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Comparing the Effects of Acupuncture and Pharmacologic Therapies on Delayed Gastric Emptying: A Prospective, Block-Randomized, Single-Blinded, Parallel Clinical Trial

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Abstract

Background: Nutritional therapy in the forms of parenteral or enteral nutrition is an important factor of care and appears to positively impact the clinical outcomes of critically ill patients.
Objectives: This study aimed to compare the effects of acupuncture and prokinetic drugs on delayed gastric emptying (DGE) in intensive care unit patients.
Methods: In a prospective, block-randomized, single-blinded, parallel group trial, 60 fully sedated, mechanically ventilated surgical patients were enrolled in two groups with 30 patients in each group in Besat hospital in Hamadan, Iran from February 2011 to October 2012. Patients in the drug treatment group received 10 mg of IV metoclopramide every eight hours. For patients with whom persistent DGE was seen, 500 mg of IV erythromycin every 24 hours was added. Patients in the acupuncture group received bilateral prolonged intermittent transcutaneous electrical acupoint stimulation of acupuncture point Neiguan. The intervention was performed for six consecutive days or until the cessation of gradual residual volume.
Results: A demographic analysis of the participants revealed no significant differences between groups ($P > 0.05$). Although the results of the RANOVA model for DGE did not show a significant time trend ($P > 0.05$) in both acupuncture and drug groups, comparing means of the both acupuncture and drug groups in all the time points after the intervention were significant ($P = 0.024$): 711.83 ± 193.28 vs. 755.00 ± 166.79 ($P = 0.358$), 564.17 ± 672.35 vs. 628.50 ± 176.77 ($P = 0.614$), 324.00 ± 146.49 vs. 472.00 ± 188.47 ($P < 0.001$), 209.00 ± 136.34 vs. 340.00 ± 211.89 ($P < 0.006$), 152.67 ± 118.93l vs. 276.17 ± 202.43 ($P < 0.006$), and 119.67 ± 101.59 vs. 225.67 ± 184.22 ($P < 0.008$) from the first to last steps, respectively.
Conclusions: Although neither acupuncture nor the drug interventions had significant effects on the improvement and obviation of DGE, the acupuncture had greater effects than prokinetic drugs on the reduction of DGE.

Keywords: Acupuncture, Gastroparesis, Pharmacologic Therapy, Transcutaneous Electric Nerve Stimulation

1. Background

Nutritional therapy in the forms of parenteral nutrition (PN) or enteral nutrition (EN) is an important factor of care and appears have a positive effect on the clinical outcomes of critically ill patients (1-3). Compared with PN, EN appears more physiological and varied clinical benefits (2, 4-9). Both European and American nutrition societies recommend using EN as first-line support in early feeds in patients with a functional gut (10-12).

Early attempts at EN are often complicated by delayed gastric emptying (DGE) (13, 14). DGE is a paresis (partial paralysis) of the stomach that results in food remaining in the stomach for a longer time than normal (15). DGE is particularly prevalent in critically ill patients and has been reported to occur in up to 50% of all mechanically ventilated patients (15-17). However, in other studies, the prevalence and magnitude of DGE in critically ill patients are inconsistently reported (18, 19). DGE in critically ill patients may lead to regurgitation or vomiting of gastric contents, which increases the risk of gastroesophageal reflux. These patients may eventually need to be aspirated, which can cause severe pulmonary aspiration (18, 19), ventilator-

associated pneumonia (20), prolonged hospital stay, or increased hospitalization costs (15). Some authors have reported that DGE is associated with other postoperative intra-abdominal complications, such as hemorrhage, pancreatic fistula, and abdominal collections (21).

In order to reduce the incidence of DGE, different methods, such as surgical techniques (16, 21), pharmacological therapies (7, 22), and alternative and complementary medicine (23), have been used. However, to the best of the researchers' knowledge, the best methods or combination regimens have not yet been found. In the study, prokinetic drugs and acupuncture were investigated as methods to reduce the incidence of DGE.

Metoclopramide is the most widely used prokinetic drug in patients who are intolerant of gastric feeding, and many intensive care unit (ICU) practitioners use it as the first drug of choice. However, the efficacy of this treatment has not been established, particularly in ventilated ICU patients, and has been challenged.

Acupuncture modulates various biomechanical responses, such as prokinetic, antiemetic, and antinociceptive effects (23).

2. Objectives

The study sought to compare the effects of acupuncture and prokinetic drugs on DGE in ICU patients.

