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Transcutaneous electroacupuncture improves dyspeptic symptoms and increases high frequency heart rate variability in patients with functional dyspepsia

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Abstract *The aim of the study was to evaluate the therapeutic value and possible mechanisms of transcutaneous electroacupuncture (TEA) in a double-blind and cross-over study in patients with functional dyspepsia (FD). Twenty-seven patients with FD were enrolled and the study consisted of two parts: (i) acute effects of TEA at PC6 and ST36 on gastric slow waves and heart rate variability and (ii) chronic (2 weeks) effects of TEA at PC6 and ST36 on dyspepsia symptoms, gastric slow waves, heart rate variability and neuropeptide Y (NPY) and motilin. The results of this study are: (i) The dyspepsia symptom score was decreased by 55% at the end of chronic TEA and the improvement was significant ($P < 0.01$); (ii) the high frequency (HF) assessed from the spectral analysis of heart rate variability was markedly increased with both acute TEA (76% increase, $P = 0.01$) and chronic TEA (75% increase, $P = 0.025$); (iii) gastric slow waves were not altered by either acute or chronic TEA; and (iv) the plasma level of NPY but not motilin was increased after chronic TEA. Non-invasive and needleless transcutaenous electroacupuncture at ST36 and PC6 markedly improves dyspepsia symptoms and the improvement may be associated with the increase in HF heart rate variability and the modulation of NPY.*

Keywords *acupuncture, functional dyspepsia, gastric myoelectrical activity, gastrointestinal motility, heart rate variability, transcutaenous electrical nerve stimulation.*

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INTRODUCTION

Functional dyspepsia (FD) is a symptom complex characterized by postprandial upper abdominal discomfort or pain, early satiety, nausea, vomiting, abdominal distension, bloating and anorexia in the absence of organic disease. Gastrointestinal motor abnormalities, altered visceral sensation and psychosocial factors have been reported to play pathophysiological roles in patients with FD. However, the underlying aetiology of FD remains poorly understood.

The outcome of the treatment for FD is unsatisfactory. Prokinetics, despite a sound pathophysiological basis, have given modest results in clinical trials, and the situation is similar for visceral analgesics.[1] Other drugs, such as acid suppressants and antidepressants have a therapeutic benefit in some patients with FD.[2,3] The patients with FD who fail to respond to conventional medications need further treatment options.

Acupuncture has been used to treat gastrointestinal symptoms in China for thousands of years. The most commonly used acupuncture points (acupoints) for the treatment of gastrointestinal symptoms are Neiguan (PC6) and Zusanli (ST36). In clinical research, manual acupuncture is commonly replaced with electroacupuncture that is more reproducible. In a comparative study, electroacupuncture was found to be as effective as manual acupuncture in treating pain.[4] Electroacupuncture at ST36 and PC6 has been documented to increase the regularity of gastric slow waves and accelerate gastric emptying of liquids in animals.[5] In recent studies, electroacupuncture was reported to

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accelerate gastric emptying of solids and improve dyspeptic symptoms and gastric dysrhythmia in patients with FD and patients with diabetes.[6,7] However, it is unknown whether similar beneficial effects can be observed in patients with FD when electroacupuncture is applied without needles, or a method called transcutaneous electroacupuncture (TEA). Transcutaneous electroacupuncture is a completely non-invasive method which is readily accepted by patients.

Accordingly, the aim of this study was to investigate the therapeutic potential of TEA for patients with FD by assessing acute and chronic effects of TEA on dyspeptic symptoms, heart rate variability (HRV) and gastric myoelectrical activity, and possible mechanisms involving certain gastrointestinal peptides.

