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Antihistamine promotes electroacupuncture analgesia in healthy human subjects: A pilot study

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ABSTRACT

Background and aim: We have previously reported that histamine H_1 receptor antagonists facilitate electroacupuncture (EA) analgesia in experimental animals. In this pilot study, we sought to determine whether the histamine H_1 receptor antagonist dexchlorpheniramine (DCPA) facilitates EA analgesia in healthy human subjects.
Experimental procedure: Forty healthy subjects aged 20–30 years were randomly allocated to 1 of 4 groups: (1) sham EA at acupoints Zusanli (ST36) and Yanglingquan (GB34) (sham EA; n = 10); (2) EA at ST36 and GB34 (n = 10); (3) EA at ST36 and GB34 plus low-dose DCPA (2 mg, n = 10); (4) EA at ST36 and GB34 plus high-dose DCPA (4 mg, n = 10). Before and after acupuncture treatment, pain thresholds were determined by transcutaneous electrical stimuli on the glabrous skin of the left upper arm.
Results: After the acupuncture session, subjects in the EA plus high-dose DCPA group had a significantly higher pain threshold elevation compared with the other 3 study groups. The change from baseline in pain threshold in the EA plus high-dose DCPA group was significantly greater than the change in pain threshold with EA only, indicating that DCPA 4 mg facilitated EA analgesia.
Conclusion: The results suggest that combining H_1 receptor antagonist treatment with EA appears to relieve pain to a greater extent compared with EA alone. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/), number NCT03805035 (https://clinicaltrials.gov/ct2/show/NCT03805035).

1. Introduction

Chronic pain, often defined as pain lasting longer than 3–6 months, or beyond the time of normal tissue healing,[1] is widely acknowledged to be associated with enormous social and economic costs.[2] In the USA, for example, an estimated 100 million adults in 2008 were affected by chronic pain, including joint pain or arthritis, and the annual cost of treating and managing chronic pain in the USA was as much as $635 billion in 2010 dollars, exceeding the yearly combined costs of cancer, heart disease, and diabetes.[3] Moreover, chronic pain is associated with impaired physical and

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List of abréviations

EA	electroacupuncture
DCPA	dexchlorpheniramine

mental functioning and reduced quality of life and is a leading cause of disability.[1,4]

Opioid analgesics constitute an important part in the management of chronic pain, but are characterized by a high potential for abuse. The widespread abuse of prescription opioids in the USA has resulted in a national crisis and other countries worldwide are also experiencing significant problems with opioid abuse. US lawmakers and national authorities have called upon healthcare systems to provide nonpharmacologic pain treatment modalities, including acupuncture, as viable alternatives to opioid medications. Good evidence for clinical efficacy is therefore needed for nonpharmacologic pain management therapies, such as acupuncture.[5]

Acupuncture has been used in traditional Chinese medicine for around 3,000 years and is nowadays practiced worldwide. The effects of acupuncture on chronic pain have been investigated in many clinical trials in a wide variety of therapeutic conditions, with substantial evidence supporting its efficacy.[6,7] Many systematic reviews have examined the evidence for the use of acupuncture in the treatment of pain and have reported positive results for the efficacy of acupuncture in the relief of arthritis and low back pain,[8–10] cancer-related pain,[11–13] pediatric pain[14] and postoperative pain.[15] Evidence does not support the use of acupuncture for neuropathic pain[16] or fibromyalgia.[17] In 2011, an overview of reviews reported that overall, acupuncture is not effective in reducing pain,[18] although the methodology of that review has been criticized by several researchers,[19–21] with one of them noting that five out of six good-quality primary studies and systematic reviews showed that acupuncture was effective in pain treatment and one study was positive overall for acupuncture.[20] Thus, the evidence suggests that acupuncture may be effective for several but not all pain conditions.

