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Integrative effects of transcutaneous electrical acustimulation on abdominal pain, gastrointestinal motility, and inflammation in patients with early-stage acute pancreatitis

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Abstract

Background/Aims: Gastrointestinal (GI) dysmotility in acute pancreatitis (AP) aggravates inflammation and results in severe complications. This study aimed to explore effects and possible mechanisms of transcutaneous electrical acustimulation (TEA) on abdominal pain, GI dysmotility, and inflammation in AP patients.

Methods: Forty-two AP patients were blindly randomized to receive TEA ($n = 21$) at acupoints PC6 and ST36 or Sham-TEA ($n = 21$) at sham points for 2 days. Symptom scores, gastric slow waves, autonomic functions (assessed by spectral analysis of heart rate variability), circulatory levels of motilin, ghrelin, and TNF-α were measured before and after the treatment. Sixteen healthy controls (HCs) were also included without treatment for the assessment of gastric slow waves and biochemistry.

Key Results: Compared with Sham-TEA, TEA decreased abdominal pain score (2.57 ± 1.78 vs. 1.33 ± 1.02, $p < 0.05$), bloating score (5.19 ± 1.21 vs. 0.76 ± 0.99, $p < 0.001$), the first defecation time (65.79 ± 19.51 h vs. 51.38 ± 17.19 h, $p < 0.05$); TEA, but not Sham-TEA, improved the percentage of normal gastric slow waves by 41.6% ($p < 0.05$), reduced AP severity score (5.52 ± 2.04 vs. 3.90 ± 1.90, $p < 0.05$) and serum TNF-α (7.59 ± 4.80 pg/ml vs. 4.68 ± 1.85 pg/ml, $p < 0.05$), and upregulated plasma ghrelin (0.85 ± 0.96 ng/ml vs. 2.00 ± 1.71 ng/ml, $p = 0.001$) but not motilin (33.08 ± 22.65 pg/ml vs. 24.12 ± 13.95 pg/ml, $p > 0.05$); TEA decreased sympathetic activity by 15.0% and increased vagal activity by 18.3% (both $p < 0.05$).

Conclusions & Inferences: TEA at PC6 and ST36 administrated at early stage of AP reduces abdominal pain, improves GI motility, and inhibits inflammatory cytokine, TNF-α, probably mediated via the autonomic and ghrelin mechanisms.

KEYWORDS
acute pancreatitis, analgesia, gastrointestinal dysmotility, inflammation, transcutaneous electrical acustimulation

Jia-lei Xuan and Ying-wei Zhu share co-first authorship.

1 | INTRODUCTION

Acute pancreatitis (AP), the localized pancreatic and systemic inflammation, is associated with severe complications. Gastrointestinal (GI) dysmotility, highly prevalent in AP patients,[1,2] results in symptoms of bloating, nausea, vomiting, and prolonged first defecation time. It is highly associated with excessive reproduction and translocation of gut flora and endotoxin, and can further aggravate the systemic inflammation manifested as the systemic inflammatory response syndrome (SIRS). Further, AP patients with persistent SIRS are prone to the severe complications, including multiple organ dysfunction syndrome (MODS) and organ failure (OF).[3] The mortality of AP was reported to be approximately 1% among all AP patients; however, patients with severe AP (SAP), characterized by persistent OF for more than 48 hours, exhibit a mortality rate ranging from less than 10% to more than 40%.[3,4] Accordingly, improving GI dysmotility at early stage is a key step in the treatment of AP. However, treatment options for GI dysmotility in early-stage AP are limited.

Electroacupuncture (EA), evolved from the conventional manual acupuncture, delivers weak electrical current to needles inserted into acupuncture points. Transcutaneous electrical acustimulation (TEA), a needleless alternative of EA, delivers electrical stimulation noninvasively via surface electrodes placed on acupoints. TEA is one novel form of transcutaneous neuromodulation and has been explored as a potential therapy for several GI motility disorders.[5–7] Acupoints, Neiguan (PC6), and Zusanli (ST36) have been frequently chosen as the stimulation locations for TEA and EA. EA/TEA at ST36 and PC6 has been reported to (1) improve GI dysmotility in several functional GI disorders, such as functional dyspepsia (FD) and constipation[6–8]; (2) inhibit inflammation via the autonomic-cytokine mechanisms in preclinical studies, including rodent models of AP and postoperative ileus[9,10]; (3) provide relief of pain,[10,11] especially inflammatory pain.[11,12]

Accordingly, we hypothesized that electrical stimulation at these acupoints would be effective in treating AP by improving GI dysmotility and inflammation. The aim of the current study was to explore the potential amelioratory effects of TEA at PC6 and ST36 on abdominal pain, GI dysmotility and inflammation in AP patients and possible mechanisms involving autonomic functions, GI hormones, and inflammatory cytokines.

Key points

- Gastrointestinal (GI) dysmotility is prevalent in patients with acute pancreatitis (AP). It is highly associated with excessive reproduction and translocation of gut flora and endotoxin, which could further aggravate systemic inflammation and result in poor prognosis.
- Improving GI motility is a key issue in the treatment of AP. Transcutaneous electrical acustimulation (TEA), a non-invasive and novel form of transcutaneous neuromodulation (TN), has been explored as a potential therapy for GI dysmotility and inflammation.
- TEA at acupoints PC6 and ST36 in patients with early-stage AP exerted an analgesic effect on abdominal pain, an ameliorating effect on GI dysmotility-related symptoms and gastric dysrhythmia and an inhibitory effect on inflammation, possibly mediated via the autonomic-endocrine mechanisms.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 44 hospitalized patients with AP in the Department of Gastroenterology, the affiliated Wuxi No.2 People's Hospital of Nanjing Medical University were consecutively recruited into the study from October 2018 to August 2020. In addition, 16 healthy volunteers were recruited to serve as controls for the assessment of gastric slow waves and GI hormones and inflammatory cytokines.

The study was approved by the Ethics Committee of the Wuxi No.2 People's Hospital (No.20180520). All subjects signed the informed consent form.

