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Electroacupuncture versus manual acupuncture for knee osteoarthritis: a randomized controlled pilot trial

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Abstract

Objective: We aimed to explore the feasibility of evaluating the comparative effectiveness and safety of electroacupuncture (EA) relative to manual acupuncture (MA) for the treatment of knee osteoarthritis (KOA).

Methods: A multicenter randomized controlled clinical trial was conducted in Beijing from September 2017 to January 2018. A total of 60 participants with KOA were randomly allocated to either EA ($n = 30$) or MA ($n = 30$) groups. Participants in the EA group were treated with EA at six to seven local traditional acupuncture points or *ah shi* points, and two to three distal points. Participants in the MA group had the same schedule as the EA group except that the electrical apparatus featured a working power indicator without actual current output, constituting a sham EA procedure, in order to blind participants. Both groups received 24 sessions over 8 weeks. The primary outcome was response rate, defined as a change of ⩾50% from baseline in the total scores of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) after 8 weeks. Secondary outcomes included pain, stiffness, function, quality of life, and acupuncture-related adverse events (AEs) at 4 and 8 weeks.

Results: Of 60 participants randomized, 53 (88%) completed the study. Response rates were 43% for the EA group and 30% for the MA group by the intention-to-treat analysis. Although significant differences were observed in WOMAC pain, stiffness, and function scores within both groups, between-group differences at 8 weeks did not reach statistical significance (odds ratio = 1.75 (95% confidence interval = 0.593–5.162)). Rates of AEs were low and similarly distributed between groups.

Conclusion: Both EA and MA interventions in KOA were feasible and appeared safe. Whether or not EA may have a stronger impact on pain and function requires further evaluation through larger, adequately powered, randomized controlled trials.

Trial registration number: NCT03274713.

Keywords

electroacupuncture, knee osteoarthritis, manual acupuncture, randomized controlled trial

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Introduction

Knee osteoarthritis (KOA) is one of the most common chronic conditions and forms of arthritis worldwide, and it is characterized by a protracted disease course, especially among elderly patients.[1–3] KOA is the leading cause of lower extremity disability among older adults.[4] The prevalence of symptomatic KOA is higher in women (10.3%) compared with men (5.7%).[5] With increasing life expectancy, osteoarthritis (OA) is anticipated to become the fourth leading cause of disability by the year 2020.[6]

Standard treatment focuses on symptom relief with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). Since the latter can cause serious gastrointestinal and cardiovascular adverse effects, there have been concerns over their long-term use.[7,8]

Acupuncture, which has been used in China and other Asian countries for the past 3000 years,[9] has the potential to effectively manage chronic pain.[10] Electroacupuncture (EA) and manual acupuncture (MA) are the most commonly used types of acupuncture therapy for KOA. Acupuncture has been shown to achieve clinically significant short-term effects when compared with minimal acupuncture or conventional therapy in patients with KOA.[11] A systematic review including 12 trials with a total of 1763 patients showed that MA was efficacious compared with sham acupuncture in terms of improving pain intensity and functional mobility in patients with KOA.[12] Our previous pilot study also showed that MA (three sessions per week for 8 weeks) compared with sham acupuncture was feasible and safe for patients with KOA.[13] EA represents an enhanced approach to acupuncture that involves the application of electrical crocodile clips to the handles of the acupuncture needles, which are connected to an EA device that provides continuous electric stimulation.[14,15] The results from a previous study showed that EA was effective for the management of KOA with respect to pain relief and functional improvement of the joint.[16]

There is evidence indicating that both EA and MA are effective at treating pain and dysfunction in patients with KOA; however, few studies have directly compared the impact of EA and MA on KOA. This multicenter randomized blinded clinical trial was conducted to compare the effectiveness of EA and MA in terms of pain relief and functional improvement in participants with KOA. Our primary hypothesis was that EA and MA would have different effects in participants with KOA. It was anticipated that the results of this study would help inform the design of a future, large randomized controlled trial.