Recent studies suggest that chronic neuroinflammation in the peripheral and central nervous systems may underpin neuropathic pain and fibromyalgia.[22,23] Abundant preclinical evidence shows analgesic qualities of anti-inflammatory cytokines in inflammatory and neuropathic pain models.[23] Moreover, evidence of brain glial activation in fibromyalgia suggests that glial modulation could be beneficial in this disease.[22] Acupuncture effectively suppresses spinal glial activation in animal models of chronic and neuropathic pain, and its ability to reduce central sensitization suggests that acupuncture is capable of mediating anti-inflammatory responses in chronic and neuropathic pain.[24] Since acupuncture alone does not appear to alleviate fibromyalgia or neuropathic pain,[16,17] combining acupuncture with an anti-inflammatory agent might be an alternative way to treat such pain.

Histamine plays an important role in inflammation modulation, usually with a proinflammatory impact.[25] Although histamine H_1 receptor antagonists are commonly used for treating allergy, we have previously reported that histamine H_1 receptor antagonism facilitates electroacupuncture (EA) analgesia in the acetic acid-induced abdominal pain model.[26] This pilot trial, therefore, sought to determine whether the histamine H_1 receptor antagonist dexchlorpheniramine (DCPA) facilitates EA analgesia in healthy volunteers. We were especially interested in comparing the effects of low- and high-dose DCPA on the modulation of EA-induced treatment efficacy and whether the combination of EA plus high-dose DCPA is superior to the other EA treatments for modulating the pain threshold.

2. Material and methods

2.1. Study design

This study was a prospective, randomized, single-center, parallel-group pilot trial. As a pilot trial, the sample size was determined by matching the numbers of study participants to the numbers of animals in our previous study.[26]

2.2. Participants

All study participants were recruited from China Medical University Hospital, Taichung, Taiwan. The inclusion criteria specified the following conditions: (i) age between 20 and 30 years[27]; good physical health according to medical history and physical examination; (iii) availability for study participation and an ability to comprehend and sign the written informed consent form. The exclusion criteria included: (i) a medical condition requiring active medical intervention or monitoring to avert danger to the participant's health or well-being (e.g., hypertension, diabetes mellitus, epilepsy)[27]; any compromise to the skin barrier (e.g., skin disease, allergy) that would interfere with the conduct of the EA procedure and assessments of the study; (iii) history of drug abuse or psychiatric disorders; (iv) taking allopathic medicine for pain; and (v) pregnancy. This study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the laws and regulations of Taiwan. The study protocol was approved by the Institutional Review Board of China Medical University Hospital, Taichung, Taiwan (CMUH107-REC3-019). The study was conducted in the acupuncture clinic of China Medical University Hospital, Taichung, Taiwan. All subjects received a full explanation of the study and signed written informed consent forms. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03805035).

2.3. Randomization and assessment procedures

Subjects were randomly assigned to one of the following four groups: (1) sham EA alone (n = 10); (2) verum EA alone (n = 10); (3) verum EA plus low-dose DCPA (2 mg, n = 10); or (4) verum EA plus high-dose DCPA (4 mg, n = 10). A computer-generated list of random numbers was used for the allocation of the participants. Each number was printed on a blank page of paper and sealed within an envelope. Subjects were allocated to the treatment group by random selection of the envelopes and none of the participants was advised of their treatment allocation or the dose of DCPA. The pain threshold was assessed before and after the EA session by two blinded independent observers using transcutaneous electrical stimuli (Fig. 1). The assessor of the pain threshold did not know which group the subjects were allocated, i.e. with or without receiving electrical stimulation or anti-histamine.