MATERIALS AND METHODS

Patient selection

Twenty-seven patients with FD (nine males and 18 females, age 20–60 years, mean 40.3 ± 4.5 years) who fulfilled the Rome II criteria were enrolled.[8] These were out-patients who visited Division of Gastroenterology from December 2005 to August 2006. The patients had dyspeptic symptoms, including abdominal pain/discomfort, and/or nausea, vomiting, early satiety, belching, abdominal bloating, anorexia for more than 3 months in the past year. No evidence of organic diseases that could be used to explain these symptoms was noted. Patients were excluded if they: (i) were unable to give informed consent; (ii) were taking prokinetic, anticholinergic or dopaminergic agents which could potentially modify gastric motility; (iii) had a history of abdominal surgery; (iv) were pregnant or preparing to conceive a child during the study period; and (v) had previous knowledge about the locations of acupoints PC6 or ST36. According to the Rome II criteria, the patients with FD were divided into three subgroups, including the ulcer-like dyspepsia group (two cases, one female, one male), the dysmotility-like dyspepsia group (21 cases, 14 females, seven males), the unspecified dyspepsia group (four cases, three females, one male).

The research protocol was approved by the ethical review board of the participating institutions, and written informed consent was obtained from all subjects before the study.

Experimental protocol

This study consisted of two phases (acute and chronic TEA).

The acute phase was composed of three randomized sessions (control, sham-TEA and TEA) on three separate days. All patients were fasted for ≥6 h before the initiation of the acute study. The protocol of each session included a 30-min fasting period and two consecutive 30-min postprandial periods. TEA or sham-TEA was applied during the first 30-min postprandial period. The test meal contained 500 kcal with 30% fat (solid meal with 100 mL of liquid). In the control session, cutaneous electrodes ('TENS/EMS Electrode Pads' from Vitalityweb.com) were placed in the acupoints P6 and ST 36 and connected to a two-channel stimulator ('Vital EMS$^{T.M.}$' from Vitalityweb.com) which was not turned on. The setting of the TEA session was the same as the control session except that two-channel (one channel for two PC6 points and the other channel for two ST36 points) electrical stimulation was performed during the first 30-min postprandial period. In the sham-TEA session, electrical stimulation was performed via cutaneous electrodes placed on sham points. The sham points were 6 cm above the kneecap where no acupoints were present. The electrical stimulus consisted of pulse trains with train on-time of 2 s and off-time of 3 s, and a pulse frequency of 25 Hz and amplitude 2–10 mA (at a level with which the patient felt stimulation but comfortable and tolerable). Similar parameter settings were used in a previous study.[9] The electrogastrogram (EGG) and electrocardiogram (ECG) were recorded simultaneously in the entire session.

A double-blind, cross-over design was used in the chronic phase. At the end of the acute study phase, the patients were randomly divided into two groups. One group was treated with TEA first for 2 weeks, followed with a 1-week washout period and a 2-week period with sham-TEA. The order of the treatment and control was reversed in the other group. During the treatment/control period, TEA was performed twice daily (30-min before the first meal in the morning and 30-min before going to sleep at night) via the acupoints/sham points. At the end of the acute phase, the patients were trained to locate the points and use the TEA device and were sent home with the device, written instructions and diagrams of the exact locations of the stimulation points. The patients were asked to come back to the hospital at the end of first 2-week treatment, and beginning and end of the second 2-week treatment. The EGG and ECG were recorded for 30 min in the fasting state and 60 min in the fed state on the following 4 days: beginning and end of the first 2-week treatment, and beginning and end of the second 2-week treatment. Dyspeptic symptoms were also noted during these four visits. In addition, blood

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samples were taken in the fasting state during each of these visits for the assessment of neuropeptide Y (NPY) and motilin.

Measurement and analysis of electrogastrogram

Gastric myoelectrical activity was measured using surface electrogastrography.[10] Before the attachment of electrodes, the abdominal skin at the recording sites was cleaned using sandy skin-preparation paste (Ominiprep; Weaver, Aurora, CO, USA) to reduce the impedance. Three disposable silver-silver chloride electrodes (Synetics Medical, Stockholm, Sweden) were placed on the abdomen. One electrode was placed at the midpoint between the xiphoid and the navel, one was placed at 4–5 cm to the left and 4–5 cm above this point, and a reference electrode was placed in the lower quadrant close to the left costal margin.[10] Two epigastric electrodes were connected to yield a bipolar EGG signal, while the other electrode was used as a reference. The EGG signal was recorded using a portable EGG recording device (Digitrapper EGG; Synetics Medical, Irving, TX, USA) with low and high cutoff frequencies of 1 and 18 cycles per minute (cpm) respectively.