3. Methods

A prospective, block-randomized, single-blinded, parallel group trial was conducted in Besat hospital in Hamadan, Iran from February 2011 to October 2012 to compare the effects of acupuncture and prokinetic drugs on DGE in ICU patients. The hospital was a general, referral, and governmental hospital with 350 beds. The hospital had different wards, including medical, surgical, neurological, pediatric, and neonatal ICUs, with different general adult and pediatric medical and surgical wards.

All parts of the study were reviewed according to the consolidated Standards for reporting trials (CONSORT) statement (Figure 1) (24). In the first step, a convenience sampling method was used. All patients who met the inclusion criteria were recruited. The inclusion criteria were hospitalization in a surgical ICU, an age between 18 and 75 years, and the presence of gastroparesis. Gastroparesis was defined as a gastric reflux volume of at least 500 mL per 24 hours measured on two consecutive postoperative days (13). The exclusion criteria were recent major abdominal surgery, a history of a partial or total gastrectomy, suspected bowel obstruction or perforation, pancreatitis, the administration of prokinetic drugs (metoclopramide, cisapride, or erythromycin) within the previous 24 hours, a known allergy to metoclopramide, cisapride, or a macrolide antibiotic, the administration of drugs known to interact with erythromycin (carbamazepine, cyclosporine, theophylline, aminophylline, digoxin, or anticoagulants), gastroparesis due to diabetes mellitus, shock status and hypotension, and the patient's refusal to receive acupuncture (Figure 1).

The sample size of this study was determined using the information obtained from a pilot study with eight patients. Considering a confidence level of 95% and a power of 80%, a required sample size of at least 28 cases was determined. In order to prevent patient attrition from affecting the results of the study, a total of 30 qualified patients were asked to participate. The major reason for patient attrition was failure to meet the inclusion criteria. Then, random allocation was conducted using Random Allocation Software® to place 30 patients in the acupuncture group and 30 in the drug group. For the allocation of the patients, a computer-generated list of random numbers was used. Patients were randomly assigned to one of two treatment groups following simple randomization procedures (computerized random numbers). Block randomization was done by a computer-generated random number list prepared by an expert statistician who had no clinical involvement in the trial. After the conclusion of the study, a nurse obtained the patients' consent or the consent of the patients' next of kin. For allocation consignment, the nurse contacted a person who was not involved in the recruitment process. In total, 60 fully sedated, mechanically ventilated surgical patients were enrolled in two groups (with 30 patients in each group).

The approval of the Institutional Review Board of the Hamedan University of Medical Sciences (Hamadan, Iran) was obtained with the number 3244/9/35/16/P/D on September 19, 2011, and the study was conducted according to the Declaration of Helsinki principles (25). Moreover, the study was registered on the Iranian registry of clinical trials with number IRCT201112014578N4. The ethical considerations of this study were related to the patients' autonomy, confidentiality, and anonymity during the study period and the study's publication. The purpose of the study was explained to all patients, and they were also informed that they were free to participate, decline participation, or withdraw from the study any time. A written informed consent form to participate in the study was obtained from each patient's next of kin.

During the first 24 hours after their admission to the ICU, all patients received a nasogastric (NG) or orogastric