The AP diagnosis was based on the 2012 Atlanta Criteria.[13] It defines three degrees of severity: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP). MAP is defined as an absence of organ failure or local/systemic complications; MSAP is defined as the presence of transient organ failure (resolved within 48 h) and/or local or systemic complications; SAP is defined as the presence of persistent organ failure (>48 h). This study recruited MAP and MSAP patients but not SAP patients because SAP patients were treated in the intensive care unit (ICU) with several invasive treatments that could affect GI motility.

Inclusion criteria for AP patients were as follows: (1) age: 18–75 years; (2) willing to sign a written consent form; (3) admitted to hospital within 24 h of the AP onset; (4) with symptom of bloating.

Exclusion criteria were as follows: (1) severe heart, liver, or kidney disease; (2) taking medicines known to affect GI motility in the preceding 2 weeks; (3) history of GI surgery; (4) diabetes mellitus, chronic constipation, or other GI motility disorders; (5) women during pregnancy; (6) skin allergy to ECG electrodes; and (7) familiar with acupoints or meridians.

Age- and sex-matched healthy controls (HCs) were recruited. They were free of any GI symptoms, previous GI surgeries, or use of any medications.

2.2 | Study procedures

The study was designed as a randomized, sham-controlled, single-blinded, and prospective trial. The enrolled AP patients were randomly divided into 2 groups (TEA and Sham-TEA) immediately after

admission within 24 h of AP onset (Day 0). In addition to the routine treatment for AP (excluding prokinetic therapies), TEA or Sham-TEA was performed in these patients for 30 min, twice daily with an interval of 8 hours for the first 2 days (Day 1–2). Before and after the TEA/Sham-TEA treatment, at 8:00 am on Day 1 (pre-treatment) and Day 3 (post-treatment), symptoms of nausea, vomiting, bloating, and abdominal pain were scored, and blood samples were intravenously collected, followed with 30-min simultaneous recordings of the electrogastrogram (EGG) and electrocardiogram (ECG).

During the entire study until the third morning (Day 3) after blood collection and EGG/ECG recording, the AP patients were kept on fasting. Before the enrollment, the patients were explained that they would be kept on fasting during the study and that keeping fasted was not a necessary part of the routine clinical management. The tolerance for enteral nutrition (EN)/feeding was evaluated every day. If a patient was judged as tolerable for EN or feeding before the end of the study, the patient was asked to choose to keep fasted until the end of the study or take EN/feeding and quit the study.

In the HCs, venous blood samples were collected at 8:00 am in the fasting state, followed with a 30-min recording of the EGG. The EGG parameters, GI hormones, and inflammation cytokines were assessed and used for comparison with the patients. No treatment was given to the HCs.

2.3 | TEA/Sham-TEA

TEA was performed via electrodes placed at acupoints of PC6 and ST36 twice daily by two watch-sized stimulators (SNM-FP03, Ningbo Maida Medical Device Inc.). Stimulation parameters were as follows: (1) on-time of 0.1 s and off-time of 0.4 s, pulse width of 0.5 ms and pulse frequency of 100 Hz for TEA at PC6; and (2) on-time of 2 s and off-time of 3 s, pulse width of 0.5 ms and pulse frequency of 25 Hz for TEA at ST36. (3) Pulse amplitude for TEA at both acupoints was 2–10 mA depending on the tolerance of the patients. For the stimulation of each acupoint, one electrode was placed right at the acupoint and the other electrode at 2 cm above or below the first electrode along the leg or the arm. Acupoint of PC6 is located at the one-sixth of remote end and five-sixth of the proximal end of the connection stripe between the transverse wrist crease and cubital crease[14] (Figure 1A). ST36 acupoint is located at the proximal one-fifth of the craniolateral surface of the leg distal to the head of the tibia in a depression between the muscles of the cranial tibia and the long digital extensor[15] (Figure 1B).

Sham-TEA was performed with the same stimulation parameters at sham points (non-acupoints area): the sham-point for PC6 was about 15 cm up (to the elbow) and laterals to PC6 and the sham-point for ST36 was about 10 cm down (to the knee joint) and laterals to ST36.[14]

2.4 | Symptom and AP severity assessments

The symptoms of abdominal pain, bloating, nausea, and vomiting were recorded before and after the treatment period (Day 1 and Day 3) and scored using the visual analogue scale (VAS) ranging from 0 to 10: "0" refers to no symptom, "1–3" refers to mild symptom, "4–6" refers to moderate symptom, "7–9" refers to severe symptom, and "10" refers to unbearable.[16] The first defecation time after the AP onset was also included in the symptom assessment. The AP severity was assessed by the score of Acute Physiology and Chronic Health Evaluation II (APACHE II).[17]

2.5 | Assessment of gastric slow waves

Gastric slow waves were recorded by a non-invasive EGG device (MEGG-04A; Ningbo Maida Medical Device). All subjects were

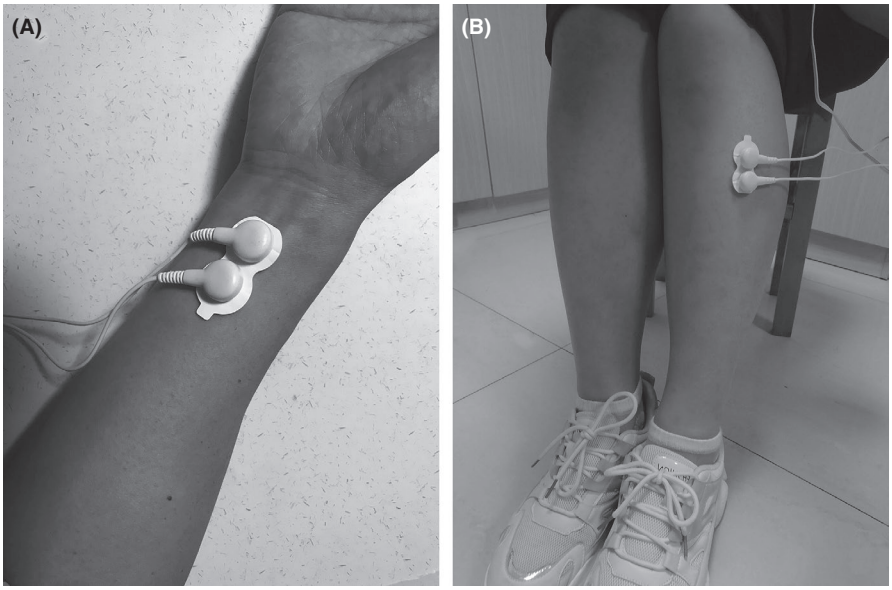

FIGURE 1 TEA on acupoints of PC6 and ST36. (A) unilateral PC6; (B) unilateral ST36. TEA: Transcutaneous electrical acustimulation; PC6: acupoint of Neiguan; ST36: acupoint of Zusanli

