

Acupuncture in Critically Ill Patients Improves Delayed Gastric Emptying: A Randomized Controlled Trial

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BACKGROUND: Malnutrition remains a severe problem in the recovery of critically ill patients and leads to increased in-hospital morbidity and in-hospital stay. Even though early enteral nutrition has been shown to improve overall patient outcomes in the intensive care unit (ICU), tube-feeding administration is often complicated by delayed gastric emptying and gastroesophageal reflux. Acupuncture has been successfully used in the treatment and prevention of perioperative nausea and vomiting. In this study we evaluated whether acupuncture can improve gastric emptying in comparison with standard promotility drugs in critically ill patients receiving enteral feeding.

METHODS: Thirty mechanically ventilated neurosurgical ICU patients with delayed gastric emptying, defined as a gastric residual volume (GRV) >500 mL for ≥ 2 days, were prospectively and randomly assigned to either the acupoint stimulation group (ASG; bilateral transcutaneous electrical acupoint stimulation at Neiguan, PC-6) or the conventional promotility drug treatment group (DTG) over a period of 6 days (metoclopramide, cisapride, erythromycin). Patients in the ASG group did not receive any conventional promotility drugs. Successful treatment (feeding tolerance) was defined as GRV <200 mL per 24 hours.

RESULTS: Demographic and hemodynamic data were similar in both groups. After 5 days of treatment, 80% of patients in the ASG group successfully developed feeding tolerance versus 60% in the DTG group. On treatment day 1, GRV decreased from 970 ± 87 mL to 346 ± 71 mL with acupoint stimulation ($P = 0.003$), whereas patients in the DTG group showed a significant increase in GRV from 903 ± 60 mL to 1040 ± 211 mL ($P = 0.015$). In addition, GRV decreased and feeding balance (defined as enteral feeding volume minus GRV) increased in more patients in the ASG group (14 of 15) than in the DTG group (7 of 15; $P = 0.014$). On treatment day 1, the mean feeding balance was significantly higher in the ASG group (121 ± 128 mL) than in the DTG group (-727 ± 259 mL) ($P = 0.005$). Overall, the feeding balance improved significantly on all days of treatment in comparison with the DTG group. Patients in the DTG group did not show an increase in feeding balance until day 6.

CONCLUSIONS: We introduce a new protocol for acupuncture administration in the critical care setting. We demonstrated that this protocol was more effective than standard promotility medication in the treatment of delayed gastric emptying in critically ill patients. Acupoint stimulation at Neiguan (PC-6) may be a convenient and inexpensive option (with few side effects) for the prevention and treatment of malnutrition in critically ill patients. (Anesth Analg 2010;X:●●●–●●●)

Early enteral nutrition via tube-feeds remains the preferred way of feeding the critically ill patient and an important means to counteract the catabolic state induced by severe illness.^{1–3} Although the impact on outcome, i.e., mortality, is still under debate,¹ meta-analyses of the available literature clearly demonstrate improvement in morbidity after early enteral nutrition in

comparison with parenteral nutrition.^{1–3} Hospital stay and infectious complications are reduced as a consequence of the prevention of postoperative breakdown of skeletal muscles and gastrointestinal mucosa, which impairs organ function, wound healing, and immune defense.

Attempted early enteral nutrition is often complicated by delayed gastric emptying, as is indicated by large gastric residual volumes (GRV) and gastroesophageal reflux,⁴ a common complication after trauma and surgery. Delayed gastric emptying is common in the intensive care unit (ICU), occurring in approximately 50% of mechanically ventilated critically ill patients.^{5,6} Factors associated with delayed gastric emptying include the admission diagnosis (such as head injuries, burns, multisystem trauma, and sepsis), electrolyte abnormalities, age, gender, drugs (such as narcotics or catecholamines), recent abdominal surgery, sepsis, and shock with circulating cytokines.^{7,8} Illness severity, quantified by the Acute Physiology and Chronic Health Evaluation Score II (APACHE II) (based on age, physiological variables, and chronic health conditions) also directly correlates with the incidence of delayed gastric

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emptying.⁷ Neurosurgical patients have also been shown to have a frequent prevalence of delayed gastric emptying during intensive care.⁴