The EGG data were analysed using the established standard method of spectral analysis.[11,12] A sampling frequency of 1 Hz was used. Electrogastrogram parameters extracted from the spectral analysis included: (i) the percentage of normal gastric slow waves; (ii) dominant frequency and dominant power of the EGG which represent the frequency and amplitude of the gastric slow waves; and (iii) dominant power ratio before and after a meal. Gastric slow waves in the range of 2–4 cpm were designated as normal.[11,12] Slow waves of 0–2 cpm were termed bradygastria and 4–9 cpm, tachygastria. An EGG recording was defined as abnormal if the percentage of 2–4 cpm slow waves was lower than 70% in either the fasting or the fed state, or there was a postprandial decrease in dominant EGG power.

Heart rate variability

The autonomic function was assessed based on spectral analysis of the HRV signal derived from an ECG recording.[13] The ECG recording was made through three surface electrodes: the right arm electrode on the manubrium of sternum, the left arm electrode at the surface marking of the V5 position (just above the fifth interspace in the anterior axillary line) and the ground electrode at right chest. The ECG signal was amplified using a special one-channel amplifier (model 2283 FTI universal Fetrode amplifier; UFI, Morro Bay, CA, USA) and digitized at sampling frequency of 6000 Hz using the analogue/digital converter installed on the sound card of the computer. The digitized ECG was further down-sampled to 500 Hz. The HRV signal was derived from the ECG recording using a special programme developed in our laboratory by identifying the R-R peaks, interpolating the R-R intervals so that the time interval between consecutive samples was equal and finally down-sampling the interpolated data to a frequency of 1 Hz.[13]

Overall power spectral analysis was then applied to the HRV signal and the percentage of power in each frequency sub-band was calculated. The percentage of power in the low-frequency (LF) band (0.04–0.15 Hz) is associated with thermoregulatory and peripheral vascular sympathetic influences, it appears that the LF wave may be mediated by both branches of the autonomic nervous system (ANS), and the percentage of power in the high-frequency (HF) band (0.15–0.50 Hz), or respiratory sinus dysrhythmia (RSD), is frequently employed as an index of cardiac vagal tone or even believed to be a direct measure of vagal tone. However, respiratory parameters can confound the relationships between RSD and cardiac vagal tone; they can dissociate under certain circumstances and RSD is affected by sympathetic tone and may not be a 'pure' vagal index. It does imply that variations in RSD magnitude currently provide an unreliable index of vagal outflow or tone.[14] Low frequency was computed as the ratio between the area under the curve (AUC) in the frequency range of 0.04–0.15 Hz and the AUC in the frequency range of 0.04–0.50 Hz. Whereas, HF was assessed as the ratio between the AUC in the frequency range of 0.15–0.50 Hz and the AUC in the frequency range of 0.04–0.50 Hz.

Assessment of dyspeptic symptoms

Symptoms that were recorded and assessed included epigastric pain, epigastric discomfort, nausea, vomiting, early satiety, belching, abdominal bloating and anorexia. Each symptom was graded and scored according to its severity as follow: 0, absent; 1, mild (not influencing usual activities); 2, relevant (diverting from but not urging modifications in usual activities); 3, severe (influencing usual activities markedly enough to urge modifications). Frequency of each symptom was also graded as follow: 0, absent; 1, occurring 1–2 days/week; 2, occurring 3–5 days/week; 3, occurring every day. The total score of the dyspeptic symptoms was an aggregate of frequency and severity ratings, ranging from 0 to 48.