asked to keep supine and quiet during the recording. After skin preparation, 4-channel EGG signals were recorded via six cutaneous electrodes placed on the abdominal skin surface, including 4 recording electrodes for the corresponding recording channels, a common reference electrode, and a grounding electrode. The distribution of these electrodes was as follows: (1) Reference electrode: at the xiphoid process; (2) Grounding electrode: at the lower edge of the left costal arch; (3) Recording electrodes for the 4 Recording Channels: Electrode 3: in the midpoint of a line connecting the xiphoid process and the umbilicus; Electrode 4: at a horizontal location 3–5 cm to the right of electrode 3; Electrodes 2 and 1: 3–5 cm and 6–10 cm away from electrode 3 in the upper left direction (45°).[18,19]

A validated spectrum analysis method was used to obtain the following EGG parameters by a special software (Ningbo MedKinetic, Inc.): (1) Percentage of normal gastric slow waves (%NGSWs), reflecting the rhythmic regularity of gastric pacing-making activity; (2) Dominant frequency (DF), representing the frequency of the gastric slow waves; (3) Dominant power (DP), referring to the amplitude of gastric slow waves.[20,21]

2.6 | Assessment of autonomic functions

A one-channel ECG was recorded via 3 cutaneous electrodes placed as follows: the right manubrium of the sternum, the fifth interspace in the left midclavicular line, and the right chest (the ground electrode).[14] The ECG signal was amplified via a special amplifier (ECG-201, Ningbo Maida Medical Device Inc.), then digitized by computer. The heart rate variability (HRV) signal was derived from the ECG by calculating R-R intervals using a previously validated software.[6] A previously validated method was used to access autonomic functions by spectral analysis.[7] The powers in the low-frequency band (0.04–0.15 Hz, LF) and in the high-frequency band (0.15–0.50 Hz, HF) reflect sympathetic activity mainly and vagal activity, respectively. The power ratio of LF/HF represents the balance between the sympathetic and parasympathetic activities. To analyze the treatment-induced alterations in the autonomic function, each of the above-mentioned spectral parameters was presented as the ratio of the post-treatment value to the pre-treatment value.

2.7 | Blood assays

Blood samples were collected from the subject in the fasting state at 8:00 am on the day before and after TEA/Sham-TEA (Day 1 and Day 3). A total of 12 ml blood was drawn into a syringes: (1) 5 ml was then placed into 2 anticoagulative tubes: one tube of 3 ml was used for the ELISA test of plasma motilin and ghrelin, and the other tube of 2 ml was used for routine blood analysis, including white blood cell count (WBC); (2) the remaining 7 ml was emptied into 2 promoting coagulating tubes: one tube of 3 ml was used for ELISA assessment of serum TNF-α, and the other tube of 4 ml was used for the blood biochemical examination including test of C-reactive protein (CRP). Blood routine examination and blood biochemical examination were performed immediately after blood drawn.

The blood samples for the ELISA analysis were added with EDTA, aprotinin, and dipeptidyl peptidase-4 (DDP-4) inhibitor, and immediately centrifuged at 1200 × *g* and 4℃ for 15 min. Then, the plasma or serum was extracted and stored at −80℃ until analysis within 6 months. The plasma concentrations of motilin and ghrelin and serum concentration of TNF-α were determined by ELISA kits (Cat No. CEA575Hu, motilin ELISA kits: Cloud-clone corp.; Cat No. BMS2192, ghrelin ELISA kits: Thermo Fisher; Cat No. HSTA00E, TNF-α ELISA Kits: R&D Systems).

2.8 | Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical analysis was performed by statistical software SPSS 21. $p < 0.05$ was defined as statistically significant. One-way analysis of variance (ANOVA) was used to compare the differences in the age and body mass index (BMI) among different groups (HCs, TEA, and Sham-TEA group). The independent sample *t* test was used to analyze the differences in the first defecation time and the parameters of the autonomic function between the TEA group and Sham-TEA group. The chi-square analysis was performed to study the differences in the percentage of sex between the two patient groups, and severity rate and distribution of etiology among 3 different groups. Two-way Repeated Measures ANOVA was applied to compare the differences of several parameters (symptom scores, APACHE II scores, parameters of EGG, GI hormones of motilin and ghrelin, and inflammatory indicators of TNF-α, WBC, and CRP) among different groups or between different periods (pre- and post-TEA/Sham-TEA treatment). The Spearman correlation was performed to assess the correlation between two different parameters.

3 | RESULTS

3.1 | Characteristics of the patients

A total of 44 AP patients and 16 HCs were recruited in this study. Two AP patients quitted the study on Day 1 (one in TEA group because of the use of medication that might affect GI motility and the other in Sham-TEA group who decided to withdraw from the study). The data of remaining 58 subjects (42 AP patients and 16 HCs) were included in the analysis. AP patients were randomly divided into TEA group ($n = 21$) and Sham-TEA group ($n = 21$). There was no significant difference in sex, age, or BMI among the HCs, the TEA group, and the Sham-TEA group (all $p > 0.05$, Table 1). No significant difference was noted in the distribution of etiology, severity classification

TABLE 1 Characteristics of healthy controls and AP patients

	HCs ($n = 16$)	TEA group ($n = 21$)	Sham-TEA group ($n = 21$)	p-Value
Age (year)	50.94 ± 14.15	51.14 ± 8.66	51.57 ± 12.99	0.986
Sex (male/female [n/n])	9/7	14/7	12/9	0.759
BMI (kg/m^2)	23.20 ± 1.48	25.07 ± 3.77	24.07 ± 3.75	0.116
Etiology				
Biliary diseases (n)	N/A	10	12	0.809
Alcohol-related (n)	N/A	2	1	
Hypertriglyceridemia (n)	N/A	9	8	
Severity				
MAP/MSAP (n/n)	N/A	17/4	16/5	0.999

Note: No significant difference was noted in any of the parameters before the treatment. AP, acute pancreatitis; MAP: mild acute pancreatitis, defined as AP with no organ failure or no local/systemic complications; MSAP: moderately severe acute pancreatitis, defined as AP transient organ failure (organ failure resolved within 48 h) and/or local or systemic complications; TEA, transcutaneous electrical acustimulation; HCs, healthy controls; BMI, body mass index; N/A, not applicable.

of AP or APACHE II score between the TEA group and Sham-TEA group (all $p > 0.05$, Table 1).