2.4. Electroacupuncture

A traditional Chinese medicine practitioner provided a brief explanation about the EA procedure for each subject before the intervention. EA was performed in a clinic room by an acupuncturist who had received full Chinese medicine training and had been in active clinical practice in the acupuncture field for at least 4 consecutive years. Each participant received a single 20-min session of EA at acupoints Zusanli (ST36) and Yanglingquan (GB34) in the left leg. Disposable acupuncture needles (0.22 × 30 mm sterile stainless needles) were inserted into the designated acupoints at a depth of 10–30 mm in a direction oblique or parallel to the surface (Fig. 2). Electrical stimulation was generated using an electrical stimulator (TENS HC-0502, Home Care Tech., Tainan, Taiwan). Sham

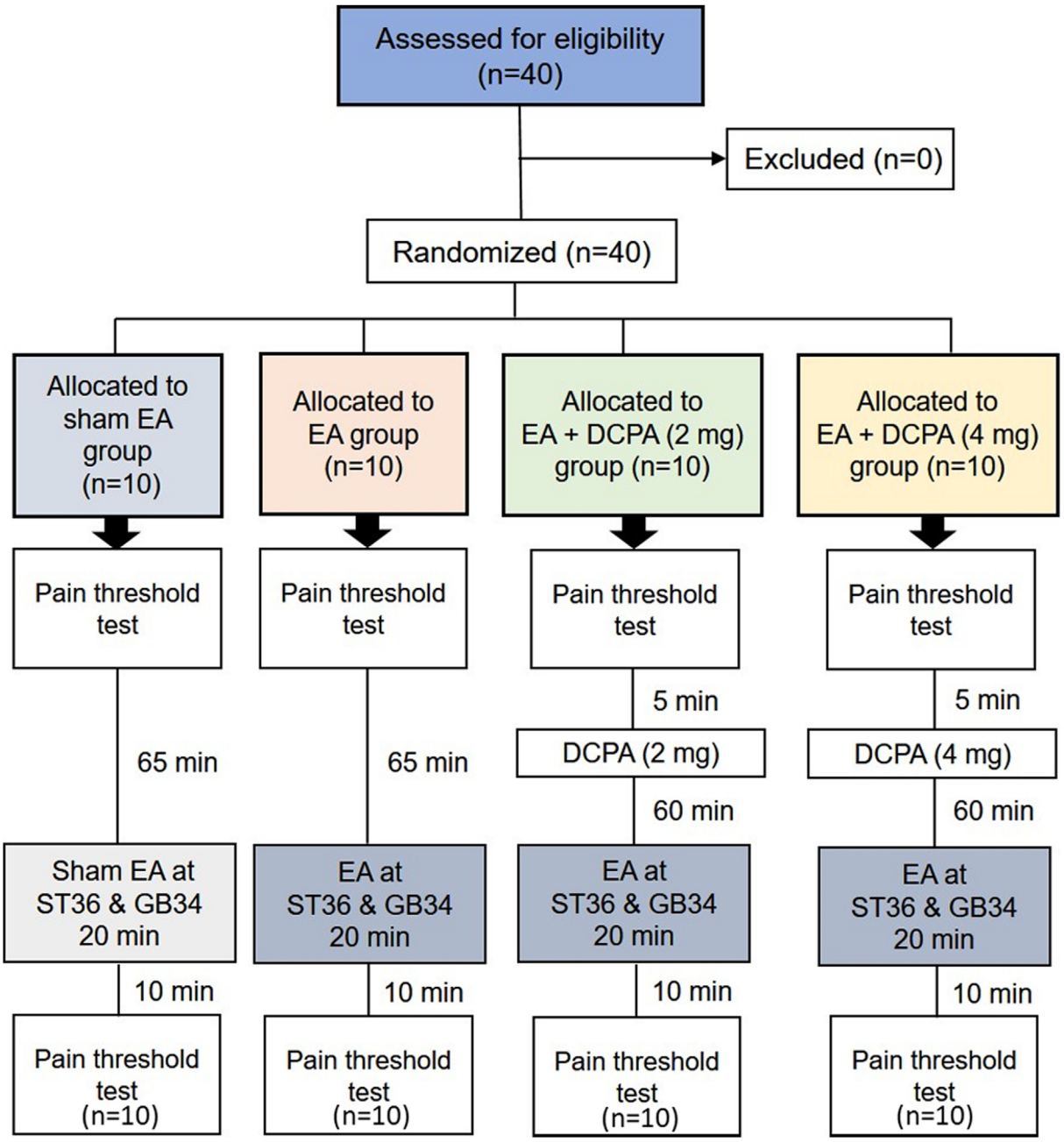

Fig. 1. Flowchart of the pilot trial. Abbreviations: EA, electroacupuncture; DCPA, dexchlorpheniramine; min, minutes.