Postoperative nausea and vomiting (PONV) is a common complication after surgery with general anesthesia and remains one of the leading reasons for overnight admission in day-surgery patients. PONV can lead to severe dehydration with the need for IV rehydration and increased mortality in certain patient populations. Prokinetic drugs have been used to resolve this problem with limited success,^{9,10} whereas acupuncture of point Neiguan (PC-6) has proven highly effective in the prevention and treatment of PONV as a nonpharmacological alternative in the direct postoperative period.¹¹ In addition previous studies have found that acupuncture modulates important components involved in the pathogenesis of delayed gastric emptying, such as relaxation of the lower esophageal sphincter and gastric myoelectrical activity.¹²⁻¹⁴ Ultimately, although the underlying pathophysiology of delayed gastric emptying and malnutrition in critically ill patients differs somewhat from acute PONV, both relate to autonomic nervous system activity and both may be amenable to acupuncture therapy. However, much less is known regarding acupuncture effects on delayed gastric emptying in the ICU setting, and more research is needed.

The aim of our study was to adapt an acupuncture stimulation technique to the ICU setting and to evaluate its effect on delayed gastric emptying in comparison with the current standard drug treatment.

METHODS

Study Design and Patients

The study was conducted as a prospective, block-randomized, blinded, parallel-group trial comparing the 6-day effectiveness of acupoint stimulation and prokinetic drugs in improving the success of nasogastric tube feeding. Thirty mechanically ventilated, analgosedated neurosurgical patients were enrolled. Approval of the IRB of the University of Regensburg (Regensburg, Germany) was obtained, and the study was conducted according to the Declaration of Helsinki principles. Written informed consent to perform the study was waived.

Inclusion criteria consisted of recent surgery of a cerebral aneurysm due to subarachnoid hemorrhage (Hunt/Hess classification III or IV), intracerebral hemorrhage, or traumatic brain injury, and presence of gastroparesis. The latter was defined as a gastric reflux volume of at least 500 mL per 24 hours measured on 2 consecutive postoperative days.

Exclusion criteria consisted of age younger than 18 years or older than 75 years, recent major abdominal surgery or trauma, history of partial or total gastrectomy, suspected bowel obstruction or perforation, pancreatitis, administration of prokinetic drugs (metoclopramide, cisapride, or erythromycin) within the previous 24 hours, known allergy to metoclopramide, cisapride, or a macrolide antibiotic, and administration of drugs known to interact with erythromycin (carbamazepine, cyclosporine, theophylline, aminophylline, digoxin, or anticoagulants).

Eligible patients were randomly assigned to the standard drug treatment group (DTG) or the acupoint stimulation group (ASG) by permuted block randomization. Patients were blinded because of their analgosedation.

Interventions

In both groups, therapy was performed for 6 consecutive days or until cessation of GRV, which was defined as no vomiting and GRV of <200 mL per day via nasogastric tubing on 2 consecutive days.

Drug Treatment

Patients in DTG received metoclopramide 10 to 20 mg IV every 8 hours as standard treatment. In case of persistence of delayed gastric emptying, Cisapride in a dosage of 3×10 mg IV every 8 hours was added. After Cisapride was withdrawn from the market because of serious side effects, erythromycin 500 mg IV every 24 hours was added instead.

Acupuncture Technique

Patients in the ASG group received bilateral prolonged intermittent transcutaneous electrical acupoint stimulation of acupuncture point Neiguan (P6). Neiguan, the sixth point on the Chinese pericardium meridian, is located on the palmar side of the distal forearm between the palmaris longus and the flexor carpi radialis muscles, 2 cun (1 cun = patient's thumb width) proximal of the distal hand crease. Stimulation was applied at a frequency of 7 Hz, with a current between 7 and 13 mA, depending on the patient's wrist size. Electrical stimulation was applied in a standardized order over 1 30-minute period and 8 5-minute periods per day; time intervals between stimulations were at least 2 hours. A custom-built transcutaneous electric nerve stimulator (TENS) timer was constructed (T. Schmid, University of Regensburg, Regensburg, Germany), providing the TENS device (TNS-SM2 AKS[®]; Schwamedico, Giessen, Germany) with battery power at specified time periods. Current was applied via electrodes (Bentreden[®], Bentrionic GmbH, Munich, Germany) at acupoint Neiguan (cathode; electrode diameter reduced to 0.5 cm) and an acupoint opposite Neiguan, on the dorsal forearm (Weiguan, TW5, anode; electrode diameter 2.5 cm). This is the 5th point on the Chinese triple warmer meridian. Electrodes were isolated on the skin with Band-Aid[®] spray to provide focused electrical flow. Patients assigned to the ASG did not receive any conventional prokinetic drug treatment.