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Analysis of peptides

Blood samples were collected in chilled EDTA and Aprotinin tubes, centrifuged at 4200 ***g*** and 4 °C for 10 min, and stored at 4 °C until extraction. Plasma NPY and motilin levels were determined with the corresponding commercial radioimmunoassay kits (Beifang Institute of Biology and Technology, Beijing, China).

Statistical analysis

All data are presented as mean ± SEM. A 2 × 2 (before treatment–after treatment by sham-TEA group–TEA group) mixed model ANOVA was conducted for the chronic design, and the student's *t*-test was used to compare the differences between two groups or two treatment arms (SPSS 13.0 for Windows – standard version; SPSS Inc., Chicago, IL, USA). Statistical significance was assigned for $P < 0.05$.

RESULTS

Effects of TEA on dyspeptic symptoms

Chronic TEA improved the dyspeptic symptoms in the patients (Fig. 1). The total symptom score in the patients with FD for the ANOVA indicated a significant main effect of treatment (df = 1, $F = 15.603$, $P = 0.002$), a significant main effect for the group factor (df = 1, $F = 4.202$, $P = 0.047$), and no significant interaction effect between the treatment and group membership (df = 1, $F = 1.258$, $P > 0.05$).

There was no significant difference ($P > 0.05$) between the groups at the time of baseline. There was a significant difference ($t = 3.890$, $P < 0.001$) between the groups after the treatment. The mean total symptom score was 16.5 ± 1.9 at baseline and decreased significantly to 4.2 ± 1.5 ($t = 3.583$, $P = 0.001$) after the 2-week TEA treatment. Chronic sham-TEA also reduced the mean total symptom score compared with the baseline (9.4 ± 1.6 *vs* 15.6 ± 2.0, $t = 3.372$, $P = 0.002$) (Fig. 1).

The effects of TEA on individual symptoms were also assessed. It was found that TEA improved abdominal bloating: the mean score for abdominal bloating was 3.2 ± 0.4 at baseline and decreased significantly to 1.0 ± 0.3 ($t = 2.537$, $P = 0.025$) after the 2-week TEA treatment. However, no significant differences were noted in other dyspepsia symptom before and after TEA treatment.

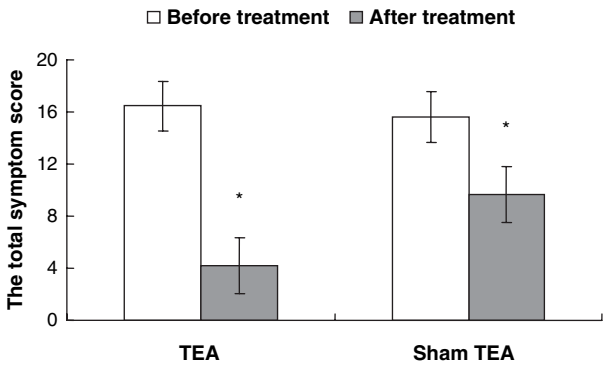

Figure 1 The effect of TEA on dyspeptic symptoms. There was significant difference between TEA and sham-TEA ($F = 4.202$, $P = 0.047$). The total symptom score in patients with functional dyspepsia after chronic TEA and sham-TEA treatments were both significantly lower than that at baseline ($F = 15.603$, $P = 0.002$). *$P < 0.01$ *vs* baseline.

Effects of TEA on autonomic functions

Acute TEA, but not sham-TEA (stimulation applied via non-acupoints), increased HF HRV during the first 30-min postprandial period (Fig. 2A,B). The HF and LF/HF ratio results indicated a significant main effect for the group factor (HF: $F = 6.484$, $P = 0.02$, LF/HF: $F = 5.768$,

