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Traditional Chinese acupuncture vs minimal acupuncture for mild to moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial

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ABSTRACT

Introduction: Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders. Acupuncture is a popular form of complementary and alternative medicine for musculoskeletal conditions, although the evidence is inconclusive. Our objective is to evaluate the efficacy of Traditional Chinese acupuncture for pain relief and function improvement in mild to moderate knee osteoarthritis (TCAKOA) participants.

Methods/analysis: 42 patients will be recruited who have been diagnosed with mild to moderate KOA and randomly allocated in equal proportions to traditional Chinese acupuncture (TCA) or minimal acupuncture (MA). They will receive acupuncture for 24 sessions over eight weeks. The primary endpoint is success rate, which will be calculated according to a change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores at 8 weeks. Secondary endpoints include pain and function measurement, global change, the quality of life, and the use of analgesic at 8 weeks, 16 weeks and 26 weeks.

Ethics and dissemination: Ethical approval of this study has been granted by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (Permission number:2016BL-010-02). We will obtain Written informed consent from all participants. Outcomes of the trial will be disseminated through peer-reviewed publications.

Trial registration numbers: ISRCTN14016893

BACKGROUND

Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders,[1] which features as a protracted course of disease. A systematic review shows that the prevalence of KOA is 27.3% in women, and 21.0% in men.[2] A cross-sectional study with 9512 participants aged 50 years or older shows that the prevalence of radiographic KOA was 43.8% in women, and 21.1% in men in South Korea.[3] KOA is the leading cause of pain and global disability.

The objective of treating KOA is the alleviation of pain and improving quality of life. Five guidelines[4-7] have evaluated treatment effects on key outcomes of KOA (including pain, function, and disability). Pharmacologic agents, comprising non-opioid/opioid oral, non-steroidal anti-inflammatory drugs (NSAIDs) oral, intra-articular steroid, topical analgesics, and hyaluronate injections are normally utilized, but may be associated with significant adverse reactions (such as peptic ulcer, hypertension, and renal damage).[6 8 9] Guidelines emphasize the potential role of non-pharmacologic treatment, such as aerobic exercise, electrical nerve stimulation (TENS), acupuncture in the treatment. Effective alternatives to pharmacological are therefore desirable.

Traditional Chinese acupuncture (TCA) is a popular form of complementary and alternative medicine. In 2005, Germany Witt and colleagues showed that 8 weeks of the semi-standardized acupuncture treatment had significantly alleviated the patient's pain and dysfunction contrasted to

the minimal acupuncture treatment and no treatment condition.[10] A meta-analysis showed that acupuncture could be considered as an effective physical treatment for KOA.[11] However, in the October 2014 publication of JAMA, Dr. Hinman et al conducted a Zelen design clinical trial to investigate acupuncture for patients suffering from chronic knee pain. The investigation declared that acupuncture did not convey more advantages compared to sham or better function in sufferers with mild or harsh chronic knee pain.[12] However, flaws may exist in the trial design, statistics, interpretation of the results.[13-27] First of all, participants aged ≥ 50 years with moderate to severe chronic knee pain have been recruited. These inclusion criteria may be more suitable for arthroscopic or joint replacement therapy according to the guidance.[1 4] Secondly, acupuncture intervention is 8–12 sessions in total. The dosage for acupuncture is far from sufficient.[15 17] Thirdly, the team registered trial as studying laser acupuncture, instead of traditional acupuncture.[28] Researchers had changed the main aim selectively.[15 27] At present, there is a controversy over whether the acupuncture has benefit for KOA.[1 4] Therefore, our aim is to investigate the intensive TCA for participants with mild to moderate KOA.

MATERIALS AND METHODS

Study design

The study proposes a two-arm, randomised, clinical pilot trial. We will enroll patients from Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University, Beijing Friendship Hospital and Beijing Jishuitan Hospital. The trial has been registered with ISRCTN at Current Controlled Trials (ISRCTN14016893). Some recruitment strategies include radio and print advertisements through the local web sites and community center as well as recruiters with general practitioners. The intervention includes 24 sessions of acupuncture and 3 time follow-up (figure 1, table 1).

Table 1 Time to visit and data collection

	−1 day Baseline	0 day Treatment phase	Follow-up phase (end of treatment)
Patients			
Informed consent	×		
Sign informed Consent		×	
Medical history	×		
Physical examination	×		
Randomization		×	
Intervention			
TCA group (n=21)		3 times/week of TCA	
Comparisons			
MA group (n=21)		3 times/week of MA	
Outcomes			
WOMAC		×	×
KOOS		×	×
VAS		×	×
SF-12		×	×
The use of analgesic			
Participant safety			
Adverse events		×	×

Inclusion criteria

1. Age 45-75 years (either sex).
2. Chronic knee pain for the last 6 months.
3. Morning stiffness ≤ 30 minutes.

Criteria above are consistent with the National Institute for Health and Clinical Excellence (NICE) Guidelines 2014 Edition.[4]

4. Radiologic confirmation of KOA (Kellgren–Lawrence grade Ⅱ or Ⅲ[29]).

Exclusion criteria

1. Recent acupuncture.
2. Other sickness impact the knee.
3. On surgical operation list.
4. Neurologic as well as psychiatric diseases.
5. Severe coagulopathy.
6. Breastfeeding or pregnancy.
7. Not fitting to take the analgesic (Celebrex, Pfizer) provided.