Patient Management

Analgesia and sedation of patients were performed according to hospital standards: piritramide (13 to 20 mcg/kg/h), or equivalent doses of other opioids, and propofol (2 to 7 mg/kg/h) were infused continuously, aimed at reaching adequate sedation and analgesia according to a Ramsay Score of 5 to 6. A semirecumbent position (30°) was mandatory during the ICU treatment. Blood glucose levels were targeted to 100 to 150 mg/dL by continuous infusion of insulin.

Enteral Feeding Protocol

All patients received a nasogastral tube draining to a bag placed 10 cm above gastric level. Correct placement of the nasogastral tube was checked by epigastric auscultation

Table 1. Demographic Data of Patients and Drugs Given During Treatment Period

| | Acupuncture group (n = 15) | Drug treatment group (n = 15) | P value |
|---|-------------------------------|----------------------------------|---------|
| <i>Demographics</i> | | | |
| Gender (female/male) | 9/6 | 6/9 | n.s. |
| Age in years | 47.5 ± 3.7 | 46.7 ± 4.26 | n.s. |
| Body mass index in kg/m ² | 26 ± 0.9 | 26 ± 0.9 | n.s. |
| Admission diagnosis (SAH/SHT/ICB) | 10/3/2 | 8/4/3 | n.s. |
| APACHE II score | 12.0 ± 1.5 | 12.1 ± 1.4 | n.s. |
| SAPS II score | 8.1 ± 1.1 | 8.5 ± 0.7 | n.s. |
| Ramsey score | 6.0 ± 0 | 6.0 ± 0 | n.s. |
| Patients with elevated intracranial pressure (>20 mm Hg) | 3 of 15 | 2 of 15 | n.s. |
| Mechanical ventilation | 15 of 15 | 15 of 15 | n.s. |
| Postoperative day of reflux occurrence | 2.9 ± 0.8 | 2.6 ± 0.5 | n.s. |
| Mean gastric residual volume on day before initiation of therapy in milliliters | 970 ± 87 | 903 ± 60 | n.s. |
| Patients with vomiting before initiation of therapy | 5 of 15 | 3 of 15 | n.s. |
| <i>Drugs</i> | | | |
| Patients with antibiotics | 13 of 15 | 14 of 15 | n.s. |
| Patients with opioids | 14 of 15 | 15 of 15 | n.s. |
| Piritramide (mean in mg/d); patients | 26.8 ± 9.3; 8 of 15 | 24.0 ± 10.4; 8 of 15 | n.s. |
| Alfentanil (mean in mg/d); patients | 2.0 ± 0.9; 7 of 15 | 1.9 ± 0.6; 10 of 15 | n.s. |
| Fentanyl (mean in mg/d); patients | 0.07 ± 0.04; 4 of 15 | 0.05 ± 0.03; 3 of 15 | n.s. |
| Morphine (mean in mg/d); patients | 0.1 ± 0.1; 1 of 15 | 0.7 ± 0.5; 3 of 15 | n.s. |
| Norepinephrine (mean in mg/d) | 12.5 ± 5.1 | 10.6 ± 3.8 | n.s. |
| Dobutamine (mean in mg/d) | 161 ± 33 | 143 ± 34 | n.s. |
| Anticholinergic drugs | 10 of 15 | 13 of 15 | n.s. |
| Cholinesterase inhibitors (mean in mg/d) | 0.83 ± 0.26 | 0.91 ± 0.28 | n.s. |
| Nimodipine (mean in mg/d); patients | 5.3 ± 2.4; 6 of 15 | 5.5 ± 2.6; 8 of 15 | n.s. |
| Nifedipine (mean in mg/d); patients | 0.6 ± 0.6; 1 of 15 | 0.2 ± 0.2; 1 of 15 | n.s. |
| Patients with psychotropic drugs | 0 of 15 | 0 of 15 | n.s. |
| Patients with barbiturates | 5 of 15 | 3 of 15 | n.s. |
| Patients with benzodiazepines (only midazolam) | 12 of 15 | 12 of 15 | n.s. |
| Midazolam (mean in mg/d) | 186 ± 32 | 199 ± 53 | n.s. |
| Patients with propofol | 13 of 15 | 13 of 15 | n.s. |

