

Clinical trial: acupuncture vs. doubling the proton pump inhibitor dose in refractory heartburn

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SUMMARY

Background

The current standard of care in proton pump inhibitor failure is to double the proton pump inhibitor dose, despite limited therapeutic gain.

Aims

To determine the efficacy of adding acupuncture vs. doubling the proton pump inhibitor dose in gastro-oesophageal reflux disease patients who failed symptomatically on proton pump inhibitors once daily.

Methods

Thirty patients with classic heartburn symptoms who continued to be symptomatic on standard-dose proton pump inhibitors were enrolled into the study. All participants underwent upper endoscopy while on proton pump inhibitors once daily. Subsequently, patients were randomized to either adding acupuncture to their proton pump inhibitor or doubling the proton pump inhibitor dose over a period of 4 weeks. Acupuncture was delivered twice a week by an expert.

Results

The two groups did not differ in demographic parameters. The acupuncture + proton pump inhibitor group demonstrated a significant decrease in the mean daytime heartburn, night-time heartburn and acid regurgitation scores at the end of treatment when compared with baseline, while the double-dose proton pump inhibitor group did not demonstrate a significant change in their clinical endpoints. Mean general health score was only significantly improved in the acupuncture + proton pump inhibitor group.

Conclusion

Adding acupuncture is more effective than doubling the proton pump inhibitor dose in controlling gastro-oesophageal reflux disease-related symptoms in patients who failed standard-dose proton pump inhibitors.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a chronic, persistent and common medical problem. Population-based studies demonstrate that 44% of the adult population in the USA report GERD-related symptoms (heartburn and/or regurgitation) at least once a month and 20% once a week.^{1, 2}

Proton pump inhibitors (PPIs) provide the highest rate of oesophageal mucosal healing and relief from a variety of GERD-related symptoms. Consequently, PPI once a day has become the mainstay of treatment for many patients with GERD. However, recent studies have demonstrated that between 25% and 42% of GERD patients who are treated with standard-dose PPI will continue to report GERD-related symptoms.³ In fact, PPI failure has become one of the most common reasons for GERD-related visits in gastrointestinal (GI) practice.

While doubling the PPI dose is currently considered the standard of care in these patients, the proper therapeutic approach in PPI failure remains to be elucidated.⁴ This is compounded by the fact that only 20%–25% of the PPI-failure patients demonstrate significant improvement in their symptoms after doubling the PPI dose.⁵ A variety of underlying mechanisms have been proposed to be responsible for patients' failure to respond to PPI once daily. They include duodeno-gastro-oesophageal reflux, weakly acidic reflux, visceral hyperalgesia, delayed-gastric emptying and others.^{6–8} Regardless of the underlying cause, studies have clearly showed that most patients who failed PPI once daily originate from the non-erosive reflux disease (NERD) group, primarily from those with normal oesophageal acid exposure (functional heartburn according to Rome II criteria).⁹

The last decade has seen a growing interest in complementary and alternative medicine techniques, especially among patients with chronic medical disorders. In one study, GERD patients who reported daily acid regurgitation were six times more likely to resort to alternative medicine approaches, such as acupuncture, aromatherapy, chiropractic, homeopathy, hypnotherapy and reflexology than those without acid regurgitation.¹⁰ Acupuncture has been utilized in various gastrointestinal disorders demonstrating a significant effect on acid secretion, gastrointestinal motility, neurohormonal levels and sensory thresholds for pain.^{11–22}

Because the majority of patients who failed standard-dose PPI belong to the NERD group, we hypo-

thesized that adding acupuncture to PPI once a day will have a better effect on GERD-related symptoms than doubling the PPI dose in patients who continued to be symptomatic on standard-dose PPI. Therefore, the aim of this trial was to test the efficacy of adding acupuncture vs. doubling the PPI dose in controlling symptoms and improving health-related quality of life parameters in patients with GERD who failed to respond symptomatically to once-daily PPI.

PATIENTS AND METHODS

Patients

Thirty adult patients (age > 18 years) with a 3-month history of GERD-related symptoms at least 2 days per week while taking standard-dose PPI (omeprazole 20 mg once daily) were enrolled into the study. All eligible patients reported some improvement in their GERD-related symptoms while on PPI therapy. Patients were referred by gastroenterologists from the gastroenterology out-patient clinic at the Southern Arizona VA Health Care System and the University of Arizona Health Sciences Center.

Patients were excluded if they had diabetes mellitus, scleroderma, severe co-morbidity, gastroparesis, active peptic ulcer disease, history of gastrointestinal surgery, use of narcotics, benzodiazepines, tricyclic antidepressants, selective serotonin re-uptake inhibitors or calcium channel blockers. Patients with atypical or extra-oesophageal manifestations of GERD, incapable of providing informed consent and unable to fully complete all phases of the study were excluded as well. Patients demonstrating erosive oesophagitis, Barrett's oesophagus or other GERD complications during upper endoscopy while on PPI once daily were also excluded. Women were required to be non-pregnant, -lactating and on a medically acceptable form of birth control. This study was approved by the Human Subject Committee of the University of Arizona.