For bilaterally eligible knees, the most symptomatic side will be evaluated in the course of the study.

Randomisation and allocation concealment

Eligible patients will be randomly assigned to TCA group or MA group in a ratio of 1:1 through central automated allocation procedures. An independent statistician generates randomisation sequence by using the SAS version 9.1.3 statistical package (SAS Institute, Cary, NC, USA). Acupuncturists will not involve in the process of randomisation.

Administrators will not be blinded because of the nature of intervention. The research assistants who collect data, the statisticians who assess outcomes and make statistical analysis will be blinded to group assignment.

Interventions

The acupuncture protocol follows the CONSORT[30] and STRICTA[31]. All acupuncturists have Chinese medicine practitioner licenses, and they have been qualified for at least ten years. All acupuncturists will receive training in the application of minimal acupuncture. Analgesics will give to participants if their pain intensity ≥ 80 on a 10-cm VAS.[32]

The protocol specifies the intervention of acupuncture to be a 20 minutes treatment which is applied 2/3 times weekly for 8 weeks, with 16–24 sessions in total permitted. Disposable, sterile steel, 0.30mm×25mm or 0.30mm×40mm needles (Huatuo disposable acupuncture needle, Suzhou Medical Co. Ltd., Jiangsu, China) will be used in two groups.

TCA group

Acupuncture points are selected on traditional Chinese Medicine theory of the “Bi” syndrome. These points are composed of 10 local points (*ST34, ST35, ST 36, EX-LE2, EX-LE5, GB33, GB34, SP9, SP10, LV8*) and 11 distal points (*GB31, GB36, GB39, GB 41, ST 40, ST41, LR3, BL60, SP6, KI3, LI4*) (figure 2). Physicians can choose 5-6 local points and 3-4 distal points. Needles will be making an optimum insertion into the skin. Acupuncturists are instructed to achieve “De Qi” and needles will be stimulated manually at least 10 seconds.

MA group

Non-acupoints in a superficial puncture (2 mm in depth) will be performed in MA group. Treatment is standardized needling without manual stimulation at 7 points at certain distances from TCA group points (table 2). The MA procedure will be given on the same schedule as the

TCA group.

Table 2 Sham acupuncture points in MA group

Sham acupuncture points	Location
MP1	ulnar margin of forearm, midpoint of the connecting line between the rasceta head and condylus medialis humeri.
MP2	2 cun above the malleolus lateralis, between the gall bladder meridian and stomach meridian on the distal part of the fibula.
MP3	2 cun above the malleolus medialis, in the center of the tibia surface area (intracutaneous without periost contact, in the direction towards the knee).
MP4	midpoint of the connecting line between ST36 and GB34
MP5	6 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP6	5 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP7	4 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP8	1 cun under the tibia head, in the medial edge of leg
MP9	midpoint of the connecting line between GB40 and ST41
MP10	3 cun above the medial edge of calcaneal
One 'cun' is defined according to the rules of traditional Chinese medicine as the width of the interphalangeal joint of patient's thumb.	

OUTCOMES

Primary outcome measurement

Success rate will be calculated according to a change from baseline in WOMAC[33 34] pain and function scores at 8 weeks. WOMAC function subscale (17 items, scored from 0-68) and pain subscale (5 items, scored from 0-20) with higher scores represent worse pain and function.

Secondary outcome measurement

Knee pain will be assessed by both WOMAC pain subscale and Visual Analogue Scale (VAS, 0-100, higher scores representing worse pain). WOMAC function subscale will be used to measure physical function. Knee injury and Osteoarthritis Outcome Score (KOOS 0-100, higher scores indicating better function) subscales comprise pain, symptoms, activities of daily living, and quality of life.[35] Health-related quality of life will use the 12-item Short Form Health Survey (SF-12 0-100, higher scores representing better quality of life).[36] The use of the analgesic at 8 weeks, 16 weeks and 26 weeks.

Adverse events will be monitored and report by acupuncturists via open-ended questioning. Patients will be suggested to state any adverse circumstances they go through, comprising discomfort or bruise in the locations pierced by needle, nausea, or the feeling of faint after the acupuncture treatment. Every crucial sign and adverse events are going to be investigated and recorded during every visit.

Sample Size

The purpose is to accumulate clinical data, obtain the outcome data of the intervention method, and prove the feasibility of the study protocol. 42 patients will be selected as the sample size according to clinical experience.