SAH = subarachnoidal hemorrhage; SHT = severe head trauma; ICB = intracerebral bleeding; APACHE II = Acute Physiology and Chronic Health Evaluation Score II; SAPS II = Simplified Acute Physiology Score II; n.s. = nonsignificant. Given mean values refer to whole treatment group.

during inflation of 20 mL of air. Start and dosage of enteral and parenteral feeding were guided by a clinical algorithm: in the first 24 hours after surgery or trauma, only crystalloid infusions were administered. Enteral nutrition was started as early as possible with a low dose (250 mL/d with an infusion rate of 25 mL/h) and was increased stepwise to 1000 mL/d on day 4. Additionally, patients received parenteral nutrition with the aim of a total daily caloric intake of 25 kcal/kg body weight. In cases of increased reflux via the nasogastric tube (>500 mL/d) we reduced the continuous intake or administered enteral nutrition by bolus (200 mL every 6 hours).

Measurements

GRV was measured in milliliters via nasogastric tubing every 24 hours. Incidents of vomiting were noted by the nursing staff, and enteral feeding was recorded in milliliters via gastric tubing every 24 hours.

Statistical Analysis

Continuous variables were expressed as mean ± SEM. For categorical data, absolute and relative frequencies were shown. Spearman rank correlation coefficients were used to examine pairwise correlations (between GRVs and feeding balances within each group). Chi-square or, if appropriate, Fisher exact tests were applied for the comparison of discrete variables between the ASG and DTG. Continuous

variables were compared between the 2 independent groups using the Mann-Whitney *U* test. *P* values <0.05 were considered significant. Statistical analysis was performed as 2-tailed using SPSS version 12 (SPSS Inc., Chicago, Illinois).

RESULTS

The prolonged intermittent transcutaneous electrical acupuncture stimulation method did not interfere with normal ICU procedures, consumed minimal extra staff time, and showed no side effects at no additional patient cost.

Demographic analysis (Table 1) revealed no significant differences between groups regarding age, gender, body mass index, diagnosis, risk scores APACHE II, and Simplified Acute Physiology Score II (SAPS II), or incidence of increased intracranial pressure. Groups were comparable with regard to postoperative onset of gastroesophageal reflux, GRV or incidences of vomiting before therapy, and drug treatment during the study (second half of Table 1).

All 15 patients in the DTG received metoclopramide as standard treatment; 5 of 15 patients additionally received Cisapride and 7 of 15 patients erythromycin.

GRV ceased in 12 of 15 (80%) patients in the ASG, and in 9 of 15 (60%) patients in the DTG, with this difference not reaching statistical significance. Within 48 hours, 7 of 15 (47%) patients in the ASG compared with 3 of 15 (20%)

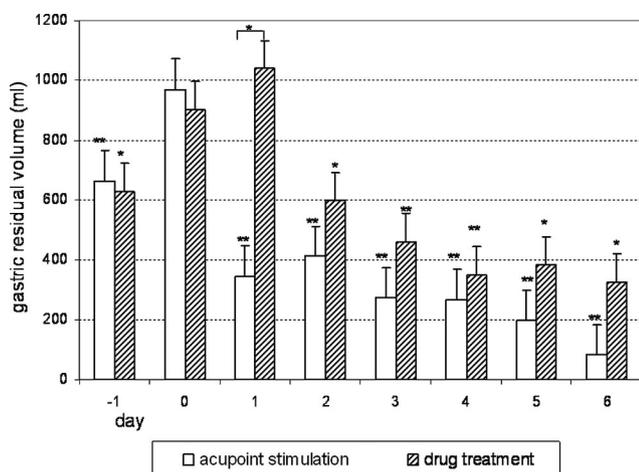


Figure 1. Mean gastric residual volume per day. The asterisks indicate significant ($*P < 0.05$) or highly significant ($**P < 0.01$) differences in comparison to day 0 within each group. The brackets mark comparison between groups on day 1.