Study design

This was a randomized, single site, age-, sex-, and BMI-matched, parallel-group trial. All patients provided written informed consent before enrollment into the study. The study duration was 5 weeks and consisted of a 1-week baseline symptom-assessment period, during which patients documented their GERD-

related symptoms while on PPI once a day (omeprazole 20 mg) using a daily GERD-symptoms diary. Patients continued to the next phase of the study if their symptom frequency was consistent with the inclusion criteria. Subsequently, patients were randomized to either omeprazole 20 mg b.d. or omeprazole 20 mg once daily and acupuncture. Patients were randomized to the two treatment arms using a stratified block randomization scheme. The group of patients who were receiving double-dose PPI were instructed to take the study medication (omeprazole 20 mg) 30 min before breakfast and 30 min before dinner. Symptoms were assessed daily, using a daily GERD symptoms diary.

Prior to randomization, patients filled the GERD Symptom Checklist and the Short Form-36 (SF-36), a validated, general and health-related quality of life questionnaire. At the end of 4 weeks of treatment, patients completed the SF-36 survey again. Patients were evaluated daily throughout the treatment period for severity and frequency of GERD symptoms by using a GERD symptoms diary.²³

Study visits

All participating subjects underwent personal interview by a single physician (D. R.) prior to enrollment into the study. Subsequently, patients were seen by the research team at the beginning and end of the baseline period and end of the second and fourth weeks of the study for collection of symptom diaries and pill count. Additionally, patients were instructed to provide their best assessment of their symptoms during baseline and treatment period when they fill the daily GERD symptom diary. Heartburn was defined as a burning feeling rising from the stomach or lower part of the chest towards the neck. Night-time heartburn was defined as heartburn that awoke the patient from sleep during the night. Regurgitation was defined as the effortless upward movement of gastric content into the oesophagus or oropharynx (sour/bitter taste).

Upper endoscopy

All eligible patients who gave their informed consent underwent a diagnostic evaluation with an upper endoscopy after an overnight fast to assess the mucosal abnormalities in the oesophagus, stomach and first portion of the duodenum. The extent of oesophageal

inflammation was determined by using the Los Angeles Classification. Upper endoscopy was performed in all patients while receiving omeprazole 20 mg once daily at the end of the baseline period.

GERD symptom checklist

All patients were evaluated by the validated GERD Symptom Checklist that assesses the occurrence of typical and atypical GERD symptoms.²⁴ The GERD Symptom Checklist evaluates the four main characteristics of GERD symptoms: duration (years), frequency (per week or month), severity (using 0–4 scale: 0 = none, 1 = mild, can be ignored if I don't think about it, 2 = moderate, cannot be ignored but does not affect my life style, 3 = severe, affects my life style, 4 = very severe, markedly affects my life style) and intensity (frequency x severity).

SF-36

Quality of life was assessed at baseline and at the end of treatment period (week 4). The SF-36 was constructed to evaluate health status and was designed for using in clinical practice, research, health policy evaluations and the general population.²⁵ This questionnaire includes a multi-item scale that assesses eight health-related domains: physical functioning, role-physical, bodily pain, general health, mental health, vitality, social functioning and role-emotional. Each SF-36 domain is measured on a scale from 0 to 100, and a 5-point difference in SF-36 score represents a 5% difference in health status. A difference in SF-36 score of 5 points or greater is considered significant.

Daily GERD symptoms diary

Patients kept a daily record of the frequency and severity of each GERD-related symptom they experienced. Symptoms such as daytime heartburn, night-time heartburn, difficulty swallowing (dysphagia), acid regurgitation and chest pain were evaluated.²³ The following scale was used to determine the severity of each symptom: mild = symptom easily tolerated and did not last long; moderate = symptom caused some discomfort but did not interfere with usual activities; severe = symptom caused much discomfort and interfered with usual activities; and disabling = symptom unbearable and interfered considerably with usual activities.

Symptom score was calculated by adding the reported daily severity (mild, 1; moderate, 2; severe, 3; and disabling, 4) multiplied by the reported daily frequency values as obtained during each week of symptom recording²³.

Acupuncture

The Traditional Chinese Medicine (TCM) assessment and intervention used in this study were developed according to both TCM texts and MEDLINE.^{26–29} Treatment protocol was established according to a literature search and a consensus among three experienced traditional acupuncturists (A. H., C. W. and E. S.). The treatment protocol was based on the most common TCM patterns or a combination of symptoms and signs pertaining to the symptom of ‘heartburn’.