Statistical analysis

The results will be analyzed by using the SPSS software (SPSS 12.0 KO for Windows ©). The accepted level of significance will be $P < 0.05$. Measurement data were expressed by mean number ± Standard Deviation, enumeration data expressed as a percentage.

The statistic analysis will be carried out based on the theory of intention-to-treat (ITT) analysis as

well as per-protocol (PP) analysis.In the case of ITT analysis, missing data will be replaced according to the principle of the last observation carried forward and the maximum likelihood regression analysis. PP analysis will be conducted with patients who have received treatments>20 times and complete the CRF. $\chi 2$ Test is going to be performed for the situation of proportions; meanwhile, the analysis of independent sample t tests is going to be conducted to examine the baseline discrepancies between the two groups. The significance of the differences in the various data in each group will be analyzed with a paired t test. Based on the baseline and temporary analgesic medicine dosage adjustment, continuous measurement results will be analyzed using covariance test, and Logistic regression analysis will be used for the two classification outcomes. Above two analyses will be present as difference in means or advantage ratio with 95% confidence intervals.

DISCUSSION

KOA is a common public health problem and a leading cause of disability. The results of this pilot study are going to concentrate on patients suffering from mild to moderate KOA and will investigate whether acupuncture can be a practicable and efficient therapy.

A suitable control group is critical for a well-designed clinical trial. Based on the literature review as well as clinical experiences, the acupoints in the MA group do not therapeutically affect KOA. Additionally, the dosage for acupuncture is sufficient. The protocol specifies the intervention of acupuncture to be a 20 minutes treatment which is applied 2/3 times weekly for 8 weeks, with 16–24 sessions in total permitted. Moreover, according to generality for the trial, the wide inclusion criteria will render it more possible that the participants fairly stand for those who have mild to moderate KOA. One potential limitation of this study is that acupuncturists are not blinded because of the nature of intervention. However, acupuncturists will not relate to the outcome assessments or data analyses.

The pilot trial will supply the clinical foundation as well as data that are demanded for evaluating the practicability for a large-scale RCT trial in the future.

Trial status

This trial is currently recruiting participants.

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Contributors:

NS, CZ L and GX S conceived of the study. CZ L, GX S, NS, JF T, and YT L initiated the study design .YD, JJ Z, DC X and HK H helped with its implementation. NS, GX S, JF T, LW Z and YC drafted and critically revised the manuscript for important intellectual content. CZ L sought funding and ethical approval. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Competing interests: None.

Patient consent: Obtained.

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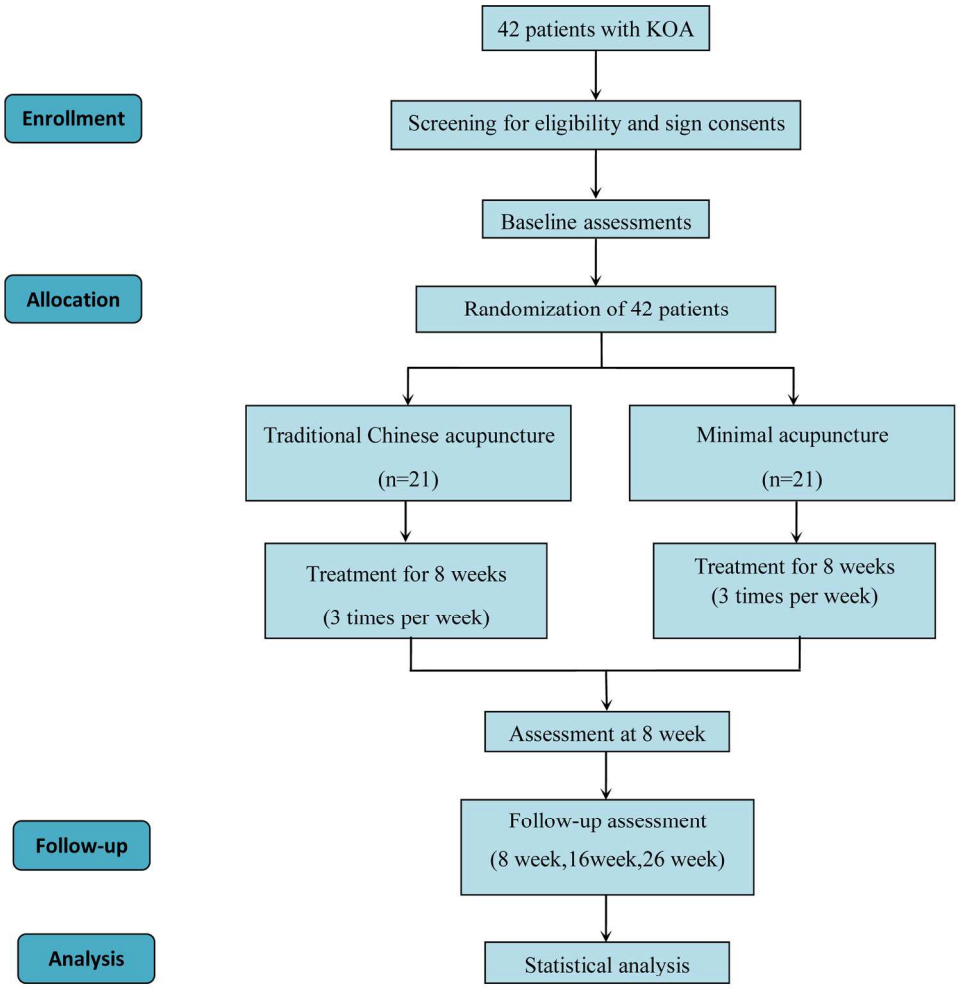