EA was performed by shallow needling of 1 mm depth and no electrical current was applied. Verum EA involved a pulse duration of 1 ms, a current intensity of 2 mA, and 2 Hz frequency. According to clinical evidence, EA at the ST36 acupoint relieves gastrointestinal discomfort, provides analgesia, and relieves unwanted symptoms during drug addiction withdrawal.[28,29] EA at the GB34 acupoint improves motor function in Parkinson's disease.[30] The Zusanli (ST36) acupoint is located 3 B-cun distal to the lower border of the patella, 1 fingerbreadth lateral to the anterior crest of the tibia, between the tibialis anterior muscle and the tendon of the extensor digitorum longus.[31] The Yanglingquan (GB34) acupoint is located on the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula. Illustrations are modified from the *WHO Standard Acupuncture Point Locations in the Western Pacific Region*, 2008 (ISBN 978 92 9061 248 7).[32]

2.5. Antihistamine administration

Sixty minutes prior to the EA session, each subject in the EA plus low-dose DCPA group received a single 2-mg DCPA tablet; each subject in the EA plus high-dose DCPA group received two 2-mg DCPA tablets. All tablets were identical in shape, color, and trademark.

2.6. Assessment of pain threshold

In each subject, the pain threshold was measured 65 min before and 10 min after the EA session. Pain thresholds were tested by transcutaneous electrical stimuli (TENS HC-0502, Home Care Tech., Tainan, Taiwan) on the glabrous skin of the left upper arm, commencing from 0 mA and increasing in intensity by 0.5 mA per