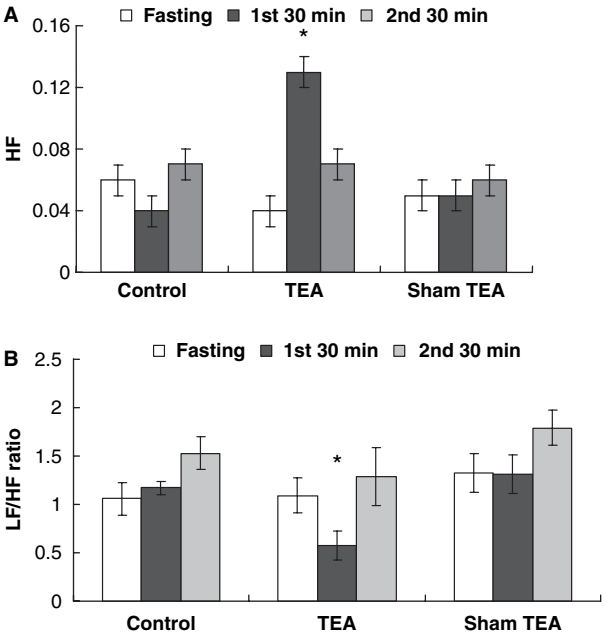

Figure 2 The effects of TEA on heart rate variability in FD patients, acute study phase. (A) There was significant difference in HF between TEA and sham-TEA and control session ($F = 6.484$, $P = 0.02$). HF values were significantly higher during acute TEA treatment than the baseline. *$P = 0.01$ *vs* baseline. (B) There was significant difference in LF/HF ratio between TEA and sham-TEA and control session ($F = 5.768$, $P = 0.03$). LF/HF ratio was obviously lower during acute TEA treatment than the baseline. *$P = 0.02$ *vs* baseline.

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$P = 0.03$). Compared with the baseline (30-min fasting recording without stimulation), the HF activity was significantly increased (0.13 ± 0.02 *vs* 0.04 ± 0.01, $t = 2.868$, $P = 0.01$) and the LF/HF ratio was significantly decreased (0.58 ± 0.15 *vs* 1.09 ± 0.18, $t = 2.528$, $P = 0.02$) during TEA. These effects were not noted with acute sham-TEA (HF: 0.04 ± 0.01 *vs* 0.06 ± 0.01, $P > 0.05$; LF/HF ratio: 1.17 ± 0.07 *vs* 1.06 ± 0.17, $P > 0.05$). Similarly, no difference was noted in the control session between the baseline (the 30-min fasting period without electrode attachment) and the first 30-min postprandial period with the electrodes attached to ST36 and PC6 and connected to the stimulator which was not turned on (HF: 0.05 ± 0.01 *vs*. 0.05 ± 0.01, $P > 0.05$; LF/HF: 1.31 ± 0.20 *vs*.1.32 ± 0.20, $P > 0.05$).

A similar increase in HF HRV was also observed with chronic TEA but not sham-TEA during the fasting period (Fig. 3A,B). The HF results for the ANOVA indicated a significant main effect of treatment (df = 1, $F = 3.268$, $P = 0.04$), a significant main effect for the group factor (df = 1, $F = 4.788$, $P = 0.04$), and no significant interaction effect between treatment and group membership (df = 1, $F = 2.366$, $P > 0.05$). In the chronic phase of the study, the HF activity was significantly higher after the 2-week TEA therapy than that before the treatment during the fasting state (0.08 ± 0.02 *vs* 0.02 ± 0.01, $t = 2.504$, $P = 0.025$); The sham-TEA application, however, did not alter the HF activity during the fasting state (0.04 ± 0.01 *vs* 0.02 ± 0.01, $P > 0.05$).

The LF/HF ratio indicated a significant main effect of treatment, df = 1, $F = 3.086$, $P = 0.04$, a significant main effect for the group factor, df = 1, $F = 3.244$, $P = 0.03$, and no significant interaction effect between treatment and group membership, df = 1, $F = 1.204$, $P > 0.05$. The LF/HF ratio was significantly lower after the 2-week TEA therapy than that before the treatment during the fasting state (0.71 ± 0.10 *vs* 1.2 ± 0.21, $t = 2.596$, $P = 0.02$). The sham-TEA application, however, did not alter the LF/HF ratio during the fasting state (0.84 ± 0.12 *vs* 0.92 ± 0.23, $P > 0.05$).