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Word count: 11510 words.

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Physical examination	×				
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Intervention		24 sessions of TCA			
TCA group (n=21)					
Comparisons		24 sessions of MA			
MA group (n=21)					
Outcomes					
WOMAC		×	×	×	×
KOOS		×	×	×	×
VAS		×	×	×	×
SF-12		×	×	×	×
The use of NSAID			×	×	×
Participant safety					
Adverse events		×	×	×	×

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Randomisation and allocation concealment

Eligible patients will be randomly assigned to TCA group or MA group in a ratio of 1:1 through central automated allocation procedures. An independent statistician generates randomisation sequence by using the SAS version 9.1.3 statistical package (SAS Institute, Cary, NC, USA). Acupuncturists will not involve in the process of randomisation.

The research assistants who collect data, the statisticians who assess outcomes and make statistical analysis will be blinded to group assignment. Participants will not be disclosed information regarding the allocation. Administrators will not be blinded because of the nature of intervention.

Interventions

The acupuncture protocol follows the CONSORT[30] and STRICTA[31]. All acupuncturists have Chinese medicine practitioner licenses, and they have been qualified for at least ten years. All acupuncturists will receive training in the application of minimal acupuncture. Celebrex will give to participants if their pain intensity ≥ 80 on a 10-cm VAS.[32]

The protocol specifies the intervention of acupuncture to be a 20 minutes treatment which is applied 2/3 times weekly for 8 weeks, with 16–24 sessions in total permitted. Disposable, sterile steel, 0.30mm×25mm or 0.30mm×40mm needles (Huatuo disposable acupuncture needle, Suzhou Medical Co. Ltd., Jiangsu, China) will be used in two groups.

TCA group

Acupuncture points are selected on traditional Chinese Medicine theory of the "Bi" syndrome. These points are composed of 10 local points (*ST34, ST35, ST 36, EX-LE2, EX-LE5, GB33, GB34, SP9, SP10, LV8*) and 11 distal points (*GB31, GB36, GB39, GB 41, ST 40, ST41, LR3, BL60, SP6, KI3, LI4*) (figure 2). Physicians can choose 5-6 local points and 3-4 distal points. Needles will be making an optimum insertion into the skin. Acupuncturists are instructed to achieve "De Qi" and needles will be stimulated manually at least 10 seconds.

MA group

Non-acupoints in a superficial puncture (2 mm in depth) will be performed in MA group. Treatment is standardized needling without manual stimulation at 7 points at certain distances from TCA group points (table 2). The MA procedure will be given on the same schedule as the TCA group.

Table 2 Sham acupuncture points in MA group

Sham acupuncture points	Location
MP1	ulnar margin of forearm, midpoint of the connecting line between the rasceta head and condylus medialis humeri.
MP2	2 cun above the malleolus lateralis, between the gall bladder meridian and stomach meridian on the distal part of the fibula.
MP3	2 cun above the malleolus medialis, in the center of the tibia surface area (intracutaneous without periost contact, in the direction towards the knee).
MP4	midpoint of the connecting line between ST36 and GB34
MP5	6 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP6	5 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP7	4 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP8	1 cun under the tibia head, in the medial edge of leg
MP9	midpoint of the connecting line between GB40 and ST41
MP10	3 cun above the medial edge of calcaneal
One 'cun' is defined according to the rules of traditional Chinese medicine as the width of the interphalangeal joint of patient's thumb.	

OUTCOMES

Primary outcome measurement

Success rate will be calculated according to a change from baseline in WOMAC[33 34] pain and function scores at 8 weeks. WOMAC function subscale (17 items, scored from 0-68) and pain subscale (5 items, scored from 0-20) with higher scores represent worse pain and function.

Secondary outcome measurement

Knee pain will be assessed by both WOMAC pain subscale and Visual Analogue Scale (VAS, 0-100, higher scores representing worse pain). WOMAC function subscale will be used to measure physical function. Knee injury and Osteoarthritis Outcome Score (KOOS 0-100, higher scores indicating better function) subscales comprise pain, symptoms, activities of daily living, and quality of life.[35] Health-related quality of life will use the 12-item Short Form Health Survey (SF-12 0-100, higher scores representing better quality of life).[36] The use of the NSAID (Celebrex, Pfizer) at 8 weeks, 16 weeks and 26 weeks.