The acupuncture protocol consisted of five acupuncture points according to the TCM pattern diagnosis (Figure 1). Acupuncture points were selected primarily to ‘calm’ and ‘regulate’ the stomach from a TCM perspective. From a biomedical perspective, this may translate to regulation of acid secretion and gastric motility. The points used for this function were: (i) Per.6 Neiguan – located two cun (a unit of relative distance used in acupuncture) proximal to the wrist crease, between the tendons of the muscles palmaris longus and flexor carpi radialis, 0.5–0.8 cun depth; (ii) St.36 Zusanli – located one cun lateral to the tibial tubercle, 0.5–1.2 cun depth. (iii) Liv.3 Taichong – on the dorsum of the foot in a depression distal to the junctions of the 1st and 2nd metatarsal bones, 0.5–0.8 cun depth; (iv) CV12 Zhangwan – midway between the umbilicus and xiphoid process, 0.3–0.5 cun depth; (v) CV17 Shan Zhong – on the sternum (level of the 4th intercostal space), 0.2–0.3 cun depth. If the pattern diagnosis included any characteristic of ‘dampness’ according to TCM terminology, such as history of loose stools or diarrhoea and sensation of epigastric heaviness, an additional point was added: (vi) Sp.9 Yinlingquan – on the lower border of the medial condyle of the tibia in the depression posterior and inferior to the medial condyle of the tibia, 0.5–1.0 cun depth.

Treatment consisted of 10 acupuncture sessions (25 min each) over 4 weeks. In the first 2 weeks, acupuncture was administered three times a week, usually every other day. During the last 2 weeks, acupuncture was administered twice a week, usually 3 days apart. The practitioners who performed the acupuncture treatments (W. C and H. A), according to the treatment

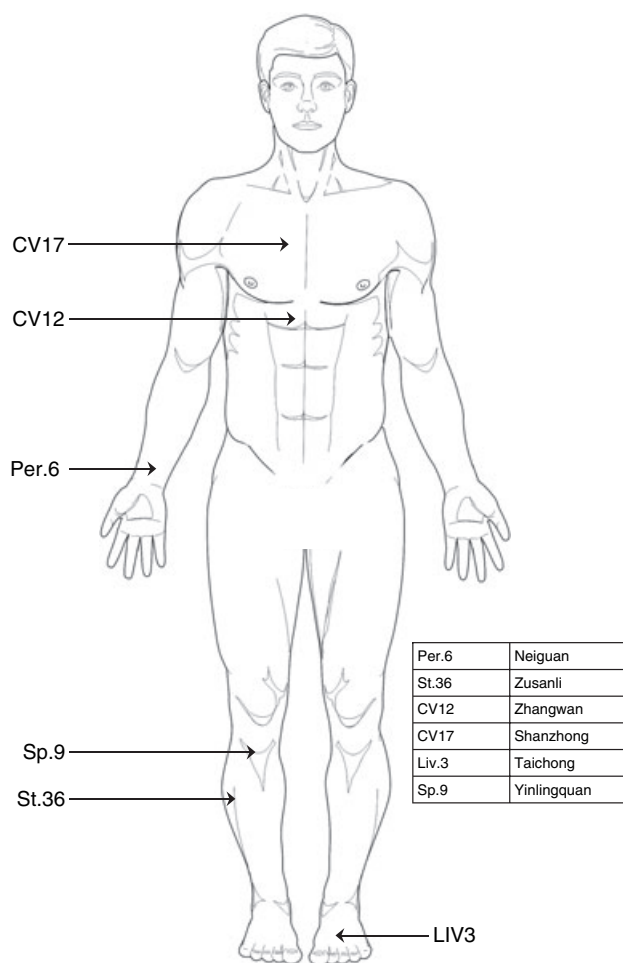


Figure 1. Traditional Chinese Medicine acupuncture points used in the treatment protocol.

protocol of this study, had more than 5 years of clinical experience.

Patients randomized to the acupuncture group were given information and informed consent was obtained from them regarding the risks and benefits of acupuncture therapy. They were also told to expect a unique needle sensation termed ‘de qi’ (a heavy, aching sensation around the needle) during needling. Patients were instructed to have a light meal at least 2 h before the acupuncture to minimize the unpleasant side-effects of light-headedness or nausea. Patients were also informed that there would be minimal practitioner–patient interaction to isolate the effect of the acupuncture *per se*. The practitioner then conducted a thorough TCM evaluation. The decision to include or omit the additional point yinlingquan (SP.9) was based on this assessment. The patient was then taken to a

quiet treatment room and placed in a supine position on a massage-type table. The point locations were swabbed with 70% isopropyl alcohol (according to clean needle technique standards), and each needle was inserted and stimulated until the patient reported 'de-qi'. The patient was then left alone, except for additional needle stimulation every 5 min. Needle retention time totaled 20 min. All needles were inserted bilaterally, except CV.17 and CV.12, using Carbo 0.20 gauge needles; length depended on body size, and varied from 30 to 40 mm. Needling depth was guided according to 'de-qi'. We used 'even' method needle stimulation (not applying the reducing or tonifying methods). On subsequent visits, the patient was taken back to the treatment room with minimal patient-provider interaction, and the above procedure was repeated.