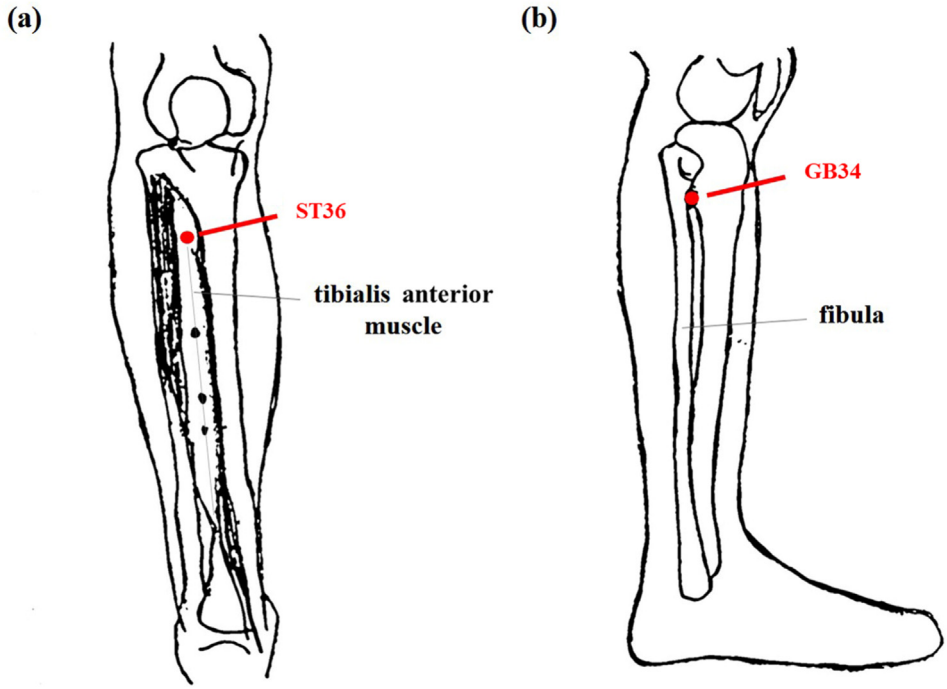

Fig. 2. Locations of ST36 and GB34 in humans. (a) The Zusanli (ST36) acupoint is located 3 B-cun distal to the lower border of the patella, 1 fingerbreadth lateral to the anterior crest of the tibia, between the tibialis anterior muscle and the tendon of the extensor digitorum longus. (b) The Yanglingquan (GB34) acupoint is located on the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula. Illustrations are modified from the *WHO Standard Acupuncture Point Locations in the Western Pacific Region*, 2008 (ISBN 978 92 9061 248 7).

second with a current frequency of 5 Hz. The pain threshold was determined as being the individual's level of minimal pain sensation during transcutaneous electrical stimuli testing.

2.7. Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Sciences version 22 software (IBM Inc., USA). For demographic data, a one-way analysis of variance and a Chi-square test was conducted on continuous and categorical data, respectively. Pain threshold data obtained prior to the EA session in the verum EA group failed the Kolmogorov-Smirnov test for normality of data among the datasets ($p = 0.002$), so the nonparametric Kruskal-Wallis test and Wilcoxon signed-rank test examined between-group and within-group differences on pain threshold data, respectively. If the significant difference has been observed with the Kruskal-Wallis test, the Mann–Whitney *U* test has been conducted as the *post hoc* analysis between different groups. The significant level was set as $p < 0.05$. To deal with the problem of multiple comparisons, the Bonferroni correction was applied to the Mann–Whitney *U* test and Wilcoxon signed-rank test, which lead the significant levels for Mann–Whitney *U* test and Wilcoxon signed-rank test at $p < 0.008$ and $p < 0.0125$, respectively.

3. Results

3.1. Demographic data

Study recruitment commenced on January 24, 2019 and stopped on June 27, 2019 when the number of subjects reached the recruitment goal. All 40 study participants were college students and all received their allocated intervention. There were no significant between-group differences in age or gender ratios (Table 1). No adverse events were reported during or immediately after the experiment.

3.2. Within-group changes in pain thresholds

No significant differences in pain thresholds were observed among the four study groups before EA. After applying the Bonferroni correction to the Wilcoxon signed-rank testing, pain thresholds were found to be significantly increased from baseline after acupuncture treatment in the EA group (effect size = 0.90), the EA plus low-dose DCPA group (effect size = 0.90), and the EA plus high-dose DCPA group (effect size = 0.89), but not in the sham EA group (effective size = 0.51) (Table 2 and Fig. 3).

3.3. Between-group changes in pain thresholds

Kruskal–Wallis testing indicated significant between-group differences for changes from baseline in pain thresholds after acupuncture treatment. A Mann–Whitney *U* test with Bonferroni correction revealed that the elevation in pain threshold after acupuncture was significantly higher for the EA plus high-dose DCPA group compared with elevations in the other three study groups; although the uncorrected p values between sham EA and EA-only group and EA plus low-dose group were less than 0.05, no significant between-group differences were observed in the remaining pairs after the Bonferroni correction (Table 3, Fig. 4). The effect size was 0.75, 0.62, and 0.66 in pain threshold change between the EA plus high-dose DCPA group and the sham group, the EA-only group, and the EA plus low-dose DCPA group, respectively.

4. Discussion

To the best of our knowledge, this pilot study is the first clinical

Table 1
Demographic characteristics.

	Sham EA	EA	EA + DCPA (2 mg)	EA + DCPA (4 mg)	P-value
Age (years)	24.1 ± 1.97	24.0 ± 2.54	22.6 ± 2.9	22.7 ± 2.58	0.398
Gender					0.813
Males (n)	7	6	7	8	–
Females (n)	3	4	3	2	–

Abbreviations: EA, electroacupuncture; DCPA, dexchlorpheniramine.

Table 2
Pain thresholds before and after sham EA and verum EA, alone or in combination with low- or high-dose dexchlorpheniramine.