Methods

Design

This was a randomized controlled trial (1:1 treatment allocation), with 8 weeks of treatment and 8 weeks of follow-up, which conformed to the Standards for Reporting Interventions in Controlled Trials of Acupuncture[17] and the Consolidated Standards of Reporting Trials[18] guidelines. The participants were evaluated at baseline and again at 4, 8, 12, and 16 weeks following the beginning of the treatment. The study was approved by the medical ethical review committee of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University (2017BL-020-01) and was prospectively registered at ClinicalTrials.gov (registration no. NCT03274713) on 7 September 2017, prior to recruitment of the first participant.

Participants

A total of 60 participants were enrolled in a 1:1 allocation ratio to EA or MA groups across three hospitals (Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, Beijing Friendship Hospital affiliated to Capital Medical University, and Beijing Jishuitan Hospital). Participants were recruited via the community through media, outpatient, and poster paper advertisements at three hospital centers (September 2017–January 2018). The inclusion criteria included the following: participants needed to be aged 45–75 years and have Kellgren–Lawrence[19] grade II or III (mild or moderate) radiographically confirmed KOA affecting one or both knees with a duration of more than 6 months and pain intensity ⩾40 on a 100-point visual analogue scale (VAS). The exclusion criteria included the following: a history of knee surgery or arthroscopy; pain in the knee caused by floating cartilage, joint effusion, or inflammatory, malignant or autoimmune disease; serious acute or chronic organic disease or mental disorder; pregnancy or breastfeeding; and history of bleeding disorder. Participants were also ineligible if they had received acupuncture treatment or participated in other clinical trials in the past 3 months.

After a brief telephone screening, participants were scheduled to visit one of the three participating sites to sign an informed consent statement and undergo a brief rheumatologic examination, including radiographic examination of the affected knee(s) by an orthopedist. Eligibility to participate was determined initially by the research investigators at each site involved. They were responsible for completion of the medical assessment and for checking eligibility criteria. Eligibility data were entered into a secure online database and were monitored centrally before confirmation of study participation. Each subject's demographic data and medical history were obtained at baseline.

Prior to the trial, the study process was explained to participants during recruitment. Participants were informed that participation in the trial was absolutely voluntary, that they could withdraw from the trial at any time, and that, in the event of their withdrawal, collected data would not be deleted and would be used in the final intention-to-treat (ITT) analysis. Research investigators fully complied with Good Clinical

Practice guidelines.[20] No participant was recruited without full, written informed consent first being obtained.

Study treatment

All acupuncturists in the study had Chinese medicine practitioner licenses and at least 3 years of clinical experience. Huatuo brand disposable, sterile steel needles (size: 0.30 mm × 40 mm; manufactured by Suzhou Medical Appliance, Jiangsu, China) were used. Acupuncture treatment was semi-standardized: all participants underwent acupuncture needling at a selection of local and distant traditional acupuncture points or *ah shi* points chosen by the acupuncturists according to the principles of traditional Chinese medicine. Needles were inserted at six to seven local points—which included ST34 (*Liangqiu*), ST35 (*Dubi*), ST36 (*Zusanli*), *Heding, Neixiyan*, GB33 (*Xiyangguan*), GB34 (*Yanglingquan*), SP9 (*Yinlingquan*), SP10 (*Xuehai*), LR7 (*Xiguan*), LR8 (*Ququan*)—and *ah shi* points, and at two to three distal points—which included GB31 (*Fengshi*), GB36 (*Waiqiu*), GB39 (*Xuanzhong*), GB41 (*Zulinqi*), ST40 (*Fenglong*), ST41 (*Jiexi*), LR3 (*Taichong*), BL60 (*Kunlun*), SP6 (*Sanyinjiao*), and KI3 (*Taixi*). In the process of treatment, we used individual syndrome differentiation. If pain occurred on the outside of the affected knee joint, GB points were mainly selected. If pain occurred in front of the affected knee joint, ST points were selected. If pain occurred in the interior of the affected knee joint, SP, LR, and KI points were chosen. If pain occurred in the rear of the affected knee, BL points were used. Needles were stimulated manually for 10 s to achieve *de qi* sensation. Both EA and MA therapies consist of 24 sessions lasting 30 min each, administered over 8 weeks (usually three sessions per week).