Tolerability and safety assessments

Adverse events were recorded during treatment by patient's report, investigator evaluation during patient's visits and by the practitioners who performed the acupuncture treatments.

Statistical analysis

Statistics was calculated using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). To test for differences in demographic characteristics, chi-squared tests of independence and *t*-tests were used. To test for mean differences in each diary symptom and SF-36 domains, descriptive statistics was tabulated, and mixed design ANOVAS were performed (within-subjects factor, time of assessment; between-subjects factor, group). Significant main effect and interactions were subsequently analysed using *post hoc t*-tests with pooled error terms. The resultant probabilities were adjusted using a Bonferroni procedure to protect against Type I errors.

The SF-36 survey was analysed by chi-squared tests of independence to determine whether the proportion of individuals reporting improved scores differed between the two groups. Change scores were rated as 1 if the measure at week 4 exceeded that at baseline. If the scores were the same on both occasions or if the score at baseline was higher than that for week 4, then the change score was given a value of 0. We then did a test of independence comparing the proportion of change scores (1 or 0) for the two groups.

RESULTS

A total of 30 patients were enrolled, and all completed the different stages of the study. Fifteen patients received double-dose PPI (twice a day) and 15 patients received standard-dose PPI (once a day) and acupuncture. All patients had a normal oesophageal examination during upper endoscopy while on standard-dose PPI.

Demographic characteristics were similar between the two groups of patients (Table 1). The majority of the patients were male (63%) and Caucasian (80%). There were no significant age [$t(28) = -1.084$, $P = 0.288$], gender [chi-squared of independence: (1) = 0.144, $P = 0.705$] or ethnicity [chi-squared of independence: (2) = 1.200, $P = 0.549$] and BMI [$t(28) = -0.313$, $P = 0.757$] differences between the two groups of patients.

Symptom assessment at baseline

Because the number of individuals reporting 'rarely' was so small in each of the three symptom categories (heartburn, regurgitation or chest pain), the category was combined with 'weekly' to create a new category 'weekly or less often'. Table 2 summarizes the comparison of heartburn, regurgitation and chest pain characteristics at baseline between the two groups of patients. Chi-squared tests were carried out for baseline responses with respect to presence of heartburn, regurgitation and chest pain symptoms to determine the equivalence of the two groups (Table 2). None of the analyses was statistically significant.

Table 1. Patient characteristics at baseline

	High-dose PPI	Acupuncture + PPI	<i>P</i> -value
Subjects (<i>n</i>)	15	15	
Age (\pm SD)	48.9 \pm 8.11	52.7 \pm 10.8	0.288
Range (years)	39–62	38–65	
Sex (M/F)	10/5	9/6	0.705
Ethnicity (%)			
Caucasian	80	80	
Hispanic	13	20	0.549
African-American	7	0	
BMI	31.4 \pm 8.7	32.3 \pm 6.2	0.757

PPI, proton pump inhibitor; BMI, body mass index.

Table 2. (a) Comparison of heartburn, acid regurgitation and chest pain characteristics at baseline between the two groups of patients. (b) Comparison of baseline heartburn, acid regurgitation and chest pain symptoms between the two groups of patients

	Double-dose proton pump inhibitor (PPI)/ <i>n</i> = 15 (%)	Acupuncture + PPI <i>n</i> = 15 (%)	
(a)			
Heartburn			
Heartburn (% yes)	73	87	
Duration (% >5 years)	73	93	
Frequency			
% Daily	33	40	
% Weekly	47	60	
% Rarely (>monthly)	20	0	
Severity (% severe or very severe)	47	40	
Intensity score	13	18	
Regurgitation			
Regurgitation (% yes)	87	100	
Duration (% >5 years)	60	73	
Frequency			
% Daily	67	13	
% Weekly	73	80	
% Rarely (>monthly)	20	67	
Severity (% severe or very severe)	47	60	
Intensity score	9	15	
Chest pain			
Chest pain (% yes)	73	73	
Duration (% >5 years)	47	80	
Frequency			
% Daily	13	27	
% Weekly	47	60	
% Rarely (>monthly)	40	13	
Severity (% severe or very severe)	40	33	
Intensity score	6	7	
Symptom	d.f.	χ^2	<i>P</i> -value
(b)			
Heartburn			
Presence (yes/no)	1	0.833	0.361
Duration >5 years (yes/no)	1	2.160	0.142
Severe or very severe (yes/no)	1	0.136	0.712
Frequency (daily vs. weekly or more)	1	0.144	0.705
Regurgitation			
Presence (yes/no)	1	2.143	0.143
Duration >5 years (yes/no)	1	0.600	0.439
Severe or very severe (yes/no)	1	0.536	0.464
Frequency (daily vs. weekly or more)	1	0.370	0.543
Chest pain			
Presence (yes/no)	1	0.000	1.000
Duration >5 years (yes/no)	1	3.588	0.058
Severe or very severe (yes/no)	1	0.144	0.705
Frequency (daily vs. weekly or more)	1	0.833	0.361