Group	Pre-treatment (mA)			Post-treatment (mA)			P-value
	Q1	Q2	Q3	Q1	Q2	Q3	
Sham EA	5.000	6.000	7.000	5.500	6.250	7.125	0.107
EA	4.750	5.000	6.500	5.375	6.000	7.500	0.004
EA + DCPA (2 mg)	4.750	6.250	7.000	5.750	7.000	8.125	0.004
EA + DCPA (4 mg)	4.375	5.500	7.000	6.375	8.000	10.000	0.005

Abbreviations: EA, electroacupuncture; DCPA, dexchlorpheniramine; Q1, lower quartile; Q2, middle quartile; Q3, upper quartile. The significant difference was deemed if $p < 0.0125$ after the Bonferroni correction.

trial to compare the pain threshold-modulating effects of sham and verum EA alone or in combination with antihistamine therapy. Sham EA provided nonsignificant elevations in the pain threshold, whereas verum EA effectively elevated pain thresholds; in particular, the effect size of pain threshold changes in verum EA combined with high-dose DCPA was superior to all other groups. No such between-group differences were observed with low-dose DCPA, which indicates that a certain concentration of antihistamine drug may be needed to enhance the analgesic effects of EA.

A meta-analysis of individual patient data from 29 high-quality randomized controlled trials (involving 17 922 patients in total) that assessed the efficacy of acupuncture for 4 chronic pain conditions (back and neck pain, osteoarthritis, chronic headache, and shoulder pain) found that verum acupuncture was superior to both sham and no-acupuncture control for each pain condition.[6] An update of this meta-analysis identified an additional 13 randomized trials comparing acupuncture needling with either sham acupuncture or no acupuncture control for nonspecific musculoskeletal pain, osteoarthritis, chronic headache, or shoulder pain, resulting in a total of 20 827 patients for analysis.[7] As with the earlier analysis, this update found that verum acupuncture was significantly superior to sham acupuncture and the control condition for all pain conditions.[7] Similarly, our results revealed that