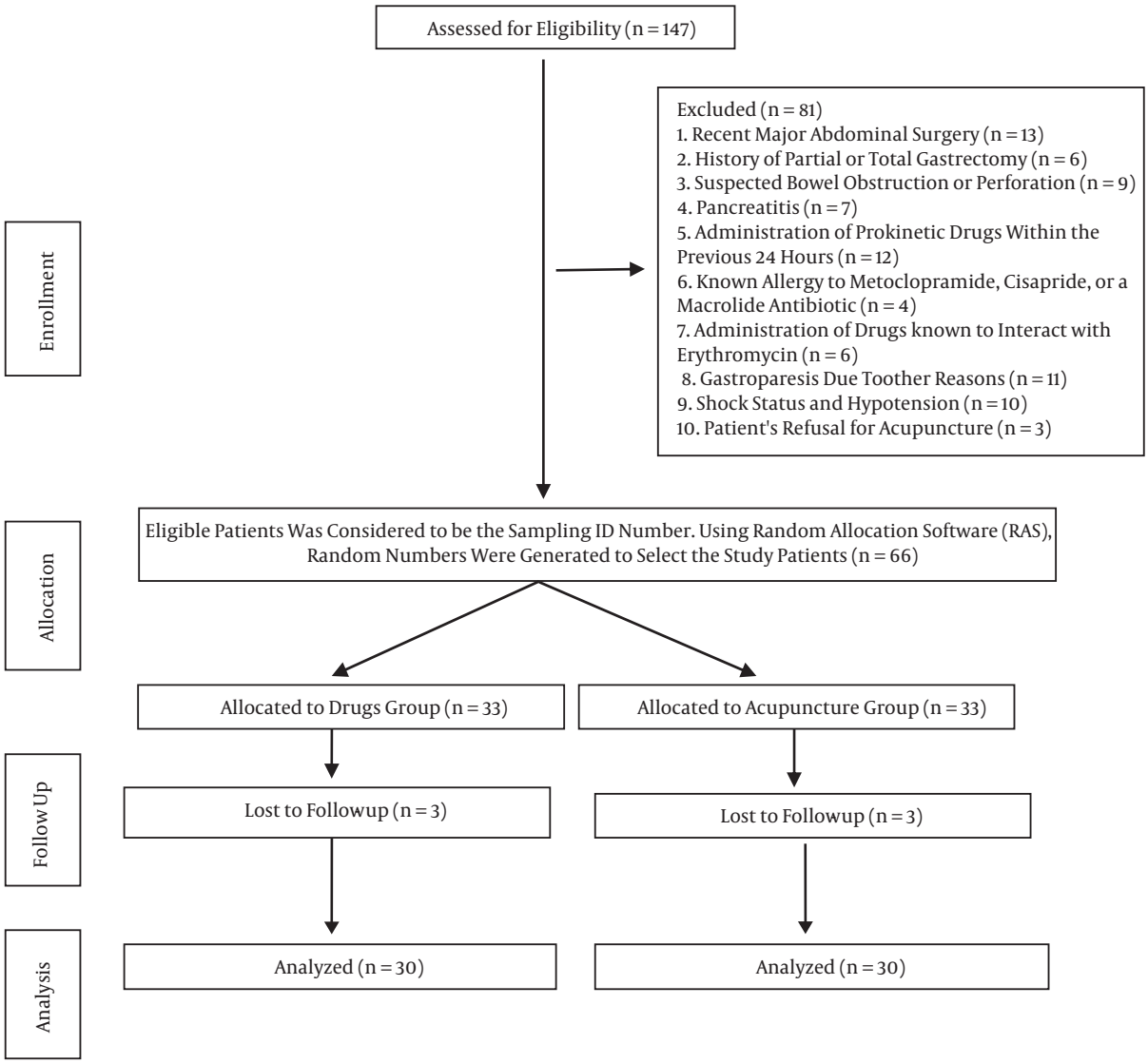

Figure 1. Flow Chart of the Sampling Process

tube draining to a bag placed 10 cm above gastric level. The correct location of the gastric tube was confirmed by a chest X-ray. A semirecumbent position (30°) was mandatory during the ICU treatment. Patients received adequate sedation and analgesia (achieving a Ramsay Score of 5 - 6) according to the ICU sedation and pain relief protocol. Piritramide (13 - 20 mcg/kg/h) or equivalent doses of other opioids and propofol (2 - 7 mg/kg/h) were continuously infused. Acupuncture was administered by one of the authors, who had successfully passed courses for Chinese acupuncture. The intervention was performed for six consecutive days or until the cessation of gradual residual volume (GRV), which was defined as no vomiting and a GRV < 500 mL per day via NG tubing for two consecutive days.

Moreover, all the patients were visited and examined from the incidents of vomiting by the attending intensivist and ICU nurses, and enteral feeding was recorded in mL via gastric tubing every 24 hours. Vomiting incidents were observed severally by the intensivist and a nurse, and in order to determine agreement between the intensivist and

nurse, a kappa agreement coefficient was run (0.91).

EN 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 2000 mL/d by the fourth day. Additionally, patients received PN with the aim of achieving a total daily caloric intake of 25 kcal/kg body weight. In cases of increased reflux via the NGT (> 500 mL/d), the researchers reduced the continuous intake or administered EN by bolus (200 mL every six hours).

Patients in the drug treatment group received 10 mg of IV metoclopramide every eight hours. In patients with persistent DGE, 500 mg of IV erythromycin every 24 hours was added.