Symptom assessment during treatment

For analysis here, the alpha level was adjusted to 0.0125 using a Bonferroni procedure. Within-group comparisons revealed that patients in the acupuncture + PPI group demonstrated a significant decrease in the mean daytime heartburn, night-time heartburn, acid regurgitation, dysphagia and chest pain scores from baseline to week 4 (Table 3), (Figures 2–6). By way of comparison, *post hoc* tests revealed that the double-dose PPI group showed no significant difference in the mean score of any variable from baseline

to week 4 (Table 3). No group differed significantly at baseline (Table 3). At the final assessment, the acupuncture group showed significantly lower scores for daytime and night-time heartburn. (Table 3)

Quality of life assessment

Table 4 presents the means and SD of the SF-36 domains scale scores for the two treatment groups at baseline and at week 4. The mean scores for the acupuncture + PPI group were higher at week 4 than at baseline, although the SD of the scores are large relative

Table 3. (a) Time effect on symptoms assessment within the acupuncture + proton pump inhibitor (PPI) group (*post hoc t*-tests). (b) Time effect on symptoms assessment within the double-dose PPI group (*post hoc t*-tests). (c) Comparison of symptoms assessment between groups at baseline. (d) Comparison of symptoms assessment between groups at week 4

Symptom	Baseline	Week 4	P-value
Acupuncture + PPI			
(a)			
Daytime heartburn	18.333 ± 1.816	3.267 ± 1.632	<0.001
Night-time heartburn	18.067 ± 1.694	3.600 ± 1.305	<0.001
Acid regurgitation	14.867 ± 2.226	3.733 ± 1.712	<0.001
Dysphagia	6.600 ± 2.267	2.933 ± 1.996	0.007
Chest pain	7.200 ± 1.813	1.267 ± 1.529	0.006
Double-dose PPI			
(b)			
Daytime heartburn	12.867 ± 1.816	16.400 ± 1.632	0.030
Night-time heartburn	12.800 ± 1.694	15.667 ± 1.305	0.065
Acid regurgitation	8.933 ± 2.226	7.400 ± 1.712	0.299
Dysphagia	6.333 ± 2.267	7.200 ± 1.996	0.495
Chest pain	6.000 ± 1.813	5.800 ± 1.529	0.920
Double-dose PPI		Acupuncture + PPI	
(c)			
Daytime heartburn	12.867 ± 1.816	18.333 ± 1.816	0.042
Night-time heartburn	12.800 ± 1.694	18.067 ± 1.694	0.036
Acid regurgitation	8.933 ± 2.226	14.867 ± 2.226	0.070
Dysphagia	6.333 ± 2.267	6.600 ± 2.267	0.934
Chest pain	6.000 ± 1.813	7.200 ± 1.813	0.643
(d)			
Daytime heartburn	16.400 ± 1.632	3.267 ± 1.632	<0.001
Night-time heartburn	15.667 ± 1.305	3.600 ± 1.305	<0.001
Acid regurgitation	7.400 ± 1.712	3.733 ± 1.712	0.141
Dysphagia	7.200 ± 1.996	2.933 ± 1.996	0.142
Chest pain	5.800 ± 1.529	1.267 ± 1.529	0.045

$\alpha = 0.0125$, *P*-value compares baseline to week 4.

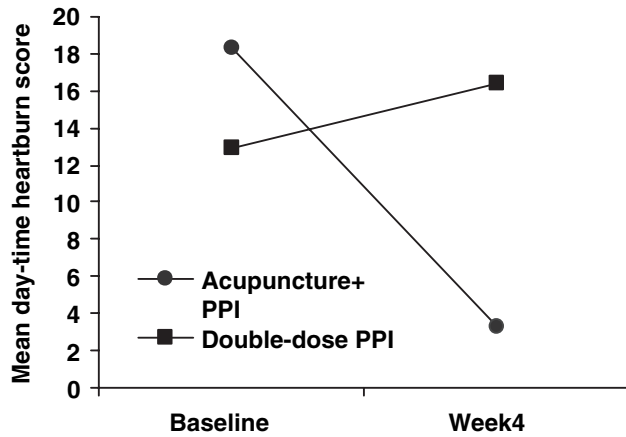


Figure 2. Comparison of mean day-time heartburn score between the two patient groups (within groups comparison – for acupuncture + PPI – $P < 0.001$; for double-dose PPI $P = NS$; between groups comparison – $P < 0.001$).