Before the treatment, there were no significant differences in symptom scores, severity scores (APACHE-II score), parameters of EGG, autonomic functions, or blood indicators between the TEA and Sham-TEA groups.

3.2 | Improvement of symptoms

3.2.1 | Reduction of GI motility-related symptom scores with TEA

TEA, but not Sham-TEA, significantly improved the GI motility-related symptom scores. Compared to that of pre-treatment, the bloating score was significantly decreased after TEA (pre- vs. post-TEA: 4.05 ± 2.09 vs. 0.76 ± 0.99, $p < 0.001$) but not after Sham-TEA (4.91 ± 1.55 vs. 5.19 ± 1.21, $p > 0.05$). After the treatment, the percentage of AP patients who reported absence of bloating was 52.4% (11/21) in the TEA group and 4.8% (1/21) in the Sham-TEA group ($p < 0.05$). Further, the TEA group showed a 21.9% decrease in the first defecation time in comparison with the Sham-TEA group (51.38 ± 17.19 h vs. 65.79 ± 19.51 h, $p < 0.05$).

There was a reduction in nausea and vomiting scores in both TEA and Sham-TEA groups after the treatment and the difference in the reduction was similar between the two treatments (decline of nausea score: 2.05 ± 2.22 vs. 1.90 ± 2.23, decline of vomiting score: 0.71 ± 1.52 vs. 0.71 ±0.90, both $p > 0.05$).

3.2.2 | More reduction of abdominal pain score with TEA

A more potent analgesic effect was noted with TEA in abdominal pain score. Although the abdominal pain score was notably decreased after the treatment in both the TEA group and the Sham-TEA group (pre- vs. post-treatment: 5.24 ± 1.55 vs. 1.33 ± 1.02 in TEA group; 5.29 ± 1.42 vs. 2.57 ± 1.78 in Sham-TEA group, both $p < 0.001$), the decrease was significantly larger in the TEA group than that in the Sham-TEA group (decline of abdominal pain score: 3.90 ± 1.73 vs. 2.71 ± 1.27, $p < 0.05$).

3.3 | Decrease of AP severity score and impact on hospital days with TEA

TEA rather than Sham-TEA significantly reduced the AP severity score. TEA treatment resulted in a 29.3% decrease in APACHE II score (referring to AP severity, pre- vs. post-treatment: 5.52 ± 2.04 vs. 3.90 ± 1.90 in TEA group, $p < 0.001$; 6.62 ± 2.84 vs. 6.29 ± 2.63 in Sham-TEA group, $p > 0.05$). Meanwhile, a significantly lower APACHE II score was noted after TEA (on Day 3) compared to that after Sham-TEA treatment (3.90 ± 1.90 vs. 6.29 ± 2.63, $p = 0.001$).

In all AP patients of this study, there was no significant difference on the hospital days between the TEA group and Sham-TEA group (11.10 ± 3.78 days vs. 14.57 ± 7.24 days, $p > 0.05$). The MAP patients in TEA group showed significantly fewer hospital days than MAP patients in Sham-TEA group (9.82 ± 2.56 days vs. 14.31 ± 7.95 days, $p < 0.05$). The MSAP patients in TEA group showed similar hospital days with MSAP patients in Sham-TEA group (16.50 ± 3.51 days vs. 15.40 ± 4.88 days, $p > 0.05$).

3.4 | Improvement of gastric dysrhythmia with TEA

The AP patients showed impaired gastric slow waves in comparison with the HCs. TEA, but not Sham-TEA, significantly improved gastric slow waves in the AP patients. TEA resulted in a 41.6% increment in the average %NGSWs and a 18.8% increment in the average DF (pre- vs. post-TEA: 42.24 ± 7.37% vs. 59.81 ± 9.59% in average %NGSWs; 2.34 ± 0.56 cpm vs. 2.78 ± 0.60 cpm in average DF, both $p < 0.05$,

Figure 2A,B). Meanwhile, a 14.4%–22.6% increment in the %NGSWs was recorded in the 4 EGG recording channels (Channel 1 to Channel 4) in the TEA group (Figure S1A–D). A 24.8% increase in DF was noted in Channel 4 (2.50 ± 1.05 cpm vs. 3.12 ± 0.65 cpm, $p < 0.05$, Figure S2D) but not in other channels (Figure S2A–C, all $p > 0.05$) in the TEA group. However, in the Sham-TEA group, none of the EGG parameters were altered with the treatment (Figure 2).

Although the average %NGSWs of post-TEA in AP patients were still lower than that in HCs (59.81 ± 9.59% vs. 73.85 ± 5.23%, $p < 0.05$, Figure 2A), the average DF of gastric slow waves after the TEA treatment in the AP patients was similar to that in the HCs (2.78 ± 0.60 cpm vs. 3.03 ± 0.23 cpm, $p > 0.05$, Figure 2B). No difference was noted in DP among HCs, the TEA group, and the Sham-TEA group either before or after treatment (all $p > 0.05$).

3.5 | Reduction of inflammatory biomarkers with TEA

TEA but not Sham-TEA resulted in a significant reduction in inflammatory biomarkers, including serum TNF-α, WBC, and CRP. In comparison with the baseline, the TEA group presented a 38.3% reduction in the serum level of TNF-α after the TEA treatment (7.59 ± 4.80 pg/ml vs. 4.68 ± 1.85 pg/ml, $p < 0.01$). This reduction was not noted in the Sham-TEA group (7.08 ± 7.49 pg/ml vs. 6.15 ± 2.33 pg/ml, $p > 0.05$, Figure 3A). It should be noted that all four values of serum TNF-α (both patient groups before and after the treatment) were significantly higher than that in the HCs (1.72 ± 0.38 vs. each of four values, $p < 0.001$).