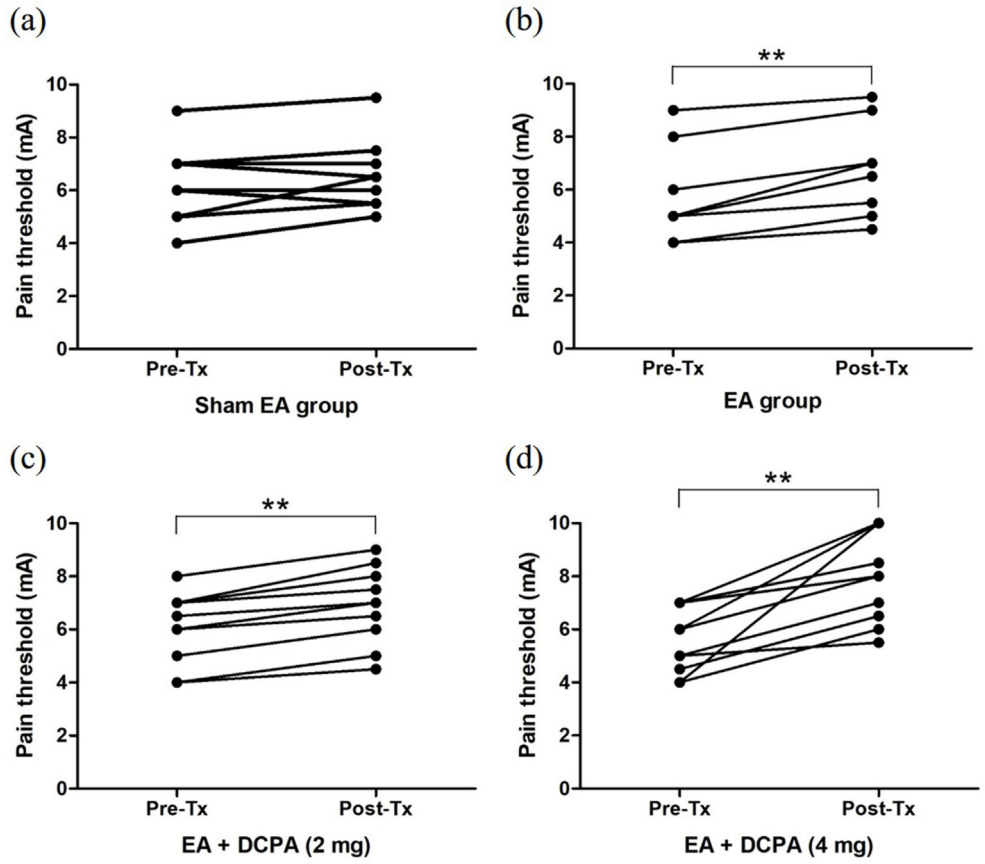

Fig. 3. Increased pain thresholds after verum EA but not after sham EA. Temporal pain threshold profiles were significantly increased from baseline after EA sessions in (b) the EA group, (c) the EA plus 2 mg DCPA group, and (d) the EA plus 4 mg DCPA group, but not in (a) the sham EA group. **$p < 0.01$ after applying the Bonferroni correction. DCPA, dexchlorpheniramine; EA, electroacupuncture; Pre-Tx, before treatment; Post-Tx, after treatment.

Table 3
Changes from baseline in pain thresholds after sham EA and verum EA, alone or in combination with low- or high-dose dexchlorpheniramine.

Group	△mA			P-value			
	Q1	Q2	Q3	(vs EA + DCPA 4 mg)	(vs EA + DCPA 2 mg)	(vs EA)	(vs sham EA)
Sham EA	−0.125	0.500	0.625	0.001	0.039	0.046	–
EA	0.500	0.750	1.125	0.006	0.934	–	0.046
EA + DCPA (2 mg)	0.500	1.000	1.000	0.003	–	0.934	0.039
EA + DCPA (4 mg)	1.375	2.000	3.325	–	0.003	0.006	0.001

Notes: Only the p-values of paired group comparisons with EA + DCPA 4 mg are represented.
Abbreviations: EA, electroacupuncture; DCPA, dexchlorpheniramine; Q1, lower quartile; Q2, middle quartile; Q3, upper quartile. The significant difference was deemed if $p < 0.008$ after the Bonferroni correction.

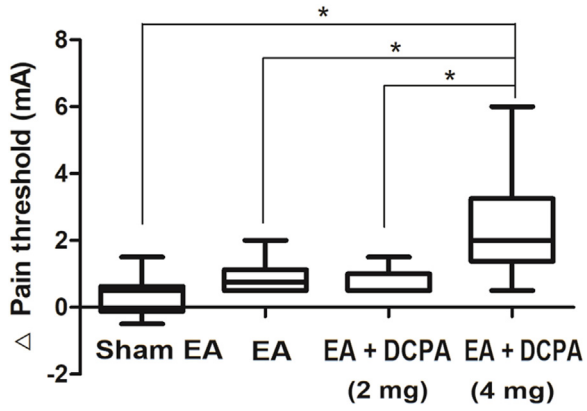

Fig. 4. The change from baseline in pain threshold was highest in subjects treated with verum EA combined with high-dose dexchlorpheniramine. The change from baseline in pain threshold was significantly higher in the EA plus 4 mg DCPA group compared with the EA plus 2 mg DCPA group, verum EA and sham EA groups, respectively. The data are presented with minimum and maximum values, lower, middle and upper quartiles for each group. *p < 0.05 after applying the Bonferroni correction. EA, electroacupuncture; DCPA, dexchlorpheniramine.

treatment with verum EA (with or without DCPA) significantly increased the pain threshold with a strong effect size, whereas sham EA had no such effect. Thus, our findings support the evidence suggesting that acupuncture can effectively treat chronic pain and is, therefore, a reasonable therapeutic option.