Adverse events will be monitored and report by acupuncturists via open-ended questioning. Patients will be suggested to state any adverse circumstances they go through, comprising discomfort or bruise in the locations pierced by needle, nausea, or the feeling of faint after the acupuncture treatment. Every crucial sign and adverse events are going to be investigated and recorded during every visit.

Sample Size

The purpose is to accumulate clinical data, obtain the outcome data of the intervention method, and prove the feasibility of the study protocol. 42 patients will be selected as the sample size according to clinical experience.

Statistical analysis

The results will be analyzed by using the SPSS software (SPSS 12.0 KO for Windows ©). The accepted level of significance will be $P < 0.05$. Measurement data were expressed by mean number ± Standard Deviation, enumeration data expressed as a percentage.

The statistic analysis will be carried out based on the theory of intention-to-treat (ITT) analysis as well as per-protocol (PP) analysis.In the case of ITT analysis, missing data will be replaced according to the principle of the last observation carried forward and the maximum likelihood regression analysis. PP analysis will be conducted with patients who have received treatments>16 times and complete the CRF. $\chi 2$ Test is going to be performed for the situation of proportions; meanwhile, the analysis of independent sample t tests is going to be conducted to examine the baseline discrepancies between the two groups. The significance of the differences in the various data in each group will be analyzed with a paired t test. Based on the baseline and temporary analgesic medicine dosage adjustment, continuous measurement results will be analyzed using covariance test, and Logistic regression analysis will be used for the two classification outcomes. Above two analyses will be present as difference in means or advantage ratio with 95% confidence intervals.

DISCUSSION

KOA is a common public health problem and a leading cause of disability. The results of this pilot study are going to concentrate on patients suffering from mild to moderate KOA and will investigate whether acupuncture can be a practicable and efficient therapy.

A suitable control group is critical for a well-designed clinical trial. Based on the literature review as well as clinical experiences, the acupoints in the MA group do not therapeutically affect KOA. Additionally, the dosage for acupuncture is sufficient. The protocol specifies the intervention of

acupuncture to be a 20 minutes treatment which is applied 2/3 times weekly for 8 weeks, with 16–24 sessions in total permitted. Moreover, according to generality for the trial, the wide inclusion criteria will render it more possible that the participants fairly stand for those who have mild to moderate KOA. One potential limitation of this study is that acupuncturists are not blinded because of the nature of intervention. However, acupuncturists will not relate to the outcome assessments or data analyses.

The pilot trial will supply the clinical foundation as well as data that are demanded for evaluating the practicability for a large-scale RCT trial in the future.

Trial status

This trial is currently recruiting participants.

Contributors:

NS, CZ L and GX S conceived of the study. CZ L, GX S, NS, JF T, and YT L initiated the study design .YD, JJ Z, DC X and HK H helped with its implementation. NS, GX S, JF T, LW Z and YC drafted and critically revised the manuscript for important intellectual content. CZ L sought funding and ethical approval. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Competing interests：None.

Patient consent：Obtained.

Ethics approval：Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University.

Provenance and peer review：Not commissioned; peer reviewed for ethics and funding approval prior to submission.