Meanwhile, TEA, but not Sham-TEA, resulted in a significant reduction in WBC and CRP (pre- vs. post- TEA: 10.36 ± 3.85 × 10^9/L

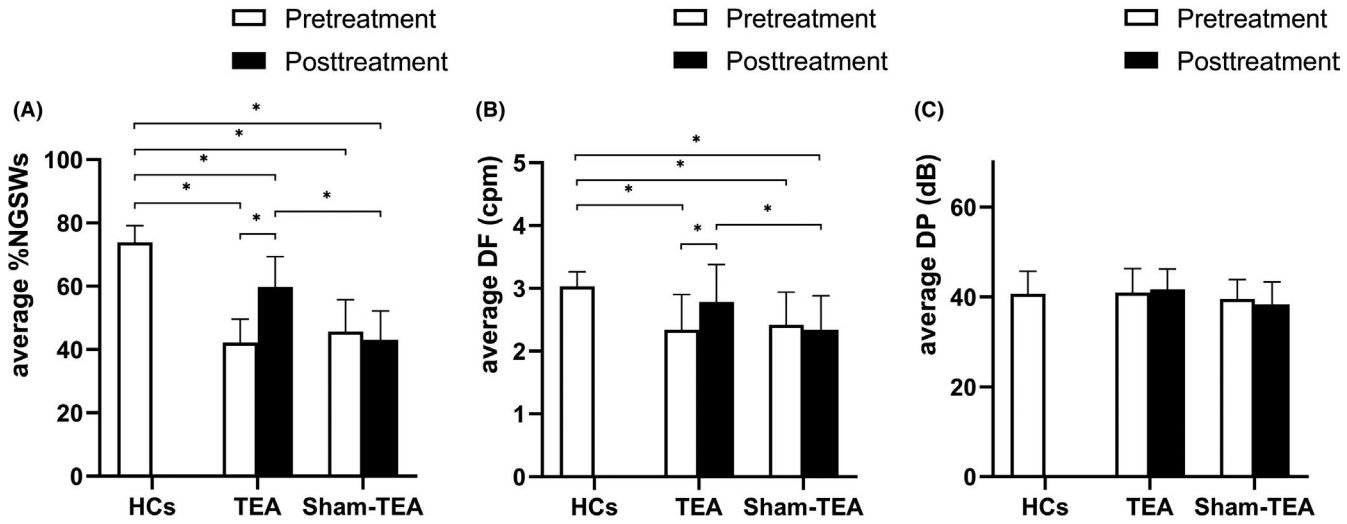

FIGURE 2 Comparisons of the average EGG parameters of the 4 recording channels among healthy controls, TEA group and Sham-TEA group. A: Average %NGSWs; B: Average DF; C: Average DP; EGG: electrogastrogram; TEA, transcutaneous electrical acustimulation; Sham-TEA: same stimulation but on non-acupoints. HCs: healthy controls; %NGSW: percentage of normal gastric slow waves; DF: dominant frequency; DP: dominant power. *p< .05 between groups

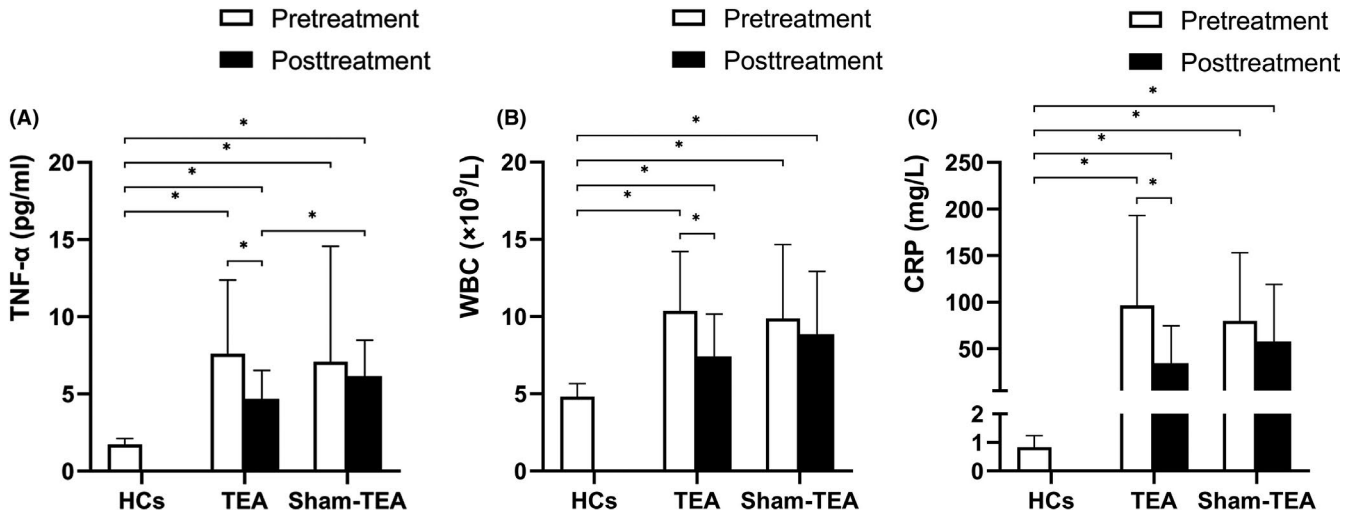

FIGURE 3 CComparisons of inflammatory indicators of TNF-α, WBC and CRP between healthy controls, TEA and Sham-TEA groups. A: TNF-α; B: WBC; C: CRP; TNF-α: tumor necrosis factor-α; WBC: white blood cell count; CRP: C-reactive protein; TEA, transcutaneous electrical acustimulation; Sham-TEA: same stimulation but on non-acupoints; HCs: healthy controls. *p< .05 between groups