Patients in the acupuncture group received bilateral prolonged intermittent transcutaneous electrical acupoint stimulation of acupuncture point Neiguan (P6). Stimulation was applied at a frequency of 7 Hz with a flow between 7 and 13 mA, depending on the patient's wrist size. Electrical stimulation was applied in a standardized order for 20 minutes every 12 hours (twice a day) for six days. Stimulations were given using a transcutaneous electrical nerve stimulation (TENS) (Bentroden®, Bentronic GmbH, Munich, Germany) device working with battery power. The flows were applied via electrodes (Bentroden®, Bentronic 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; 2.5 cm electrode diameter). The needle had a diameter of 2.5 cm (13). All devices were calibrated daily according to the hospital's protocol, and the TENS device was calibrated daily according to the company's protocol specified by the company's application specialist, but this specialist did not explain the purpose of the daily calibration. Patients assigned to the acupuncture group did not receive any prokinetic drug treatment.

3.1. Statistical Analysis

All analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL). Frequency (percent) and mean (standard deviation) were presented for qualitative and quantitative variables, respectively. The normality of the study variables was tested by the Kolmogorov-Smirnov one-sample test. Normality was confirmed for the residual volume variable for all the recorded times. Therefore, repeated measurements of analysis of variance (ANOVA) were performed to assess the changes of the mean values over time for the acupuncture and drug groups, and this was followed by the Sidak post hoc test. The assumption of the sphericity of the covariance matrix was evaluated using Mauchly's test and, depending on the results of this test, P values were presented based on the Greenhouse-Geiser correction. In addition, Hotelling's T2 test evaluated the differences between the acupuncture and drug groups at all recorded time points, which was followed by independent sample t-tests for investigating the differences between the acupuncture and drug groups separately at each time point. The comparisons of background variables, including age, sex, APACHE II score, intubation hours, hospitalization days in the ICU, heart rate, systolic and diastolic blood pressures, temperature, opium consumption, and antibiotic and midazolam prescriptions, were investigated between the two groups using a t-test, a chi-squared test, or Fisher's exact test. P values < 0.05 were considered significant.

4. Results

4.1. Description of Patients' Demographical Characteristics

A demographic analysis revealed no significant differences between groups regarding age, gender, APACHE II scores, intubation hours, hospitalization days in the ICU, heart rate, systolic and diastolic blood pressures, temperature, and opium, antibiotic, and midazolam consumption. In the acupuncture group, 24 patients (80.0%) were male and 6 (20.0%) were female. In the drug group, 22 patients (73.3%) were male and 8 (26.7%) female. The mean age of the patients was 47.63 (± SD 14.15) years in the acupuncture group and 48.17 (± SD 13.53) years in the drug group (Table 1).

4.2. Effects of Acupuncture and Prokinetic Drugs on the Outcome Variable (DGE)

The repeated measures ANOVA model was used to assess the concurrent effect of the time trend, the intervention (group variable), and the interaction between time and group on the outcome variable (DGE). The results of the repeated measures ANOVA model for DGE did not show significant a time trend (P > 0.05) in both the acupuncture and drug groups, and the results of the repeated measures ANOVA model for the outcome variable did not show a significant interaction between time and group (P > 0.05). Moreover, the difference between the means of both the acupuncture and drug groups at all time points after the intervention was significant (P = 0.024) (Table 2). Figure 2 displays the estimated time trend of the means in the acupuncture and drug groups.

5. Discussion

Today, complementary and alternative medicines have found good acceptance in different communities, and there has been a growing trend in the use of acupuncture. With acupuncture, stimulation of specific points on