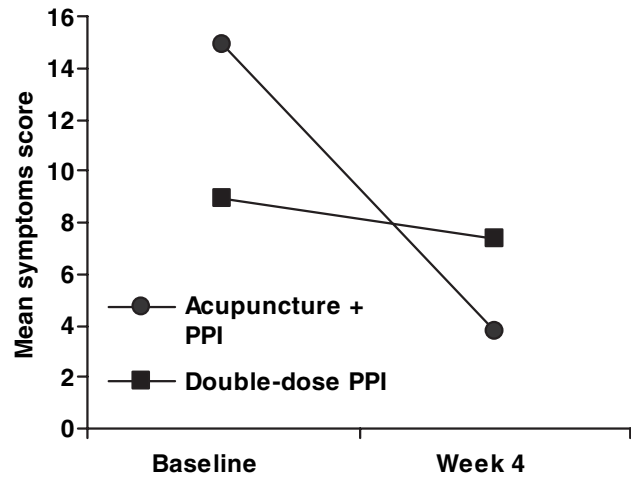


Figure 4. Mean acid regurgitation score between groups (within groups comparison: for acupuncture + PPI – $P < 0.001$; for double-dose PPI $P = NS$; between groups comparison – $P = NS$).

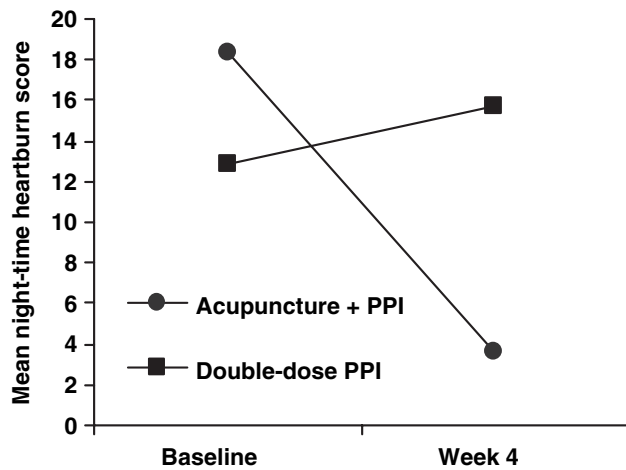


Figure 3. Mean night-time heartburn score between the two patient groups (within groups comparison: for acupuncture + PPI – $P < 0.001$; for double-dose PPI $P = NS$; between groups comparison – $P < 0.001$).

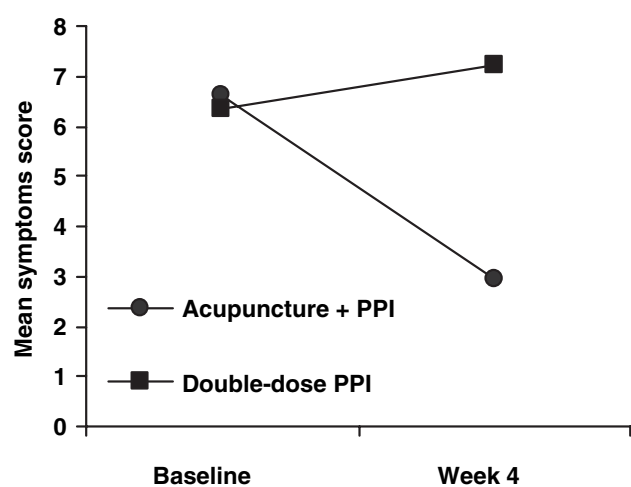


Figure 5. Mean dysphagia score between groups (within groups comparison: for acupuncture + PPI – $P < 0.001$; for double-dose PPI $P = NS$; between groups comparison – $P = NS$).

to the size of the mean for each domain. Mean scores for the double-dose PPI group typically remained about the same or fell, with the exception of Physical and Social Function, which both improved slightly. (again, the SD were large for both baseline and week 4.)

Mixed design ANOVAS were non-significant for all main effects and interactions for all variables with the exception of General Health, for which the time–group interaction was significant [$F_{(1,28)} = 5.86, P = 0.022$].