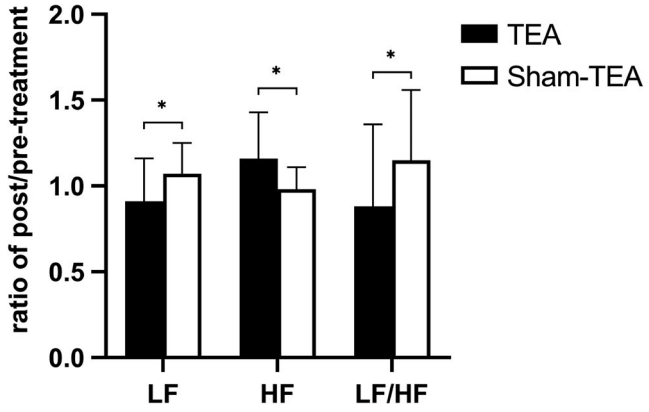

FIGURE 4 Comparisons of variations of autonomic functions analyzed by HRV between TEA and Sham-TEA groups. HRV, heart rate variation; TEA, transcutaneous electrical acustimulation; Sham-TEA, same stimulation but on non-acupoints; LF, the power in the low-frequency band, representing mainly sympathetic activity; HF, the power in the high-frequency band, reflecting purely parasympathetic or vagal activity; LF/HF, the power ratio of LF/HF, reflecting the balance between the sympathetic and parasympathetic activities. To analyze the variations of autonomic function through TEA/Sham-TEA treatment, the above-mentioned HRV parameters were recorded as the ratio of post-treatment value to pre-treatment value. $^*p < 0.05$ between groups

vs. 7.41 ± 2.74 × 10^9/L in WBC; 96.33 ± 96.69 mg/L vs. 34.57 ± 40.03 mg/L in CRP, both $p < 0.05$; Figure 3B,C).

3.6 | Mechanism of TEA involving autonomic functions

TEA improved autonomic functions, reflected as an increase in vagal activity and a decrease in sympathetic activity. In comparison with the Sham-TEA group, the TEA group exhibited a 15.0% decrease in sympathetic activity (LF ratio of post-TEA value/pre-TEA value: 1.07 ± 0.18 vs. 0.91 ± 0.25, $p < 0.05$), a 18.3% increase in vagal activity (HF ratio of post-TEA value/pre- TEA value: 0.98 ± 0.13 vs. 1.16 ± 0.27, $p < 0.01$) and a 23.4% decrease in sympathovagal balance (LF/HF ratio of post-TEA value/pre-TEA value: 1.15 ± 0.41 vs. 0.88 ± 0.48, $p < 0.05$, Figure 4).

3.7 | Mechanism of TEA involving GI hormones

TEA but not Sham-TEA significantly upregulated the plasma level of ghrelin. Compared to that of pre-treatment, the plasma level of ghrelin was increased with TEA (pre- vs. post-TEA: 0.85 ± 0.96 ng/ml vs. 2.00 ± 1.71 ng/ml, $p = 0.001$) but not Sham-TEA (pre- vs. post-Sham-TEA: 0.79 ± 0.65 ng/ml vs. 0.85 ± 0.60 ng/ml, $p > 0.05$, Figure 5A). The plasma ghrelin level of post-TEA was 1.35 times higher than that of post-Sham-TEA in AP patients ($p < 0.05$) and was comparable to that of HCs (3.05 ± 0.77 ng/ml, $p > 0.05$ vs. post-TEA).

Neither TEA nor Sham-TEA altered the plasma level of motilin (pre- vs. post-treatment: 33.08 ± 22.65 pg/ml vs. 24.12 ± 13.95 pg/ml in TEA group; 30.24 ± 21.05 pg/ml vs. 26.75 ±20.81 pg/ml in Sham-TEA group, both $p > 0.05$, Figure 5B). Moreover, the plasma levels of motilin in the 2 AP groups were notably lower than that in the HCs (141.44 ± 54.66 pg/ml, all $p < 0.05$ vs. TEA/Sham-TEA group).

3.8 | Correlation analysis in AP patients with TEA

In the TEA group, a negative correlation was noted between the bloating score and the percentage of normal gastric slow wave ($r = -0.651$, $p < 0.05$). The percentage of normal gastric slow waves was negatively correlated with clinical inflammatory measurements, including WBC ($r = -0.463$, $p < 0.01$) and CRP ($r = -0.440$, both $p < 0.01$). The serum TNF-α level was positively correlated with the bloating score ($r = 0.367$, $p < 0.05$) and abdominal pain score ($r = 0.512$, $p = 0.001$).

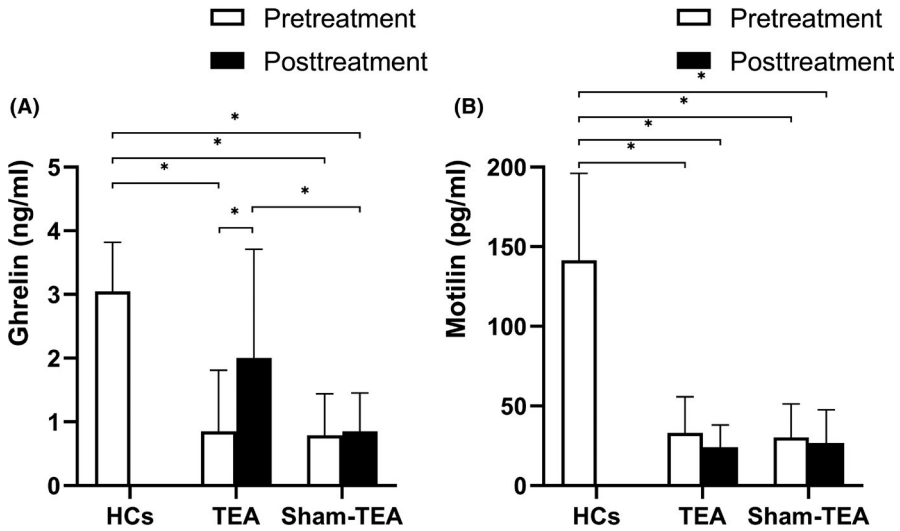

FIGURE 5 Comparisons of GI hormones of ghrelin and motilin between healthy controls, TEA and Sham-TEA groups. (A): ghrelin; (B) motilin; TEA, transcutaneous electrical acustimulation; Sham-TEA, same stimulation but on non-acupoints; HCs, healthy controls. $^*p < 0.05$ between groups

The APACHE II score, reflecting AP severity, exhibited a positive correlation with the bloating score ($r = 0.318$) and the serum TNF-α level ($r = 0.380$, both $p < 0.05$).