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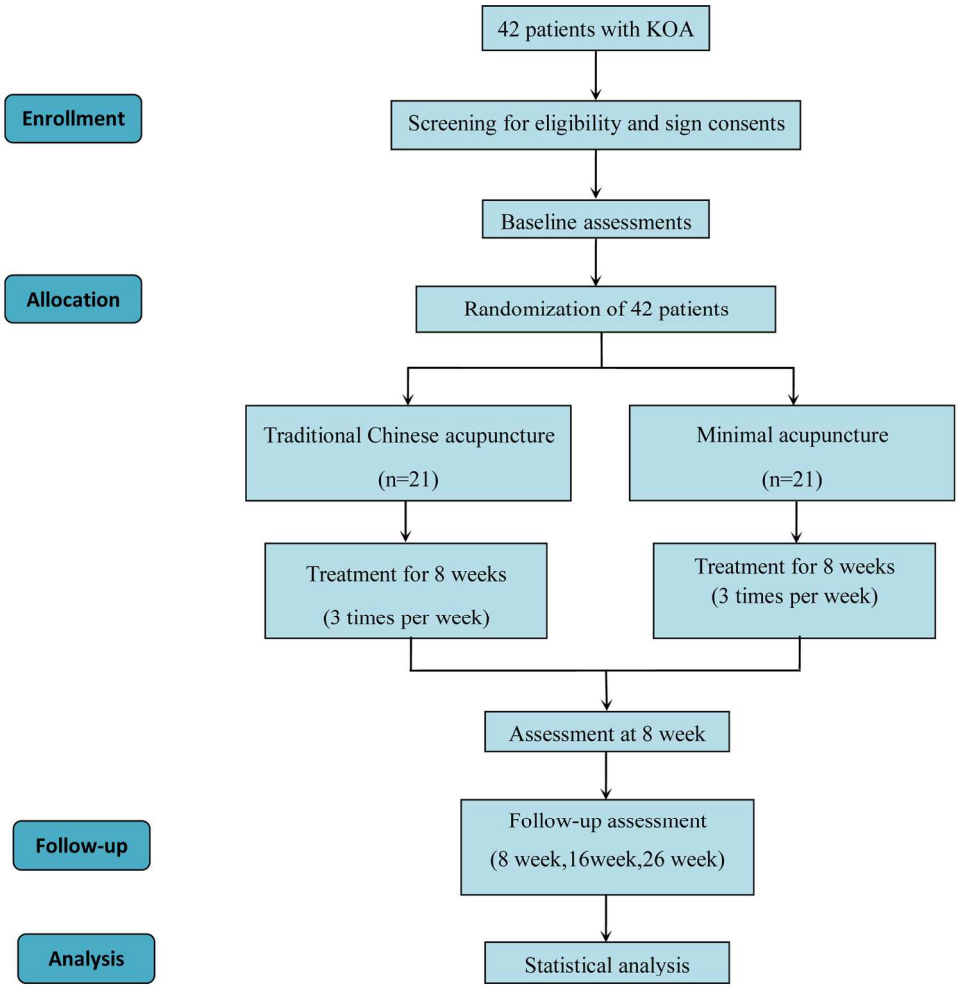

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Traditional Chinese acupuncture vs minimal acupuncture for mild to moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial

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Keywords:	Knee Osteoarthritis, Acupuncture, Clinical trials < THERAPEUTICS, PAIN MANAGEMENT

Traditional Chinese acupuncture vs minimal acupuncture for mild to moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial

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Keywords: knee osteoarthritis; acupuncture; clinical trials ; pain management; minimal acupuncture

Word count: 11510 words.

ABSTRACT

Introduction: Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders. Acupuncture is a popular form of complementary and alternative medicine for musculoskeletal conditions, although the evidence is inconclusive. Our objective is to evaluate the efficacy of Traditional Chinese acupuncture for pain relief and function improvement in mild to moderate knee osteoarthritis (TCAKOA) participants.

Methods/analysis: 42 patients will be recruited who have been diagnosed with mild to moderate KOA and

randomly allocated in equal proportions to traditional Chinese acupuncture (TCA) or minimal acupuncture (MA). They will receive acupuncture for 24 sessions over eight weeks. The primary endpoint is success rate, which will be calculated according to a change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores at 8 weeks. Secondary endpoints include pain and function measurement, global change, the quality of life, and the use of NSAID (Celebrex, Pfizer) at 8 weeks, 16 weeks and 26 weeks.

Ethics and dissemination: Ethical approval of this study has been granted by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (Permission number:2016BL-010-02). We will obtain Written informed consent from all participants. Outcomes of the trial will be disseminated through peer-reviewed publications.

Trial registration numbers: ISRCTN14016893

BACKGROUND

Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders,[1] which features as a protracted course of disease. A systematic review shows that the prevalence of KOA is 27.3% in women, and 21.0% in men.[2] A cross-sectional study with 9512 participants aged 50 years or older shows that the prevalence of radiographic KOA was 43.8% in women, and 21.1% in men in South Korea.[3] KOA is one of the leading cause of pain and global disability.

The objective of treating KOA is the alleviation of pain and improving quality of life. Five guidelines[4-7] have evaluated treatment effects on key outcomes of KOA (including pain, function, and disability). Pharmacologic agents, comprising non-opioid/opioid oral, non-steroidal anti-inflammatory drugs (NSAIDs) oral, intra-articular steroid, topical analgesics, and hyaluronate injections are normally utilized, but may be associated with significant adverse reactions (such as peptic ulcer, hypertension, and renal damage).[6 8 9] Guidelines emphasize the potential role of non-pharmacologic treatment, such as aerobic exercise, electrical nerve stimulation (TENS), acupuncture in the treatment. Effective alternatives to pharmacological are therefore desirable.

