable antibiotics tobramycin 80 mg, polymyxin B 100 mg and amphotericin B 500 mg as a solution via the nasogastric tube, and q.i.d. application of a 2% concentration of each of the antibiotics in a sticky paste (Orabase) in the oral cavity [14]. Enteral feeding via a nasogastric tube was administered in all patients, aimed at covering full calorie and protein requirements. Cisapride was added in case of gastric retention, at > 500 ml/24h, and lactulose and enemas were given when defecation did not occur once a day. Analgesia and sedation were given as needed with intravenous boluses of morphine and diazepam of 5–10mg, or with morphine and midazolam as a continuous infusion. Neuromuscular blocking agents were only given to facilitate intubation of the trachea and during surgery.

**Protocol**

Indistinguishable syringes containing neostigmine (5 mg in 50 ml NaCl 0.9%) or placebo (50 ml NaCl 0.9%) were produced by the hospital pharmacy. The infusion was started at 4 ml/h (i.e. 0.4 mg neostigmine/h, or placebo). If no stools were produced after 8 h the infusion rate was doubled. The primary endpoint was the estimated production of more than 100 ml of stools. Secondary endpoints were the need for discontinuation of the study medication due to prolongation of the PQ-interval on the EKG, painful abdominal cramping, or excessive production of saliva or sputum. A second study period was instituted in patients not passing stools after receiving the trial medication for 24 h. These non-responders received placebo if the first study medication had been neostigmine, and vice versa, while the same double-blind protocol for administration was followed.

**Measurements**

Every 3 h, the passage of stools, the volume of gastric retention, and the amount of administered enteral feeding was noted by the nurses. The severity of abdominal cramping was assessed by pain or agitation of the patient as absent, minor, or severe. The heart rate and rhythm were continuously recorded, the PQ interval was measured on a daily EKG, and an additional EKG was made in case of suspected rhythm or conductance disturbances. The amount of sputum was graded at least every 6 h on a subjective scale (normal, much, excessive), as was the amount of saliva. Severity of disease was quantified by the APACHE II score over the first 24 h after ICU admission [15]. Severity of multiple organ failure at the time of randomization was graded by the Goris score, attributing 0, 1 or 2 points to each of seven organ systems, to a maximum of 14 [16]. Patients were followed until discharge from the hospital or death, and complications that were possibly related to neostigmine were recorded.

**Data analysis**

Values are presented as mean and 95% confidence interval (CI) or as median and interquartile range (IQ) for non-parametric data. The two-sided Fisher’s exact test was used to compare nominal variables, the two-tailed Mann-Whitney test for continuous values.

**Results**

Thirty patients were randomized. One had to be excluded because of emergency surgery before the study medication was started. The records of five patients were lost due to a fire. So, 24 patients were evaluable, and their characteristics are summarized in Table 1. No significant differences were found between the patients receiving neostigmine or placebo (Table 2). Two patients died during their stay in the ICU, and six died after discharge from the ICU. No patient received adrenaline or noradrenaline prior to, during, or after the study.