Moreover, the HF (reflecting vagal activity) and ghrelin presented significant correlations with inflammatory biomarkers and %NGSWs in TEA group before and after TEA treatment. The HF was mildly correlated with the bloating score ($r = -0.345$), %NGSWs ($r = 0.380$), and serum TNF-α level ($r = -0.381$, all $p < 0.05$). The plasma level of ghrelin was positively correlated with motility-related bloating score ($r = -0.455$) and %NGSWs ($r = 0.501$) and was negatively correlated with WBC ($r = -0.468$) and CRP ($r = -0.375$, all $p < 0.05$).

3.9 | Adverse event

No treatment-related side effects were noted in any of the AP patients with TEA or sham-TEA during the study.

4 | DISCUSSION

In this study, the TEA or Sham-TEA was given in the early stage of AP as an adjunctive treatment. We found that (1) The TEA treatment resulted in a 43.9% more reduction in abdominal pain score compared to the Sham-TEA treatment, indicating an analgesic effect. (2) TEA but not Sham-TEA reduced the bloating score (by 81.2%) and increased the %NGSWs (by 41.6%) compared to pre-treatment; TEA decreased the first defecation time by 21.9% compared to Sham-TEA, suggesting a prokinetic effect on the gut. (3) TEA exhibited a 38.3% decrease in serum TNF-α level and a significantly more decrease in WBC and CRP in comparison with Sham-TEA, demonstrating an anti-inflammatory effect of TEA. (4) TEA rather than Sham-TEA decreased the APACHE II score (by 29.3%), suggesting an ameliorating effect on clinical outcome of AP. (5) The possible mechanisms included the regulation of the autonomic function reflected as an upregulation of vagal activity and downregulation of sympathetic activity, and the upregulation of ghrelin.

4.1 | Choices of TEA and experimental conditions

The choice of stimulation locations (ST36 and PC6) and parameters used for the TEA treatment in this study was based on a number of previous studies. EA and TEA using these acupoints and stimulation parameters have been consistently shown effective in improving GI motility.[22] In several previous clinical studies, EA/TEA at PC6 and/or ST36 was reported to be effective in treating several functional GI diseases, including gastro-esophageal reflux diseases,[23,24] FD,[6,8] and constipation.[7] In addition, EA/TEA at PC6 and/or ST36 was reported to be also effective in suppressing inflammation and visceral pain in several animal and clinical studies (discussed later in Section 4.2 and 4.3). Therefore, TEA at PC6 and ST36 was chosen to treat AP in this study. To the best of our knowledge, this was the first clinical study to investigate the therapeutic potential of TEA for AP.

In the present study, to exclude the effect of EN/feeding on GI motility, the AP patients were kept on fasting during the 3-day study. Alternative was provided to the patients to quit the study when they were judged as tolerable for EN/feeding before the end of the study. Actually, 92.9% (39/42) of the AP patients were judged as tolerable for EN or feeding only after the end of the study. A total of 3 AP patients (2 patients in the TEA group and 1 patient in Sham-TEA group) were judged as tolerable for EN/feeding at the second day (Day 2) and all chose to stay in the study.

4.2 | Prokinetic effect of TEA in patient with AP

Improving GI dysmotility at early stage of AP has been regarded as a key issue in the AP treatment. GI dysmotility could lead to the overgrow and translocation of bacteria and aggravate the systemic inflammation,[25] and further result in deterioration and poor prognosis. However, treatment options are limited for GI dysmotility at the early stage of AP. The use of oral prokinetic drugs is limited by the fact that the patient has to keep fasted in order to avoid stimulating pancreatic secretion in early AP. EN, known to improve GI motility, can only be administrated invasively via a nasojejunal/nasogastric tube. It is recommended only when the GI function is evaluated to be tolerable for EN; moreover, its application is limited due to intolerance, side effects, and/or failure in the tube placement. Therefore, it is of great clinical significance to investigate the therapeutic potential of TEA for AP due to its noninvasiveness and feasibility during the early stage of the disease. The GI prokinetic effect of TEA in AP was investigated in the current study. Gastroparesis-like symptoms were used in the evaluation of GI dysmotility in AP in a few previous clinical studies.[26,27] In the current study, we evaluated the motility-related outcomes, including first defecation time and gastric slow waves in addition to the subjective symptoms. It was showed that TEA rather than Sham-TEA resulted in significant improvement in the gastroparesis-like symptoms and gastric slow waves, and a reduction in the first defecation time. These findings suggested the prokinetic effect of TEA on GI dysmotility in AP.

4.3 | Anti-inflammation effect of TEA in patients with AP

We explored the anti-inflammatory effect of TEA in AP patients. The 2-day TEA treatment resulted in a 38.3% decrease in serum TNF-α, a 28.5% decrease in WBC, and a 64.1% decrease in CRP. EA/TEA at ST36 was previously reported to have an anti-inflammatory effect in several studies involving animals[28–30] and humans.[31,32] McNearney et al.[31] reported that TEA on PC6 and ST36 improved the impaired gastric myoelectrical activity and lowered plasma IL-6 level in scleroderma patients. However, there was a lack of study investigating the effect of EA/TEA on inflammatory cytokines in AP patients. In

this study, TEA was found to notably decrease the serum level of TNF-α, a major inflammation cytokine. In addition, the inflammation biomarkers (TNF-α, WBC, or CRP) were found significantly correlated with the gastric slow waves and symptoms. Interestingly, TEA also significantly reduced the AP severity score (APACHE II score), which exhibited a positive correlation with bloating score and TNF-α. These findings suggested that TEA might inhibit the progression of AP by improving gastric motility and suppressing inflammation.