EA group. An electrical apparatus (HANS-200A acupoint nerve stimulator, Nanjing Jisheng Medical Co., Ltd, Nanjing, China) producing a density wave with a frequency of 2/100 Hz was connected to the needles with alligator clips to stimulate pairs of needles inserted at ST36-GB34 and ST34-SP10. The fixed current intensity was uniformly 0.2 mA.

MA group. Patients in the MA group had the same schedule as the EA group except that the electrical apparatus featured a working power indicator and sound without actual current output. The middle wire was cut, although the appearance of the unit was identical. Thus, the EA instrument appeared to be "on," but the actual power was not energized (Supplemental Figure). After elicitation of *de qi* sensation by MA, needles were retained for 30 min. Although no manual manipulation of the needles was performed in the MA group after initially achieving *de qi* sensation, in consideration of blinding assessment, the stimulation associated with needle retention was still expected to induce therapeutic effects. Accordingly, the only difference between the groups by design was that the EA group received real EA with electric current, while the MA group received sham EA without current.

Randomization, allocation concealment and blinding

Eligible participants were randomly assigned to the EA group or MA group in a 1:1 ratio using a central web-based randomization tool. The blocked randomization sequence was generated with SAS 9.3 software (SAS Institute, Cary, NC, USA) by an independent statistician who was not involved in the implementation or statistical analysis of the trial. Randomization was stratified within the three enrollment hospitals using a random block size of six. The sequence was embedded into the software (Beijing Guide Technology Co., Ltd, Beijing, China). The clinical research coordinator input the participant information on a tablet computer and was given a random number.

The research assistants obtained a participant's allocation from the computer. Throughout the whole study, the EA device operator was responsible for screening, recruiting participants, and allocating random numbers to participants who had been included. The research investigator, namely, the outcome assessor, was responsible for the assessment of scales. All acupuncturists, research investigators, participants, and intervention supervisors, as well as the statisticians who conducted the statistical analysis, were blinded to group allocation.

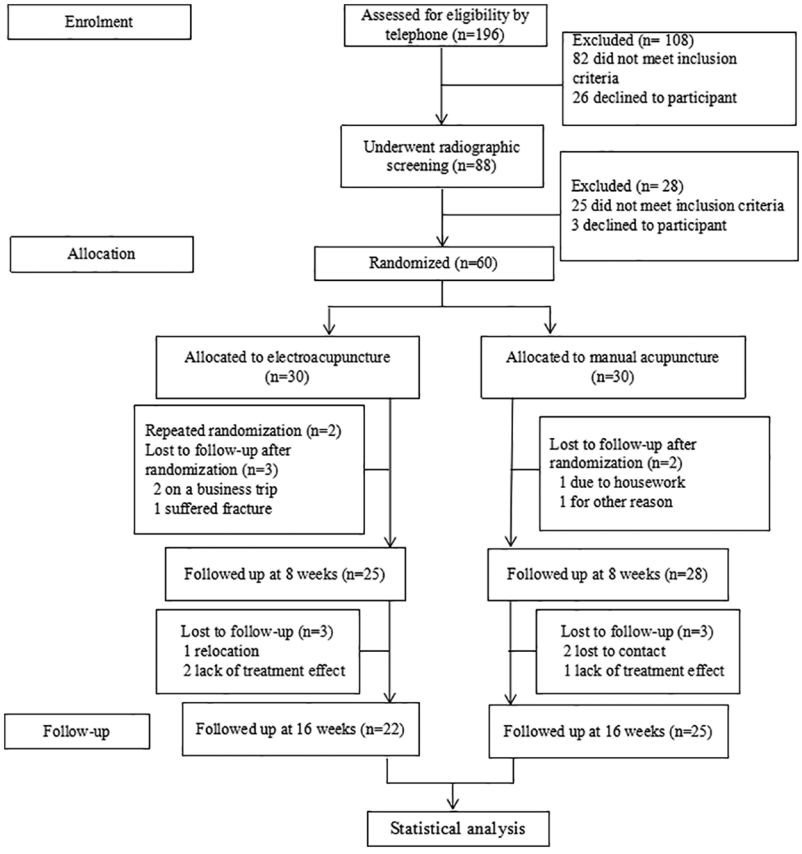
Without knowing the group allocation, the acupuncturists performed the acupuncture procedures on both groups of participants. After needles were inserted and manipulated, the acupuncturists kept away from the participants and the EA device operator delivered either verum or sham EA according to the group allocation. A blinding assessment test was used to compare the number of participants within the two groups who considered themselves to have been assigned to the EA group at week 4 and week 8.