Table 1. Patients' Demographic Characteristics

Characteristics	Total, n = 60, Mean ± SD	Acupuncture Group, n = 30	Drug Group, n = 30	Statistical Test and P Value
Age, Mean ± SD	47.90 ± 13.73	47.63 ± 14.15	48.17 ± 13.53	T = -0.149[a], P = 0.882
APACHE II, Mean ± SD	16.27 ± 1.67	16.20 ± 1.58	16.33 ± 1.77	T = - 0.308[a], P = 0.759
Intubation Hour, Mean ± SD	157.60 ± 30.94	154.40 ± 28.99	160.80 ± 32.96	T = - 0.799[a], P = 0.428
Hospitalization Days, Mean ± SD	13.30 ± 6.14	12.70 ± 6.30	13.90 ± 6.03	T = - 0.754[a], P = 0.454
Systolic BP, mmHg, Mean ± SD	122.35 ± 10.43	123.30 ± 14.13	121.40 ± 4.46	T = 0.703[a], P = 0.487
Diastolic BP, mmHg, Mean ± SD	73.50 ± 9.90	74.50 ± 11.94	72.50 ± 7.39	T = 0.780[a], P = 0.439
Heart Rate, bpm Mean ± SD	73.95 ± 11.81	70.40 ± 12.84	77.50 ± 9.63	T = - 0.745[a], P = 0.119
Temperature, °C, Mean ± SD	37.02 ± 0.43	37.15 ± 0.31	36.89 ± 0.50	T = - 0.899[a], P = 0.528
Gender, No. (%)				χ^2 = 0.000[b], df = 1, P = 0.680
Male	46 (76.7)	24 (80.0)	22 (73.3)	
Female	14 (23.3)	6 (20.0)	8 (26.7)	
Opium Consum, No. (%)				χ^2 = 0.000[b], df = 1, P = 1.000
Morphine	11 (18.3)	5 (16.7)	6 (20.00)	
Methadone	49 (81.7)	25 (83.3)	24 (80.0)	
Antibiotic Consum, No. (%)				χ^2 = 0.000[b], df = 1, P = 1.000
Yes	54 (90.0)	27 (90.0)	27 (90.0)	
No	6 (10.0)	3 (10.0)	3 (10.0)	
Midazolam Consum, No. (%)				χ^2 = 0.003[b], df = 25, P = 0.958
Yes	8 (13.3)	4 (13.3)	4 (13.3)	
No	52 (86.7)	26 (86.7)	26 (86.7)	

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; BP, blood pressure; bpm, beat per minute; Consum, consumption.
[a] Based on an independent t-test.
[b] Based on a chi-squared test.

the skin surface is done with different methods, including heat, pressure, laser, or piercing the skin with a needle (26, 27). A previous randomized clinical trial compared common medical procedures and acupuncture as a nonpharmacologic method to improve gastroparesis and gastric emptying in ICU patients (13). This previous study demonstrated that the protocol was more effective than standard promotility medication for the treatment of DGE in critically ill patients. The results of the current study conflict with the previous study's results because the current results showed that there were no statistically significant differences between acupuncture and prokinetic drugs for the treatment of DGE in critically ill patients. The reason for the difference in these results may be the differences in the statistical analysis methods used in each study. In the previous study, the researchers used a Student's t-test to compare the results in each step, but comparing the steps using a t-test cannot demonstrate the differences between two groups over time. In contrast, the current study was analyzed using a RANOVA test, which can show the differences between two groups over time by comparing measurements recorded at different times within the intervention and control groups and which can compare the two groups at each recorded time.

Acupuncture was more effective at reducing DGE than prokinetic drugs. However, the drug method was cost effective, had fewer complications, and was safer and more convenient than acupuncture. Acupuncture is used widely in the clinical field without many side effects regardless of the country in which the acupuncture is performed or the mode of practice. Surveys show that serious adverse events are rare in standard acupuncture practice performed by adequately trained acupuncturists because in order to perform acupuncture, the acupuncturist must be an expert in the technique (28). In other words, acupuncture is generally considered a relatively safe procedure; however, it is by no means entirely free of adverse effects (29). In particular, tissue trauma and organ failure are possible complications when the acupuncture needle penetrates a vital organ. Cardiac tamponade is considered an extremely

Table 2. Delayed Gastric Emptying Before Intervention to Five Time Points After Intervention

Variables			Mean ± SD	P Value[a]	Within Acup P[b]	Within Drug P[c]	Between Groups P[d]
Delayed Gastric Emptying	Delayed Gastric Emptying 0	Acupuncture	711.83 ± 193.28	0.358	0.863	0.505	0.024
		Drug	755.00 ± 166.79				
	Delayed Gastric Emptying 1	Acupuncture	564.17 ± 672.35	0.614			
		Drug	628.50 ± 176.77				
	Delayed Gastric Emptying 2	Acupuncture	324.00 ± 146.49	P < 0.001			
		Drug	472.00 ± 188.47				
	Delayed Gastric Emptying 3	Acupuncture	209.00 ± 136.34	P < 0.006			
		Drug	340.00 ± 211.89				
	Delayed Gastric Emptying 4	Acupuncture	152.67 ± 118.93	P < 0.006			
		Drug	276.17 ± 202.43				
	Delayed Gastric Emptying 5	Acupuncture	119.67 ± 101.59	P < 0.008			
		Drug	225.67 ± 184.22				

Abbreviation: Acu, acupuncture.
[a]The P value was based on an independent sample t-test for the comparison of the acupuncture and drug groups at each time point.
[b]The P value was based on a repeated measures ANOVA for testing the changes over time within the acupuncture group. Dependent on the results of Mauchly's test, P values presented are based on the Greenhouse-Geiser test.
[c]The P value was based on a repeated measures ANOVA for testing the changes over time within the drug group. Dependent on the results of Mauchly's test, the P values presented are based on the Greenhouse-Geiser test.
[d]The P value was based on Hotelling's T2 test for an overall comparison of the acupuncture and drug groups.