4.4 | Analgesic effect of TEA in patients with AP

TEA was also found to have an analgesic effect in the present study. Juel et al.[33] performed a randomized, sham-controlled, and crossover clinical trial to evaluate the analgesic effect of acupuncture on visceral pain in healthy volunteers. In this well-designed study, a hollow inner tube with a sharp tip was fitted into an outer tube and subjects were blinded to the stimulations so that the evaluation of pain would not be disturbed. In this study, the TEA treatment was performed through surface electrodes instead of invasive needles or sharp tips; meanwhile, sham-TEA on non-acupoints was used to ensure the present study as a single-blind one in which the patients were blind to their treatment (TEA or Sham-TEA).

The analgesic effect of EA at ST36 and/or PC6 was reported in a few previous studies. Feng et al.[34] reported suppression of post-laparotomy pain through EA at ST36 and SP6 in a rat model. Sim et al.[35] reported that the preoperative EA at ST36 and PC6 in patients resulted in a reduction in postoperative consumption of analgesic drugs. The analgesic effect of EA/TEA was previously reported in chronic pancreatitis (CP) but not in AP. Juel et al.[36] showed a short lasting (1 week) analgesic effect of acupuncture in CP. However, Ballegaard et al.[37] reported in a crossover, sham-controlled prospective study that EA showed no pain relief in patients with CP. In the present study, a significant larger decrease was noted in the abdominal pain score with TEA in comparison with Sham-TEA. This notable analgesic effect of TEA in AP might be attributed to the following factors: (1) Administration of TEA in the early stage of AP could promote GI motility and inhibit the systemic inflammation, which might contribute to the analgesic effect. (2) The use of appropriate stimulation parameters: pulse frequency of 100 Hz for TEA at PC6 and 25 Hz for TEA at ST36. It was reported in a rodent model of incisional pain that 100-Hz EA could reduce mechanical nociception.[38] In a rat model of postoperative ileus, the EA treatment performed at ST36 and PC6 with the same stimulation parameters as the current study was shown to have ameliorating effects of GI dysmotility, inflammation, and pain.[10] The finding of the present study suggested that the TEA treatment might be a novel option for treating abdominal pain in patients with AP.

4.5 | Autonomic-endocrine mechanisms of TEA

The enhancement of vagal activity with EA/TEA was reported in several previous studies and considered as one of major mechanisms involved in the prokinetic effects of EA/TEA.[39,40] EA at ST36 was reported to improve gastric slow waves in a rat model of FD[39] and normalize impaired colonic motility induced by rectal distension in dogs[40]; the prokinetic effects were inhibited by atropine, an antagonist of acetylcholine (Ach).[39,40] The increase in vagal activity was reported to be associated with the improvement of dyspepsia symptoms in FD patients with the TEA treatment at PC6 and ST36.[6] Moreover, vagal nerve activation has been reported to exert anti-inflammatory effects in several experimental and clinical studies.[41–43] Borovikova et al.[41] revealed that direct electrical stimulation on the peripheral vagal nerve in rats during endotoxemia inhibited TNF synthesis in liver, decreased peak serum TNF level, and prevented the development of shock. In the present study, TEA resulted in an 11.3% increase in vagal activity and a 12.8% decrease in sympathetic activity. Meanwhile, the HF (reflecting vagal activity) was significantly correlated with not only GI motility-related indicators of the bloating score and %NGSWs but also inflammation-related indicator of serum TNF-α. These findings seemed to indicate an autonomic mechanism involved in both prokinetic and anti-inflammatory effects of TEA.

GI hormones might also be involved in the mechanisms of EA/TEA for both prokinetic and anti-inflammatory effects in AP. Several prokinetic GI hormones, such as circulatory motilin and ghrelin, were reported to be decreased in AP.[1,44,45] Miao et al.[46] treated AP patients with a special kind of traditional Chinese Medicine named Tongfu powder via umbilical compress therapy and reported improvement in GI dysmotility concurrent with an increase in motilin. However, motilin was not altered with the TEA treatment in the present study. Ghrelin is regarded as a new therapeutic target for improving pancreatic pathophysiology[47] due to its prokinetic[48] and anti-inflammatory effects.[49] Administration of exogenous ghrelin before or early in the course was reported to exert a remission of AP.[50,51] The TEA treatment performed in the present study revealed a notable increase in the plasma ghrelin level. Further, the ghrelin level was significantly correlated with the bloating score and the %NGSWs and inflammatory biomarkers of WBC and CRP. This might suggest a ghrelin-related mechanism involved in the prokinetic and anti-inflammatory effects of TEA.

Based on the findings in the literature and present study, we speculated that the increased release of ghrelin with TEA observed in this study might be attributed to the TEA-induced enhancement in vagal activity. Shrestha et al.[52] reported that 1 mM of Ach increased the secretion of ghrelin by nearly 37.0% in cultured gastric tissue in vitro. Bansal et al.[53] treated mice with traumatic brain injury by direct vagal stimulation and showed an upregulation of the ghrelin level in plasma and tissues of the GI tract and brain as well as a downregulation of serum TNF-α.

4.6 | Limitations of the study

There were a few limitations in this pilot study: (1) the sample size was small; (2) the ratio of patients with MSAP was low and no SAP

patients were included; (3) there were no follow-ups to investigate alterations in GI motility and inflammation after termination of the TEA treatment.

In conclusion, TEA at PC6 and ST36 administrated in the early stage of AP exerts an analgesic effect on abdominal pain, an ameliorating effect on gastric slow waves, and an inhibitory effect on inflammation, resulting in improvement of AP. The integrative effects of TEA may possibly be mediated via the autonomic-endocrine mechanisms.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

Gao-jue Wu, Lei Gong, and Jiande DZ Chen designed the research study. Jia-lei Xuan, Ying-wei Zhu, Wen-hui Xu, Han Zhao, and Gao-jue Wu performed the research. Jia-lei Xuan and Gao-jue Wu analyzed the data and wrote the manuscript. Jiande DZ Chen gave technical support in terms of performing EGG, HRV, and TEA. Gao-jue Wu, Lei Gong, and Jiande DZ Chen performed critical revision of the manuscript for important intellectual content. All authors critically reviewed the manuscript and approved the final version.

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