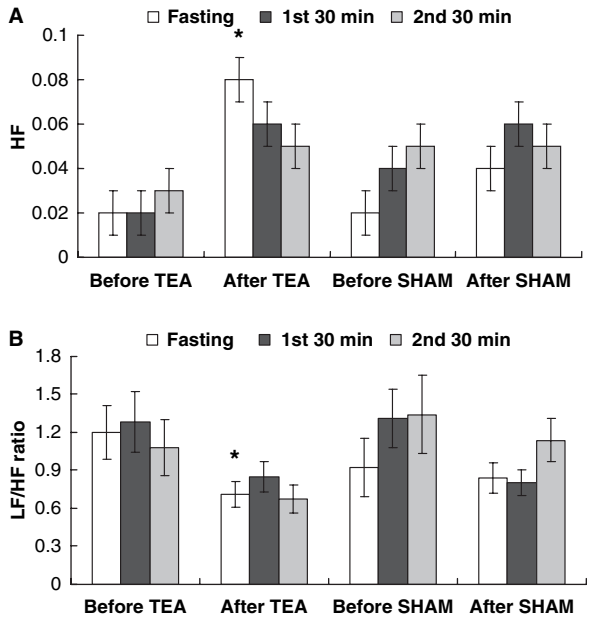

Figure 3 The effects of TEA on heart rate variability in FD patients, chronic study phase. (A) There was significant difference in HF between TEA and sham-TEA ($F = 4.788$, $P = 0.04$). HF values were significantly higher after 2-week TEA treatment than before TEA treatment during the fasting state. *$P = 0.025$ *vs* before TEA. (B) There was significant difference in LF/HF between TEA and sham-TEA ($F = 3.244$, $P = 0.03$). LF/HF ratio was obviously lower after chronic TEA treatment than before TEA treatment during the fasting state. *$P = 0.02$ *vs* before TEA.

Effects of TEA on gastric slow waves

Normal EGG was observed in 11 patients whereas 16 patients showed abnormal EGG (percentage of slow waves below 70% in either fasting or fed state or these was a decrease in dominant power). In the control session during the acute phase of the study, the spectral analysis of the EGG revealed a mean percentage of normal slow waves of 84.6%, a mean frequency of 3.01 cpm and power of 34.98 dB.

Acute or chronic TEA or sham-TEA showed no effects on any of the EGG parameters. The results are presented in Tables 1 and 2.

Table 1 Effects of acute TEA treatment on EGG in patients with functional dyspepsia in the acute study

	Session		
	Control	TEA	Sham-TEA
Dominant frequency (cpm)			
Fasting	2.99 ± 0.06	3.01 ± 0.04	3.03 ± 0.05
Postprandial			
1st 30 min	3.08 ± 0.06	3.16 ± 0.05	3.09 ± 0.05
2nd 30 min	3.16 ± 0.05	3.09 ± 0.04	3.05 ± 0.05
Dominant power (dB)			
Fasting	36.02 ± 2.10	34.98 ± 1.58	34.44 ± 1.73
Postprandial			
1st 30 min	36.86 ± 2.11	34.70 ± 1.22	34.94 ± 1.65
2nd 30 min	36.1 ± 2.32	34.77 ± 2.07	35.43 ± 2.13
Percentage of normal slow waves (%)			
Fasting	80.3 ± 3.2	84.6 ± 3.3	85.7 ± 2.6
Postprandial			
1st 30 min	73.4 ± 3.1	77.6 ± 3.7	74.1 ± 3.0
2nd 30 min	70.8 ± 3.4	74.8 ± 3.5	73.3 ± 3.3

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Table 2 Effects of chronic TEA treatment on EGG in patients with functional dyspepsia in the chronic study