Outcome measures

Primary outcome measurement. The response rate was calculated according to a change of 50% from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[21–23] total scores (pain, stiffness, and function) at 8 weeks.

Secondary outcome measurement. Knee pain was assessed by WOMAC pain subscale (five items, scored from 0 to 20) and VAS (scored from 0 to 100, with 0 representing no pain and 100 representing unbearable pain). Stiffness and function were assessed by WOMAC stiffness subscale (two items, scored from 0 to 8) and function subscale (17 items, scored from 0 to 68). The standard 12-item Short-Form Health Survey (SF-12, 0–100, with higher scores representing better quality of life),[24] an abbreviated form

Figure 1. Participant flowchart.



of the SF-36 that yields the physical and mental component summaries (PCS and MCS, respectively),[25] was used to assess the health-related quality of life of the participants. Data collection was performed by investigator B who was blind to participants' assignment at baseline and 4, 8, 12, and 16 weeks later, while the credibility/expectancy questionnaires were administered after the first treatment.

Distribution of rescue medication. During the study period, all participants were advised not to take any NSAIDs or analgesics except for a "rescue analgesic" (one tablet of 200 mg Celebrex orally as needed, once per day). The use of NSAIDs (Celebrex, Loxonin) was recorded at 4, 8, 12, and 16 weeks. Celebrex/Loxonin was given to participants if their pain intensity was ⩾80 on a 100-point VAS.[26]

Incidence of adverse events. All participants were required to report adverse events (AEs) voluntarily throughout the treatment period. AEs were recorded and assessed by investigator B if they occurred during the study. Acupuncture-related AEs usually included local bleeding, hematoma, pallor, sweating or dizziness, fainting, unbearable prickling sensation, or retained needle feeling after treatment.[27]

Sample size calculation

The aim of this pilot study was to explore the feasibility of comparing the effectiveness of EA and MA in terms of pain relief and functional improvement in participants with KOA after 8 weeks of treatment. The exploratory nature of the study did not necessarily require a formal sample size calculation. Thus, a sample size of 60 participants (30 per group) was determined to be sufficient to achieve the pragmatic purpose of the trial (i.e., the collection of information, such as aggregate values of the outcomes and their variation, and feasibility-related information necessary for designing a future clinical trial) according to clinical experience.

Statistical analysis

The results were analyzed using the Statistical Package for the Social Sciences version 12.0 KO for Windows (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant. Data were expressed using means and SD or percentages as appropriate. Between-group mean differences and two-sided 95% confidence intervals (CIs) were also presented to assess superiority.

Table 1. Demographic and baseline characteristics.