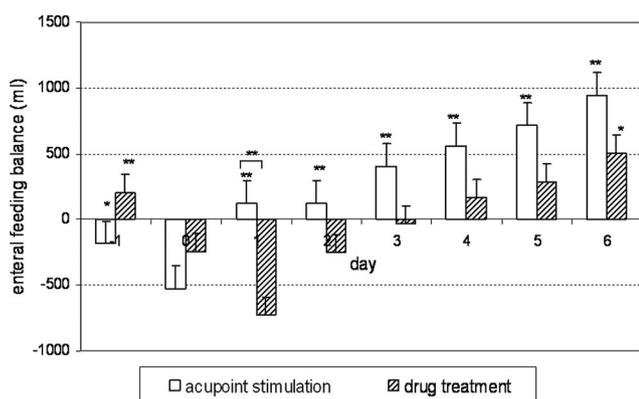


Figure 2. Mean enteral feeding balance (volume of enteral feeding minus gastric residual volume). The asterisks indicate significant ($*P < 0.05$) or highly significant ($**P < 0.01$) differences in comparison to day 0 within each group. The brackets mark comparison between groups on day 1.

patients in the DTG were below the threshold level of 200 mL GRV per 24 hours ($P < 0.05$).

Before treatment (from day -1 to day 0), mean GRV increased significantly within both groups (ASG: 664 ± 69 mL to 970 ± 87 mL, $P = 0.008$; DTG: $629 \text{ mL} \pm 92$ mL to $903 \text{ mL} \pm 60$ mL, $P = 0.038$). When compared with the day before treatment (day 0), each of the following days showed significantly reduced mean GRVs ($P \leq 0.003$) for the ASG group, whereas days 2 to 6 also showed significantly reduced mean GRVs ($P \leq 0.05$; Fig. 1) for the DTG group.

On the first day of treatment (day 1), mean GRV was significantly ($P = 0.015$) lower in the ASG ($346 \text{ mL} \pm 71$ mL) than in the DTG ($1040 \text{ mL} \pm 211$ mL; Fig. 1). In comparison with the day before treatment (day 0), GRV decreased in the ASG in 14 of 15 patients (93%), significantly more than the 7 of 15 (47%) patients in the DTG with decreased GRV ($P = 0.014$).

In comparison with before treatment, GRV increased, whereas nutrition balance, defined as volume of enteral nutrition minus reflux volume, decreased in all patients. In

both groups, nutrition balance decreased significantly before treatment from day -1 to day 0 (ASG: $-180 \text{ mL} \pm 122$ mL to $-523 \text{ mL} \pm 151$ mL, $P = 0.025$; DTG: $203 \text{ mL} \pm 222$ mL to $-239 \text{ mL} \pm 158$ mL, $P = 0.004$) (Fig. 2).

When compared with the day before treatment (day 0), in the ASG, each of the following days showed increased feeding balances ($P = 0.001$ to 0.003); in the DTG this occurred only on day 6 ($P = 0.044$) (Fig. 2).

After the first day of treatment, nutrition balance (Fig. 2) was significantly ($P = 0.005$) higher in the ASG ($121 \text{ mL} \pm 128$ mL) than in the DTG ($-727 \text{ mL} \pm 259$ mL) (Fig. 2). In comparison with the day before treatment (day 0), on day 1, nutrition balance increased in the ASG in 14 of 15 (93%) patients, whereas in the DTG it increased in 7 of 15 (47%) patients, showing a significant difference between the 2 groups ($P = 0.014$).

DISCUSSION

Early enteral nutrition remains the mainstay of physiological nutritional support in critically ill patients. Malnutrition, caused by delayed gastric emptying and gastroesophageal reflux, is still a cause of increased patient morbidity in the ICU. None of the commonly used prokinetic drugs can reliably treat and prevent delayed gastric emptying in a timely fashion.

We present the first prospective, randomly controlled and single-blinded study to show that acupoint stimulation significantly improves gastroparesis and delayed gastric emptying in critically ill patients when compared with standard pro-motility drugs.