We have previously reported that chlorpheniramine monotherapy administered at 0.6 mg/kg fails to modulate pain, but when administered with EA, effectively facilitates EA analgesia in mice.[26] It has been suggested that H_1 receptor antagonist therapy may directly or indirectly facilitate opioid binding to opioid receptors,[33] interact with substance P,[34] and have antiserotonergic and/or antiadrenergic effects,[35] all of which are associated with pain modulation. Thus, antihistamine administration may mediate the pain modulation system and act in synergy with EA to facilitate its analgesic effects. Indeed, our results revealed that EA with high-dose DCPA is associated with a greater change in pain threshold than either EA alone or sham EA. Considering the results from our preclinical and pilot studies, a certain concentration of antihistamine may be needed to enhance the analgesic effect of EA.

If the DCPA dose is high enough, its combination with EA may be of benefit in clinical pain conditions, particularly in neuropathic pain and fibromyalgia. Two literature reviews have reported that EA alone may not be effective in the treatment of neuropathic pain or fibromyalgia.[16,17] The suggestion that chronic neuroinflammation in the peripheral and central nervous systems may underpin neuropathic pain and fibromyalgia[22,23] indicates a possible pain-modulating role for antihistamine therapy. This is supported by preclinical investigations into spontaneous neuropathic pain, in which peripherally-acting H_1 receptor antagonists may be useful in this condition.[36] Moreover, it has been reported that antihistamines may interact with substance P to modulate pain,[34] which has therapeutic implications for patients with fibromyalgia-related pain, whose cerebrospinal fluid levels of substance P are higher than those in healthy subjects.[37]

Preclinical and clinical evidence has shown analgesic effects with several other antihistamines, including diphenhydramine, hydroxyzine, orphenadrine, pyrilamine, phenyltoloxamine, promethazine, methdilazine, and tripelennamine.[34,38,39] However, the chlorpheniramine only has been reported with the antimuscarinic and antiserotonin effect but not analgesic effect.[39] One preclinical study has reported analgesic effects with chlorpheniramine in mice subjected to intraperitoneal injections of 0.7% acetic acid,[35] although that study administered a very high dosage of chlorpheniramine (2.5 mg/kg, equating to ~7.3 mg of DCPA for a human adult weighing 70 kg, based on body surface area conversion calculations) that may not be suitable for comparison with our study dose of DCPA. Interestingly, in a clinical study, the addition of 4 mg chlorpheniramine effectively potentiated the analgesic effect of antimigraine medication combining acetylsalicylic acid (250 mg), paracetamol (150 mg) and caffeine (30 mg) compared with a tablet containing the usual combination of 250 mg acetylsalicylic acid, 250 mg paracetamol, and 65 mg caffeine.[40] Hence, the efficacy of our results may be due to the synergistic effect between EA and DCPA, rather than DCPA itself.

Several limitations in the present study should be noted. First, as this was a pilot study, relatively few subjects were enrolled. Having only 10 subjects in each group may mean that the study has low statistical power and is subject to the risk of a type II error. Second, the study was conducted with healthy volunteers rather than with patients experiencing clinical pain. Observing modulating effects of EA on pain thresholds in healthy subjects does not necessarily mean that such effects will be reported in patients with clinical pain. Finally, due to scheduling issues, the pain threshold was only tested once in each subject. No repeated-measures or averaging measures were conducted that could be used to avoid any possible influence from random outlying measurements.

5. Conclusions

In conclusion, elevated pain thresholds were observed in the verum EA groups; these thresholds were further increased when EA was combined with 4 mg DCPA treatment. EA with high-dose DCPA is associated with a greater change in pain threshold than EA alone. A larger randomized controlled trial is currently investigating the validity of our study results in patients with trigeminal neuralgia.

Data availability

All the data generated during this study were statistically analyzed and are presented in the figures and tables. The dataset could be available on request from the corresponding authors.

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Foot notes

None.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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