Characteristic	EA group ($n = 28$)	MA group ($n = 30$)	p-value
Age (years)	58.89 ± 6.75	59.70 ± 7.36	0.666
Women, n (%)	23 (82%)	21 (70%)	0.280
Body mass index (kg/m^2)[a]	25.12 ± 3.74	24.74 ± 2.68	0.663
Educational background (years)	12.82 ± 2.88	12.77 ± 3.04	0.944
Duration of disease (months)	69.93 ± 56.69	73.20 ± 56.71	0.784
WOMAC total points (0–96)	32.79 ± 10.80	33.13 ± 10.61	0.911
WOMAC pain subscale (0–20)	7.0 ± 3.34	6.77 ± 2.42	0.761
WOMAC stiff subscale (0–8)	2.14 ± 1.46	2.57 ± 1.48	0.242
WOMAC function subscale (0–68)	23.64 ± 7.37	23.80 ± 9.71	0.945
Quality of life (SF-12)[b]	57.65 ± 4.98	56.98 ± 5.45	0.789
VAS score (0–100)	54.82 ± 11.90	54.77 ± 8.38	0.542

EA: electroacupuncture; MA: manual acupuncture; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SF-12: Medical Outcomes Study 12-item Short-Form Health Survey; VAS: visual analogue scale/score. Data are mean ± SD unless otherwise specified.
[a]BMI was calculated as weight in kg divided by height in m^2.
[b]Higher values indicate better status.

ITT analysis was carried out for all randomized patients, and data analysis was conducted using two-sided significance tests at a 5% significance level. Missing data were replaced according to the principle of the last observation carried forward method. Per-protocol (PP) analysis was also applied for those patients who had received treatments ⩾20 times and completed the case report form as required. We mainly used the ITT analysis for all outcomes, while the PP analysis was also performed for the main outcome for sensitivity analysis. Pearson's chi-squared test was performed for proportions and independent sample t-tests were conducted to examine for baseline discrepancies between the two groups. A paired t-test was used to analyze the secondary outcomes in each group. A kappa statistic was used for the assessment of blinding.

Results

The flow of participants through the trial is illustrated in Figure 1. In total, 60 participants were randomly assigned to EA and MA groups. Randomization had to be repeated for two participants for whom the tablet computer failed to obtain a random number in a timely fashion due to a delayed response from the system, requiring the operator to request a new random number. The remaining 58 participants were included in the ITT analysis (28 in the EA group and 30 in the MA group). Three participants (10%) in the EA group and two (6.7%) in the MA group dropped out during the trial; 25/28 (89%) in the EA group and 28/30 (93%) in the MA group were included in the PP analysis. Characteristics of treatment groups at baseline are presented in Table 1. There were no significant differences in the treatment conditions or any baseline demographic or clinical characteristics ($p > 0.05$).

Primary outcome

After 8 weeks of treatment, the response rate (defined as a change of ⩾50% from baseline in WOMAC total scores) was 43% for the EA group and 30% for the MA group by ITT analysis, and 48% for the EA group and 32% for the MA group by PP analysis (Table 2). Neither analysis showed a statistically significant difference in the response rate between the two groups ($p > 0.05$).

Secondary outcomes

As shown in Table 3, there were no statistically significant differences between EA and MA groups in total WOMAC score pain subscale, stiffness subscale, function subscale or VAS score at week 4, week 8, week 12, or week 16 according to ITT analysis. SF-12 scores among patients in the EA group were significantly greater than those in the MA group at week 4, week 8, week 12, and week 16.

There was no significant difference between the two groups in the number of participants who considered themselves to have been assigned to the EA group ($p > 0.05$). After 8 weeks, 11 participants (21%) were unsure to which group they had been allocated (50% EA group, 50% MA group). From the remaining participants, that is, those who

Table 2. Differences in WOMAC index response rate between study groups at 8 weeks.

Outcome	Intention-to-treat				Per-protocol			
	EA group ($n = 28$)	MA group ($n = 30$)	*p*-value	Odds ratio (95% CI)	EA group ($n = 25$)	MA group ($n = 28$)	*p*-value	Odds ratio (95% CI)
Effective, *n* (%)	12 (43)	9 (30)	0.309	1.75 (0.59–5.16)	12 (48)	9 (32)	0.239	1.95 (0.64–5.95)
Non-effective, *n* (%)	16 (57)	21 (70)			13 (52)	19 (68)		

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EA: electroacupuncture; MA: manual acupuncture; CI: confidence interval.

thought they knew to which group they had been allocated, only 47% answered correctly, suggesting that blinding had been well maintained (Table 4).