The underlying pathophysiology for the development of impaired gastrointestinal motility, gastroesophageal reflux, and feed intolerance is multicausal and includes effects of surgery, immobilization, mechanical ventilation, and medication (i.e., opioids). The mechanisms that lead to improved gastric motility and improved nutrition balance after acupoint stimulation is not yet known, but several favorable effects of acupuncture on the gastrointestinal tract have been described.¹²⁻¹⁴ Zou et al. demonstrated that electrical acupoint stimulation at Neiguan in healthy volunteers significantly inhibits the frequency of transient lower esophageal sphincter relaxations,¹⁵ one possible cause of delayed enteral nutrition in critically ill and mechanically ventilated patients.¹⁶ This inhibition may be mediated via efferent vagal innervations, which is modulated by higher cortical and subcortical circuitries, specifically activated by stimulation of Neiguan.¹⁷⁻²¹ Patients with systemic sclerosis have unique and persistent alterations in gastric myoelectrical activity with acupressure to Neiguan.²² Chang et al. reported that cutaneous electrical stimulation of acupuncture points may enhance gastric myoelectrical regularity in healthy volunteers^{23,24} and diabetic patients with gastric dysrhythmia.²⁵ Furthermore, several experimental studies on animals have demonstrated a possible modulating effect of acupoint stimulation on variables of gastric motility and acid secretion.²⁶⁻³⁰ Finally, acupuncture and other forms of acupoint stimulation on acupoint Neiguan were found superior to placebo procedures for PONV and also highly effective against chemotherapy-induced or pregnancy-related nausea and vomiting.³¹⁻³³

To our knowledge, this is the first study to evaluate the effects of acupuncture on gastroparesis in a prospective fashion, examining a narrow but homogenous neurosurgical ICU patient population. Tubefeed intolerance improves spontaneously without treatment in a certain percentage of patients. Therefore, onset of gastric reflux within 48 hours of treatment is often taken as an indicator for therapeutical success.³⁴ In our study, 7 of 15 patients in the ASG and only 3 of 15 in the DTG had a GRV decrease of 200 mL within 48 hours, suggesting that acupoint stimulation had a faster effect on GRV and nutrition balance than did standard drug treatment.

In the present study on critically ill patients, electrical acupoint stimulation using a TENS device and a TENS timer proved to be feasible and did not interfere with normal ICU procedures and routines, at no additional patient cost. The procedure consumed little extra time of the participating staff and did not lead to any adverse side effects. Our new method for prolonged intermittent acupoint stimulation over several days has been developed after pilot trials with classical needle acupuncture. Needling was found incompatible with the intensive care setting because of skin injury and concomitant inflammation at the needle insertion site, and needle dislocation during bedding, hygiene care, or transportation. While the “placebo effect” plays a notable role in acupuncture therapy, this phenomenon was significantly reduced in our study, because all of our patients were sedated and measurably unconscious.

This present study included a relatively small number of patients, and further multicenter studies are needed to confirm these results. Furthermore, acupoint stimulation should also be attempted on patients with intra-abdominal surgery, who are prone to a higher risk for delayed gastric emptying. Also, future studies should not only compare acupuncture and drug treatment, but also integrate a third group, in which the 2 treatment approaches are combined, because the ultimate goal should be to delineate the best treatment for delayed gastric emptying in critically ill patients.

Acupuncture therapy has been used successfully in the fields of pain, gynecology, and obstetrics, among others over the past decade, and its applications are growing. The critical care setting is a promising but largely unexplored field for acupuncture therapy.³⁵

Acupuncture in critically ill patients offers the possibility of replacing a pharmacological intervention with a nondrug treatment showing only few, nonserious side effects.³⁶ This seems favorable in the ICU setting in which the combination of many drugs obscures pharmacokinetics and enhances side effects.

CONCLUSIONS

In the present study, acupuncture at Neiguan was superior to conventional prokinetic drug treatment in improving delayed gastric emptying and preventing malnutrition in a neuro-ICU patient population. The described prolonged intermittent transcutaneous electrical acupoint stimulation proved to be a feasible, low-risk method that could serve as an adjunct to common drug regimens aimed at reducing

overall medication exposure and critical care patient morbidity. ■■

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