	TEA		Sham-TEA	
	Before	After	Before	After
Dominant frequency (cpm)				
Fasting	2.99 ± 0.04	3.04 ± 0.06	2.96 ± 0.06	2.95 ± 0.04
Postprandial				
1st 30 min	3.13 ± 0.05	3.19 ± 0.05	3.07 ± 0.06	2.92 ± 0.06
2nd 30 min	3.11 ± 0.04	2.98 ± 0.05	3.09 ± 0.04	3.11 ± 0.05
Dominant power (dB)				
Fasting	30.39 ± 1.26	29.34 ± 2.08	31.61 ± 2.32	32.61 ± 2.12
Postprandial				
1st 30 min	31.13 ± 2.12	29.80 ± 1.99	33.09 ± 2.0	32.75 ± 2.43
2nd 30 min	30.96 ± 2.25	29.32 ± 2.16	31.53 ± 2.06	31.99 ± 2.12
Percentage of normal slow waves (%)				
Fasting	85.6 ± 3.4	81.4 ± 3.0	82.1 ± 3.0	83.1 ± 3.1
Postprandial				
1st 30 min	78.8 ± 3.2	78.9 ± 3.1	75.9 ± 3.3	77.5 ± 3.0
2nd 30 min	78.5 ± 3.3	76.5 ± 3.2	73.4 ± 3.1	72.8 ± 3.1

Effects of TEA on plasma NPY and motilin levels

Chronic TEA but not sham-TEA increased plasma NPY concentration. The fasting plasma NPY level indicated a significant main effect of treatment (df = 1, $F = 4.523$, $P = 0.04$), a significant main effect for the group factor (df = 1, $F = 12.682$, $P = 0.02$), and no significant interaction effect between treatment and group membership (df = 1, $F = 1.386$, $P > 0.05$). The fasting plasma NPY level was 53.94 ± 7.33 pg mL^{-1} at baseline and increased to 99.45 ± 13.52 pg mL^{-1} ($t = 3.054$, $P = 0.01$) after the 2-week TEA treatment. There was no difference in the fasting plasma NPY level before and after the 2-week sham-TEA treatment (65.75 ± 8.50 *vs* 60.67 ± 12.51 pg mL^{-1}, $P > 0.05$).

Neither chronic TEA nor sham-TEA showed any effects on the plasma fasting motilin level. The plasma fasting motilin level indicated neither significant main effect of treatment ($F = 1.628$, $P > 0.05$) nor significant main effect for the group factor ($F = 3.292$, $P > 0.05$), and no difference was noted before and after the 2-week TEA or sham-TEA treatment: TEA: 148.67 ± 15.40 *vs* 147.23 ± 15.89 pg mL^{-1}, $P > 0.05$, sham-TEA: 169.67 ± 21.71 *vs* 145.90 ± 21.02 pg mL^{-1}, $P > 0.05$.

DISCUSSION

In this study, we found that TEA at the acupoints of ST36 and PC6 improved dyspepsia symptoms in patients with FD after a chronic treatment and also solely improved abdominal bloating. Acute and chronic TEA increased HF HRV, but did not affect gastric myoelectrical activity.

Acupuncture or electroacupuncture has been used to treat the symptoms of upper abdomen, such as nausea and vomiting. Hu *et al.*[15] reported that electroacustimulation at point PC6 reduced significantly the severity of the symptoms of motion sickness. The number of emetic episodes induced by morphine[16] or cyclophamide[17] was significantly reduced by electrical acupuncture at the PC6 point in ferrets. Electroacupuncture at both the PC6 and the ST36 points reduced the incidence of vomiting induced by vasopressin in dogs.[18] A few papers reported the effect of acupuncture or electroacupuncture on dyspeptic symptoms in patients with FD. In one study with FD patients, acupuncture was demonstrated to be effective in reducing dyspeptic symptoms.[19] Xu *et al.*[6] found that electroacupuncture at the ST36 and PC6 point improved dyspeptic symptoms in patients with FD.