AEs were uncommon and did not occur more frequently in either group. Specific AEs are detailed in Table 5. There was no significant bleeding in either group.

During the trial, no participant in either group took rescue medication.

Discussion

In this double-blinded randomized clinical pilot trial, we analyzed the effects of EA and MA (as complementary therapies) on pain, stiffness, physical function, and quality of life in patients with KOA. Although, by design, the study lacked statistical power, the results suggested that EA treatment for 8 weeks was no more effective than MA at reducing the pain, stiffness, and physical dysfunction associated with KOA. In our study, the primary outcome measurement chosen was effective response rate, which was calculated as the proportion of patients whose total WOMAC score decreased by ⩾50%. After treatment, the effective response rate of the EA group was 48% and that of the MA group was 32%, suggesting that they have similar effects, although equivalence cannot be proven, given the design considerations of this superiority trial.

According to our trial, the effective response rate would have been 71% for the EA group and 53% for the MA group if the primary outcome measurement were to have been changed to the proportion of participants with decreases in the WOMAC function score of 6 points and VAS score of 20 points after treatment.[28] In our trial, the WOMAC scores for pain, stiffness, and function and SF-12 of participants in both the EA and MA groups were improved after 8 weeks compared with those before treatment, suggesting that both EA and MA were effective for the treatment of KOA. In future trials, the primary outcome measurement could arguably be further refined.

We used different types of measurements to evaluate the results obtained, testing whether or not the changes were all in the same direction and thereby checking the consistency of the effectiveness end points. The effective response rate of the EA and MA groups after 8 weeks would have been 64% and 50%, respectively, had the proportion of patients whose WOMAC total score decreased ⩾36% been used to define the effective response rate.[13] There would similarly have been no significant difference between the two groups. Similar results in terms of function and pain have been reported by a randomized clinical trial of participants with KOA,[29] which demonstrated that neither laser acupuncture nor traditional Chinese acupuncture conferred benefit over sham after 12 weeks. Contrary to our trial, a systematic review and individual patient data meta-analysis on the efficacy of acupuncture for chronic headache and OA pain showed statistically significant improvements in pain with acupuncture compared

Table 3. Outcomes at 4, 8, 12, and 16 weeks (intention-to-treat analysis).