Traditional Chinese acupuncture (TCA) is a popular form of complementary and alternative medicine. In 2005, Germany Witt and colleagues showed that 8 weeks of the semi-standardized acupuncture treatment had significantly alleviated the patient's pain and dysfunction contrasted to the minimal acupuncture treatment and no treatment condition.[10] A meta-analysis showed that acupuncture could be considered as an effective physical treatment for KOA.[11] However, in the October 2014 publication of JAMA, Dr. Hinman et al conducted a Zelen design clinical trial to investigate acupuncture for patients suffering from chronic knee pain. The investigation declared that acupuncture did not convey more advantages compared to sham or better function in sufferers with mild or harsh chronic knee pain.[12] However, flaws may exist in the trial design, statistics, interpretation of the results.[13-27] First of all, participants aged ≥ 50 years with moderate to severe chronic knee pain have been recruited. These inclusion criteria may be more suitable for arthroscopic or joint replacement therapy according to the guidance.[1 4] Secondly, acupuncture intervention is 8–12 sessions in total. The dosage for acupuncture is far from sufficient.[15 17] Thirdly, the team registered trial as studying laser acupuncture, instead of traditional acupuncture.[28] Researchers had changed the main aim selectively.[15 27] At present, there is a controversy over whether the acupuncture has benefit for KOA.[1 4] Therefore, our aim is to investigate the intensive TCA for participants with mild to moderate KOA.

MATERIALS AND METHODS

Study design

The study proposes a two-arm, randomised, clinical pilot trial. We will enroll patients from

Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University, Beijing Friendship Hospital and Beijing Jishuitan Hospital. The trial has been registered with ISRCTN at Current Controlled Trials (ISRCTN14016893). Some recruitment strategies include radio and print advertisements through the local web sites and community center as well as recruiters with general practitioners. The intervention includes 24 sessions of acupuncture and 3 times follow-up (figure 1, table 1).

Table 1 Time to visit and data collection

	Baseline	**Treatment phase**		**Follow-up phase**	
	−1 day	0 day	8 weeks	16 weeks	26 weeks
Patients					
Informed consent	×				
Sign informed Consent		×			
Medical history	×				
Physical examination	×				
Randomization		×			
Intervention		24 sessions of TCA			
TCA group (n=21)					
Comparisons		24 sessions of MA			
MA group (n=21)					
Outcomes					
WOMAC		×	×	×	×
KOOS		×	×	×	×
VAS		×	×	×	×
SF-12		×	×	×	×
The use of NSAID			×	×	×
Participant safety					
Adverse events		×	×	×	×

Inclusion criteria

1. Age 45-75 years (either sex).
2. Chronic knee pain for the last 6 months.
3. Morning stiffness ≤ 30 minutes.

Criteria above are consistent with the National Institute for Health and Clinical Excellence (NICE) Guidelines 2014 Edition.[4]

4. Radiologic confirmation of KOA (Kellgren–Lawrence grade Ⅱ or Ⅲ[29]).

Exclusion criteria

1. Recent acupuncture.
2. Other sickness impact the knee.
3. On surgical operation list.
4. Neurologic as well as psychiatric diseases.
5. Severe coagulopathy.
6. Breastfeeding or pregnancy.
7. Not fitting to take the NSAID (Celebrex, Pfizer) provided.

For bilaterally eligible knees, the most symptomatic side will be evaluated in the course of the study.

Randomisation and allocation concealment

Eligible patients will be randomly assigned to TCA group or MA group in a ratio of 1:1 through central automated allocation procedures. An independent statistician generates randomisation sequence by using the SAS version 9.1.3 statistical package (SAS Institute, Cary, NC, USA). Acupuncturists will not involve in the process of randomisation.

The research assistants who collect data, the statisticians who assess outcomes and make statistical analysis will be blinded to group assignment. Participants will not be disclosed information regarding the allocation. Administrators will not be blinded because of the nature of intervention.

Interventions

The acupuncture protocol follows the CONSORT[30] and STRICTA[31]. All acupuncturists have Chinese medicine practitioner licenses, and they have been qualified for at least ten years. All acupuncturists will receive training in the application of minimal acupuncture. Celebrex will give to participants if their pain intensity ≥ 80 on a 10-cm VAS.[32]

The protocol specifies the intervention of acupuncture to be a 20 minutes treatment which is applied 3 times weekly for 8 weeks, with 24 sessions in total permitted. Disposable, sterile steel, 0.30mm×25mm or 0.30mm×40mm needles (Huatuo disposable acupuncture needle, Suzhou Medical Co. Ltd., Jiangsu, China) will be used in two groups.

TCA group

Acupuncture points are selected on traditional Chinese Medicine theory of the "Bi" syndrome. These points are composed of 10 local points (*ST34, ST35, ST 36, EX-LE2, EX-LE5, GB33, GB34, SP9, SP10, LV8*) and 11 distal points (*GB31, GB36, GB39, GB 41, ST 40, ST41, LR3, BL60, SP6, KI3, LI4*) (figure 2). Physicians can choose 5-6 local points and 3-4 distal points. Needles will be making an optimum insertion into the skin. Acupuncturists are instructed to achieve "De Qi" and needles will be stimulated manually at least 10 seconds.

MA group

Non-acupoints in a superficial puncture (2 mm in depth) will be performed in MA group. Treatment is standardized needling without manual stimulation at 7 points at certain distances from TCA group points (table 2). The MA procedure will be given on the same schedule as the TCA group.