The acupuncture + PPI group mean changed from 46 to 55, while the double-dose PPI group mean changed from 44 to 42. The significant interaction effect can be interpreted as showing that the change for the acupuncture + PPI group was significantly higher than that of the high-dose PPI group. There was also a significant group effect for vitality; the average vitality score (across both time periods) was significantly higher for the acupuncture group than for the double-

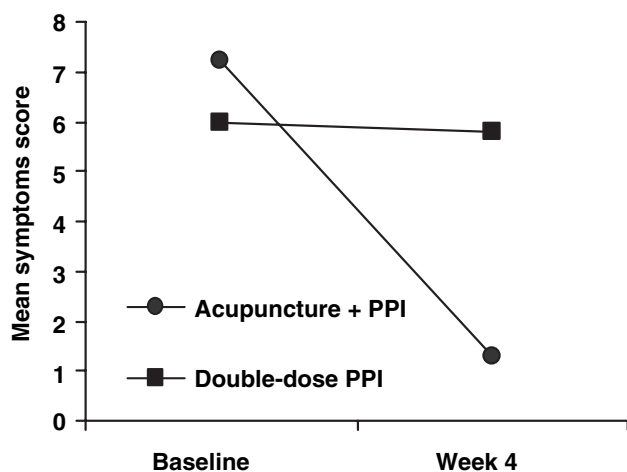


Figure 6. Mean chest pain score between groups (within groups comparison: for acupuncture + PPI $P < 0.001$; for double-dose PPI $P = \text{NS}$; between groups comparison $- P = \text{NS}$).

dose PPI group. Because there was no differential change across groups, the difference in vitality scores appears to be unrelated to the treatment. No other effects were significant; however, the lack of statistical effect is almost certainly because of the very large variability within groups. If the mean differences are real, a larger sample size would be required to find these differences statistically significant.

The chi-squared tests for bodily pain [chi-squared (1) = 5.40, $P = 0.020$] and general health [chi-squared (1) = 5.00, $P = 0.025$] were significant. In the case of bodily pain, the proportion of individuals reporting improvement to no improvement was 8:7 in the acupuncture + PPI group vs. 2:13 in the double-dose PPI group. For general health, the comparable ratios were

12:3 in the acupuncture group vs. 6:9 in the high-dose PPI group.

Tolerability and safety assessments

Acupuncture treatment was completed in all patients. One patient (7%) reported a mild wrist pain that resolved within 2 weeks with no additional interventions. This patient completed the study and continued to receive acupuncture treatments for GERD-related symptoms even after the end of the study with no additional side-effects.

DISCUSSION

Proton pump inhibitor failure in GERD patients represents an important diagnostic and therapeutic dilemma for the practicing clinician. Furthermore, doubling the PPI dose, which has become the standard of care, appears to improve the symptoms in only a modest number of GERD patients who failed PPI once daily.¹¹ While various mechanisms have been suggested to contribute to PPI failure, the proper therapeutic approach in this situation remains to be elucidated.

The primary goal of our study was to evaluate the efficacy of an alternative/complementary therapeutic approach in GERD patients who failed standard-dose PPI. In this study, we were able to show for the first time that therapeutic intervention in the form of acupuncture was more efficacious than adding a second PPI in controlling residual symptoms of patients who failed PPI once daily.

Acupuncture resulted in a significant improvement in daytime heartburn, night-time heartburn and acid

Table 4. Comparison of SF-36 scale scores (mean \pm SD) between the two groups of patients at baseline and at the end of treatment period (week 4)

SF-36 domains	Acupuncture + proton pump inhibitor (PPI)		Double-dose PPI	
	Baseline	Week 4	Baseline	Week 4
Physical function	58.0 \pm 30.4	69.7 \pm 19.8	48.7 \pm 30.1	50.3 \pm 28.0
Role physical	41.7 \pm 41.9	66.7 \pm 46.0	41.7 \pm 45.0	40.0 \pm 44.1
Bodily pain	49.5 \pm 30.2	57.0 \pm 31.1	45.8 \pm 17.9	40.9 \pm 19.3
General health	45.7 \pm 15.5	55.0 \pm 18.0	43.8 \pm 14.8	41.9 \pm 20.0
Vitality	51.3 \pm 23.8	51.0 \pm 23.4	34.7 \pm 20.4	32.0 \pm 19.3
Social function	59.2 \pm 32.6	66.7 \pm 34.0	57.5 \pm 28.7	61.7 \pm 26.9
Role emotional	64.4 \pm 36.7	71.1 \pm 43.4	51.1 \pm 45.2	51.1 \pm 39.6
Mental health	68.8 \pm 22.1	70.7 \pm 22.8	61.9 \pm 24.4	60.0 \pm 21.4

regurgitation when compared with doubling the PPI dose. Interestingly, the effect of acupuncture was noted after only 10 sessions of treatment.

The mechanism by which acupuncture improves GERD-related symptoms reported by GERD patients remains to be elucidated. Numerous studies have demonstrated that acupuncture may suppress gastric acid secretion in both humans and animals.³⁰ Acupuncture was shown to lower the maximal acid output in patients with peptic ulcer disease¹⁴ and the basal acid output in healthy volunteers.¹⁵ The inhibitory effect of acupuncture on gastric acid secretion was found to be mediated by interconnected neural and humoral pathways.³⁰ However, it is unlikely that suppression of gastric acid secretion is the main reason for the superiority of acupuncture over doubling the PPI dose in controlling the refractory heartburn. Studies have shown that the majority (60%–70%) of patients who failed PPI once a day demonstrated normal oesophageal acid exposure during pH testing.^{31, 32} The latter finding may also explain the very limited efficacy of PPI twice daily in refractory GERD patients.