Outcome	EA group ($n = 28$)	MA group ($n = 30$)	Between-group difference
WOMAC total points			
Week 4	20.64 (15.89, 25.39)	22.87 (18.82, 26.91)	−2.22 (−8.57, 4.13)
Week 8	15.14 (11.79, 18.49)	18.60 (14.90, 22.30)	−3.46 (−8.64, 1.72)
Week 12	13.14 (9.85, 16.72)	15.63 (11.85, 19.03)	−2.49 (−7.64, 2.66)
Week 16	12.82(8.88, 16.92)	16.70(12.60, 20.85)	−3.88 (−9.89, 2.13)
WOMAC pain			
Week 4	3.90 (2.93, 4.83)	4.37 (3.63, 5.11)	−0.47 (−1.70, 0.76)
Week 8	2.93 (2.08, 3.79)	3.73 (2.73, 4.73)	−0.80 (−1.85, 0.25)
Week 12	2.54 (1.77, 3.31)	3.43 (2.53, 4.18)	−0.90 (−2.05, 0.26)
Week 16	2.79 (1.96, 3.60)	3.60 (2.59, 4.62)	−0.81 (−2.18, 0.55)
WOMAC stiffness			
Week 4	1.43 (1.03, 1.83)	1.85 (1.26, 2.45)	−0.40 (−1.14, 0.33)
Week 8	0.93 (0.70, 1.16)	1.03 (0.79, 1.27)	−0.10 (−0.25, 0.05)
Week 12	0.64 (0.32, 1.00)	0.77 (0.38, 1.17)	−0.12 (−0.66, 0.41)
Week 16	0.39 (0.17, 0.61)	0.72 (0.32, 1.12)	−0.33 (−0.84, 0.18)
WOMAC function			
Week 4	15.32 (11.63, 19.01)	16.67 (13.63, 19.71)	−1.35 (−6.17, 3.48)
Week 8	11.39 (8.67, 14.11)	14.86 (11.97, 17.74)	−3.46 (−7.66, 0.73)
Week 12	10.04 (7.42, 12.66)	11.07 (8.59, 13.55)	−1.03 (−4.85, 2.79)
Week 16	9.39 (6.46, 12.26)	12.33 (9.14, 15.31)	−2.94 (−7.30, 1.42)
VAS score (0–100)			
Week 4	39.21 (24.44, 53.98)	40.87 (24.79, 56.95)	−1.66 (−3.96, 0.64)
Week 8	26.04 (12.20, 39.88)	31.00 (13.71, 44.71)	−4.96 (−9.96, 0.04)
Week 12	21.83 (6.19, 37.47)	25.83 (8.60, 43.06)	−4.00 (−8.47, 0.47)
Week 16	21.82 (6.17, 37.46)	23.86 (3.86, 43.86)	−2.04 (−5.08, 1.00)
SF-12 score			
Week 4	58.43 (53.17, 63.69)	57.89 (52.24, 63.54)	0.54 (0.12, 0.96)
Week 8	60.14 (55.65, 64.63)	58.80 (51.78, 65.82)	1.34 (0.80, 1.88)
Week 12	62.21 (55.95, 68.47)	60.87 (54.28, 67.46)	1.34 (0.75, 1.93)
Week 16	63.64 (57.48, 69.80)	61.87 (55.19, 68.55)	1.77 (0.68, 2.86)

EA: electroacupuncture; MA: manual acupuncture; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: visual analogue scale/score; SF-12: Medical Outcomes Study 12-item Short-Form Health Survey. Data are mean or mean difference (95% CI).

with sham acupuncture.[30] Moreover, differences between EA and sham acupuncture were demonstrated in a large randomized, placebo-controlled acupuncture trial.[31] As for the secondary outcome, there was no statistically significant difference between EA and MA groups in total WOMAC score—pain subscale, stiffness subscale, and function subscale—or VAS score to ITT analysis. SF-12 scores among patients in the EA group increased significantly more than those in the MA group after treatment; however, the difference between groups did not reach the reported minimal clinically important difference for this parameter, which ranges from 2.0 to 7.8 points (on a 0–100 scale).[32]

We speculate that the putative improvements in both EA and MA groups may occur, at least in part, through

Table 4. Success of blinding (calculated using kappa statistic).

Patients responses	Week 4		Week 8	
	EA group ($n=26$)	MA group ($n=29$)	EA group ($n=25$)	MA group ($n=28$)
"EA group", *n* (%)	23 (88.46)	19 (65.52)	21 (84.00)	15 (53.57)
"MA group", *n* (%)	1 (3.85)	4 (13.79)	2 (8.00)	4 (14.29)
"Uncertain", *n* (%)	2 (7.69)	6 (20.69)	2 (8.00)	9 (32.14)
K	0.745		0.697	

EA: electroacupuncture; MA: manual acupuncture; *K*: kappa statistic.

Table 5. Adverse events related to acupuncture (calculated using kappa statistic).