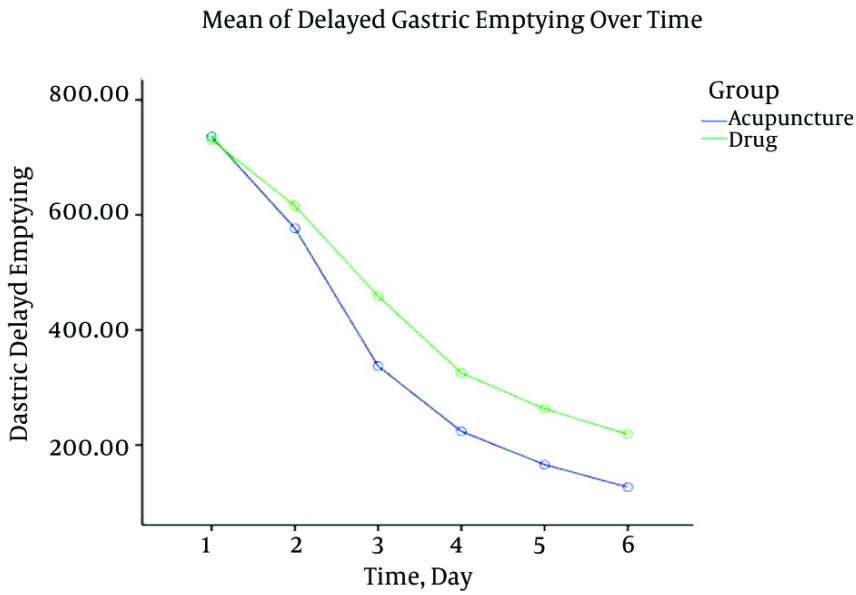

Figure 2. Displays the Estimated Time Trend of the Mean in the Acupuncture and Drug Groups

rare adverse event of acupuncture (29). In addition, advanced devices, such as a TENS device, are needed to perform acupuncture, and there is greater risk of infection with acupuncture than with prokinetic drugs.

The acupuncture method conveyed no additional cost to the patient, did not conflict with ICU common processes, and did not cost the ward staff more time. In many acupuncture procedures, placebo groups are used, How-

ever, in the current study, due to the patients' sedation and analgesia, a placebo group was not required (13, 27).

Although stimulation of the P6 point was shown to improve DGE in different published studies, the recovery mechanisms of gastrointestinal motility in critically ill patients have not been well described (26, 30), and the researchers think that the different mechanisms might be responsible for the lack of statistically significant differences between the use of acupuncture and prokinetic drugs.

Zou et al. showed that acupuncture in healthy patients that is followed by a reduction in the frequency of repeated lower esophagus esphincter relaxation is probably caused by the stimulation of the efferent vagus nerve (31). However, some studies have examined and reported positive acupuncture effects on gastric movement and acid secretion in animal models (32).

The strength of the present study was that the acupuncture was performed by an expert in alternative medicine. The methodology and all the manuscript sections were conducted according to the CONSORT statement. The ICU personnel were alert and all the nurses had fundamental critical care support certification.

The study's limitations were that the different methods, different acupuncturists, and the patients' responses to the interventions might be responsible for the differences in the results of this study and other studies. One supporting event for this thought is that different patients had different responses to same procedures. Moreover, the drugs available in different countries have not been purchased from the same company, which might have contributed to the differences in results between this study and other studies.

5.1. Conclusion

Although neither acupuncture nor prokinetic drug interventions had a significant effect on the improvement or obviation of the patients' DGE, acupuncture had a greater effect than prokinetic drugs. While the time trend results of each group were statistically significance post intervention, when each step was compared, the overall results of each group did not have the same results.

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Footnotes

Authors' Contribution: Farshid Rahimibashar, Ebrahimi Khoshraftar, Reza Tahmasebi, Mohammadreza Hajiesmaeili, Shahram Seifi, Alireza Sedaghat, Amir Vahedian-Azimi, Hosna Forooghirad, and Ali Dabbagh were responsible for the study conception and design, the data collection and analysis, the drafting of the manuscript, and critical revisions for important intellectual content to the paper.

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