While electroacupuncture has been proven effective in treating certain functional gastrointestinal diseases, the insertion of acupuncture needles is required and the treatment has to be done at a doctor's office. The method proposed in this study, TEA, did not require the insertion of any needles and the procedure could be by the patient at his/her home. This is more attractive than electroacupuncture and was well accepted by the patients as the compliance of the therapy was 100%; none of the patients quitted the study. It is similar to transcutaneous electrical nerve stimulation except that the stimulation electrodes in this study were placed on the acupuncture points related to the targeting disorder. To the best of our knowledge, this was the first study investigating the efficacy of TEA for the treatment of FD.

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Electrogastropgraphy has previously been shown to be an accurate and reliable method for studying gastric myoelectrical activity. Several studies have reported EGG abnormalities in FD patients.[20,21] Meanwhile, it is known that electroacupuncture may affect the gastric myoelectrical activity. A number of studies have investigated the effect of electroacupuncture on the gastric slow waves. Ouyang *et al.*[5] showed that electroacupuncture at ST36 and PC6 increased the regularity of gastric slow waves in both the proximal and distal stomach. Chang *et al.*[7] found that electrical stimulation at ST36 increased the percentage of normal EGG frequency and decreased the percentage of tachygastrial frequency in diabetic patients. Electroacupuncture at ST36 and PC6 increased the percentage of regular slow waves, resulting in the normalization of dysrhythmia in healthy human.[22] However, the results of this study showed that TEA at ST36 and PC6 points did not change the EGG parameters in the patients with FD, suggesting that TEA may not treat disorders induced by gastric myoelectrical disturbances. The lack of efficacy in normalizing gastric slow waves noted in this study could be attributed to the indirect stimulation of acupuncture points without insertion of needles.

Altered HF and LF/HF HRV in patients with FD have been previously reported.[23,24] It has been proposed that the autonomic dysfunctions could play a role in the development of disturbed gastric motility and perception. Spectral analysis of the HRV is a non-invasive and simple method for the quantitative evaluation of autonomic activity.[25,26] We used this method to evaluate the effect of TEA on HRV in patients with FD and found a significant increase in HF and a significant decrease in LF/HF after the TEA treatment. This result is in good agreement with others reported by Ouyang *et al.*[5] and Tatewaki *et al.*[27] In the acute experiment, TEA was applied during the first 30-min postprandial period and there was an increase in HF HRV during the corresponding time period. In the chronic arm of the study, TEA was performed in the fasting state daily and it increased the HF HRV in the fasting state. Although we have no proof that this is responsible for the improvement in dyspeptic symptoms, it is consistent with the hypothesis that the visceral effects of TEA are at least partially mediated by the autonomic nerve pathway.

To study possible involvement of certain neuropeptides, we assessed plasma NPY and motilin before and after TEA. Neuropeptide Y is a 36 amino acid peptide produced in the central, sympathetic and enteric nervous system.[28] The physiological role of NPY includes the inhibition of stimulated intestinal and pancreatic exocrine secretions and the inhibition of gastrointestinal motility. Neuropeptide Y is also a powerful stimulant of food intake and acts via vagal mechanisms.[29] A significant increase in plasma NPY levels was noted after the TEA treatment; it is speculated that NPY might be involved in the effects of TEA on the dyspeptic symptoms and vagal activity. Motilin is a 22 amino acid polypeptide, secreted from endocrine cells of the small intestinal mucosa, and stimulates the contraction of smooth muscle in the gastrointestinal tract.[30] In our study, the plasma motilin levels were not altered by the TEA treatment. However, the insignificance in the alteration of motilin could be attributed to the fact that motilin was measured in the fasting state and its level is known to be associated with the phase III of the migrating motor complex. In the present study, the blood samples were taken during an unknown phase of the migrating motor complex.

In summary, TEA at ST36 and PC6 significantly improves dyspeptic symptoms and increases HF HRV but does not improve gastric slow waves in patients with FD. The effect of TEA treatment may be associated with the modulation of NPY, not unlikely motilin. This non-invasive and easy-to-implement method of TEA may be a potential therapy for treating dyspeptic symptoms in FD patients.

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