	EA group ($n=28$)	MA group ($n=30$)	*p*-value
Hemarthrosis	9	11	0.466
Post-needling sensation	2	3	0.533

EA: electroacupuncture; MA: manual acupuncture.

blockade of the cyclooxygenase-2 enzyme, leading to a rapid reduction in signs and symptoms of KOA.[33] Acupuncture is considered to be a secure and powerful tool for repelling pain.[34] Moreover, its apparently anti-inflammatory effects may be explained by the fact that EA stimulation induces endogenous opioid peptides, which decrease pro-inflammatory cytokines such as interleukin-6 in peripheral sites, decrease cytokines and substance P[35] in the spinal cord, and are involved in the inhibition of affective pain.[36]

The strengths of this pilot study include the fact that it was performed prospectively and the trial procedure was well supervised. The participants appear to have been blinded successfully, given that they were unable to accurately identify the group to which they had been randomized. This trial met the methodological demands of adequate randomization and blinding of outcome assessors and participants. In this trial, 30.6% of individuals screened were recruited over a 16-week period, which is similar to the recruitment rate of an outpatient study.[11] The successful recruitment rate reflects the large number of participants suffering from KOA and participants' willingness to be involved in a trial. The dropout rate was 8.3% and the compliance rate was 91.7%. Although 24 sessions of acupuncture require a large amount of time, the study suggested that these treatments could be achieved with minimal difficulty. No serious AEs occurred in either group during the 16-week follow-up. During this trial, no participant took rescue medications in either group. On the basis of the recruitment and compliance rate achieved, we believe a future, adequately powered, randomized controlled trial could be feasible.

There are several limitations of this study that must be taken into consideration. First, we did not set up a sham treatment group to control for the nonspecific effects of acupuncture, which might have introduced performance bias. Sham acupuncture, sometimes also called superficial acupuncture or minimal acupuncture, is a type of control involving penetrating needles. Compared with verum acupuncture, sham acupuncture needles are applied either at traditional acupuncture point locations but at a shallower depth or at sites not corresponding to traditional acupuncture points at similar or shallower depth.[37] Second, the small sample size in this exploratory pilot trial increases the possibility of a type II error (i.e., a real effect of acupuncture being missed because of insufficient power). For future trials, sample size estimation could be calculated, for example, using PASS software, based on the data derived from this pilot trial. In order to detect a difference of 13% in WOMAC total scores (which were decreased by 43% and 30%, respectively, in the EA and MA groups of this pilot study) between two groups distributed using a 1:1 ratio, with 80% power and $\alpha=0.05$, the sample size required would be at least 215 per group. With the consideration of a 20% dropout rate, at least 269 patients would be required per group for a future study. Third, the results in this pilot study are mostly based on the specific characteristics of participants in the Beijing area, although it was a multicenter trial. Even with a reasonable sample size, results of the study are mostly based on specific populations, and whether or not (and the extent to which) they can be applied to other groups (e.g., people in other parts of China and internationally) needs careful consideration. Therefore, expanding the recruitment area may be important in future trials.

In summary, potential differences in clinical effect between EA and MA interventions could be better distinguished in future trials by increasing the sample size, expanding the area of recruitment, and extending the follow-up time. This pilot trial helps supply a clinical foundation as well as useful data to evaluate the practicability of a large-scale randomized controlled trial in the future.

Conclusion

In conclusion, both EA and MA (three sessions per week for 8 weeks) interventions are feasible and appear safe for participants with KOA. Whether or not EA may have a stronger impact on pain and function requires confirmation by larger, adequately powered, randomized controlled trials.

Contributions

All authors contributed to the study concept and design. T.-Q.W., L.-Q.W., G.-X.S., and C.-Z.L. contributed to the design of the study and drafting/editing of the manuscript. J.-F.T., L.-L.L., Y.-Q.H., J.-W.Y., J.-J.Z., Y.-T.L., and H.-K.H. participated in the design of the trial. C.-Z.L. sought funding and ethical approval. All authors contributed to the refinement of the trial and approved the final version of the manuscript accepted for publication.

Declaration of conflicting interests

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Ethics approval and consent to participate

This study was approved by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University on 15 May 2017 (ref: 2017BL-020-01). After extensive consultation, the participants signed informed consent to participate in the study.

Patient consent

Signed informed consent was obtained from the participants in the study.

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Supplemental material

Supplemental material for this article is available online.

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