Acupuncture was also found to enhance the gastric peristalsis, as was observed by ultrasonography, and to accelerate gastric emptying in dyspeptic patients with documented delayed-gastric emptying.^{16, 17} Additionally, in uncontrolled trials of patients with systemic sclerosis and achalasia, acupuncture was found to improve oesophageal peristalsis and lower oesophageal sphincter relaxation.¹⁸ Delayed-gastric emptying has been shown to contribute to failure of PPI once daily in controlling GERD-related symptoms.³³ However, it is unclear how common delayed-gastric emptying is in patients who failed PPI once daily. Given the fact that most of the patients who failed PPI once daily originate from the NERD group, who lack any evidence of a significant oesophageal or gastric dysmotility, then it is unlikely that improvement in gastric motor function is the main mechanism for the high-therapeutic efficacy of acupuncture.³⁴

Another mechanism that is more likely to explain the beneficial effect of acupuncture is related to its possible effect on visceral hypersensitivity. In patients with chest pain, acupuncture has been reported to reduce oesophageal pain perception to intra-oesophageal balloon distention.²⁰ As mentioned previously, our patient population most likely originated from the NERD group. This GERD group demonstrated the lowest symptom response rate to PPI once daily³⁴, pri-

marily because of a large subgroup of patients with either mild or normal oesophageal pH testing.⁹ Those with normal pH testing have been shown to demonstrate increased mechano- and partial chemosensor sensitivity to balloon distention or acid perfusion, respectively.^{35, 36} Thus, it is highly likely that acupuncture achieves its effect by modulating visceral sensation in patients who failed PPI once daily. This hypothesis should be further evaluated in the future using studies that will determine the effect of acupuncture on oesophageal sensitivity during oesophageal acid perfusion or balloon distention.

Several recent studies suggested that duodeno-gastro-oesophageal reflux and weakly acidic reflux are important underlying mechanisms for PPI failure.^{7, 8} It is also possible that acupuncture may reduce duodeno-gastro-oesophageal reflux or weakly acidic reflux by unknown mechanisms. Alternatively, acupuncture may modulate oesophageal pain perception and thus neutralize the sensory stimulatory effect of both duodeno-gastro-oesophageal reflux and weakly acidic reflux.

We did not add a sham acupuncture arm to this study because of the increasing recognition in the acupuncture literature that superficial (needling of the skin), sham (needling of non-acupuncture points) and placebo (needling with blunt tip that does not penetrate the skin) acupuncture also provide an active therapeutic effect.³⁷ This is particularly the case in pain conditions that are predominantly associated with an affective component.^{38–40} A recent study demonstrated that a system of slow-conducting unmyelinated (C) afferents responds to light touch.⁴¹ By using functional magnetic resonance imaging, the authors showed that stimulation of C tactile afferents after light touch results in activation of the insular region but not of the somatosensory cortex. Activation of the C tactile afferents results in a 'limbic touch' that may underlie emotional and hormonal responses commonly seen following caressing, for example.⁴¹ Thus, it is likely that control procedures used in many acupuncture studies aimed at being inert may activate the C tactile afferents that alleviate unpleasantness and re-establish patients' sense of well-being.³⁷ Therefore, neither minimal, superficial, sham acupuncture nor placebo needles may be regarded as placebo, because they are not inert.³⁷

Our study included a small number of subjects in each arm. However, because of the profound therapeutic effect of acupuncture and the very limited effect of

PPI twice daily on symptoms report, even our small sample size was able to demonstrate clear superiority of acupuncture in addition to PPI once daily over doubling the PPI dose in GERD patients who failed PPI once daily.

We did not compare acupuncture alone to doubling the PPI dose because all of the patients included in this study demonstrated some response to PPI once a day, albeit incomplete. This study is also closer to the common clinical scenario that many physicians face in their everyday practice where other therapeutic modalities (such as baclofen, sucralfate, tricyclics and others) are commonly added to PPI once daily in patients with GERD who failed PPI once a day. Lastly, this is a short-term study with positive results. However, long-term evaluation of the value of acupuncture in patients who failed PPI once a day is

obviously needed. It is unclear if only one course of treatment is needed to improve patients' symptoms or if subjects may have to undergo treatment on a regular basis.

In conclusion, adding acupuncture when compared with doubling the PPI dose was more effective in controlling the GERD-related symptoms in patients who were unresponsive to standard-dose PPI.

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