Table 2 Sham acupuncture points in MA group

Sham acupuncture points	Location
MP1	ulnar margin of forearm, midpoint of the connecting line between the rasceta head and condylus medialis humeri.
MP2	2 cun above the malleolus lateralis, between the gall bladder meridian and stomach meridian on the distal part of the fibula.
MP3	2 cun above the malleolus medialis, in the center of the tibia surface area (intracutaneous without periost contact, in the direction towards the knee).
MP4	midpoint of the connecting line between ST36 and GB34
MP5	6 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP6	5 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP7	4 cun above the upper edge of the patella(between the spleen and stomach meridian)
MP8	1 cun under the tibia head, in the medial edge of leg
MP9	midpoint of the connecting line between GB40 and ST41
MP10	3 cun above the medial edge of calcaneal
One 'cun' is defined according to the rules of traditional Chinese medicine as the width of the interphalangeal joint of patient's thumb.	

OUTCOMES

Primary outcome measurement

Success rate will be calculated according to a change from baseline in WOMAC[33 34] pain and function scores at 8 weeks. WOMAC function subscale (17 items, scored from 0-68) and pain subscale (5 items, scored from 0-20) with higher scores represent worse pain and function.

Secondary outcome measurement

Knee pain will be assessed by both WOMAC pain subscale and Visual Analogue Scale (VAS, 0-100, higher scores representing worse pain). WOMAC function subscale will be used to measure physical function. Knee injury and Osteoarthritis Outcome Score (KOOS 0-100, higher scores indicating better function) subscales comprise pain, symptoms, activities of daily living, and quality of life.[35] Health-related quality of life will use the 12-item Short Form Health Survey (SF-12 0-100, higher scores representing better quality of life).[36] The use of the NSAID (Celebrex, Pfizer) at 8 weeks, 16 weeks and 26 weeks.

Adverse events will be monitored and report by acupuncturists via open-ended questioning. Patients will be suggested to state any adverse circumstances they go through, comprising discomfort or bruise in the locations pierced by needle, nausea, or the feeling of faint after the acupuncture treatment. Every crucial sign and adverse events are going to be investigated and recorded during every visit.

Sample Size

The purpose is to accumulate clinical data, obtain the outcome data of the intervention method, and prove the feasibility of the study protocol. 42 patients will be selected as the sample size according to clinical experience.

Statistical analysis

The results will be analyzed by using the SPSS software (SPSS 12.0 KO for Windows ©). The accepted level of significance will be $P < 0.05$. Measurement data were expressed by mean number ± Standard Deviation, enumeration data expressed as a percentage.

The statistic analysis will be carried out based on the theory of intention-to-treat (ITT) analysis as well as per-protocol (PP) analysis.In the case of ITT analysis, missing data will be replaced according to the principle of the last observation carried forward and the maximum likelihood regression analysis. PP analysis will be conducted with patients who have received treatments>16 times and complete the CRF. $\chi 2$ Test is going to be performed for the situation of proportions; meanwhile, the analysis of independent sample t tests is going to be conducted to examine the baseline discrepancies between the two groups. The significance of the differences in the various data in each group will be analyzed with a paired t test. Based on the baseline and temporary analgesic medicine dosage adjustment, continuous measurement results will be analyzed using covariance test, and Logistic regression analysis will be used for the two classification outcomes. Above two analyses will be present as difference in means or advantage ratio with 95% confidence intervals.

DISCUSSION

KOA is a common public health problem and a leading cause of disability. The results of this pilot study are going to concentrate on patients suffering from mild to moderate KOA and will investigate whether acupuncture can be a practicable and efficient therapy.

A suitable control group is critical for a well-designed clinical trial. Based on the literature review as well as clinical experiences, the acupoints in the MA group do not therapeutically affect KOA. Additionally, the dosage for acupuncture is sufficient. The protocol specifies the intervention of

acupuncture to be a 20 minutes treatment which is applied 3 times weekly for 8 weeks, with 24 sessions in total permitted. Moreover, according to generality for the trial, the wide inclusion criteria will render it more possible that the participants fairly stand for those who have mild to moderate KOA. One potential limitation of this study is that acupuncturists are not blinded because of the nature of intervention. However, acupuncturists will not relate to the outcome assessments or data analyses.

The pilot trial will supply the clinical foundation as well as data that are demanded for evaluating the practicability for a large-scale RCT trial in the future.

Trial status

This trial is currently recruiting participants.

Contributors:

NS, CZ L and GX S conceived of the study. CZ L, GX S, NS, JF T, and YT L initiated the study design .YD, JJ Z, DC X and HK H helped with its implementation. NS, GX S, JF T, LW Z and YC drafted and critically revised the manuscript for important intellectual content. CZ L sought funding and ethical approval. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Competing interests： None.

Patient consent： Obtained.

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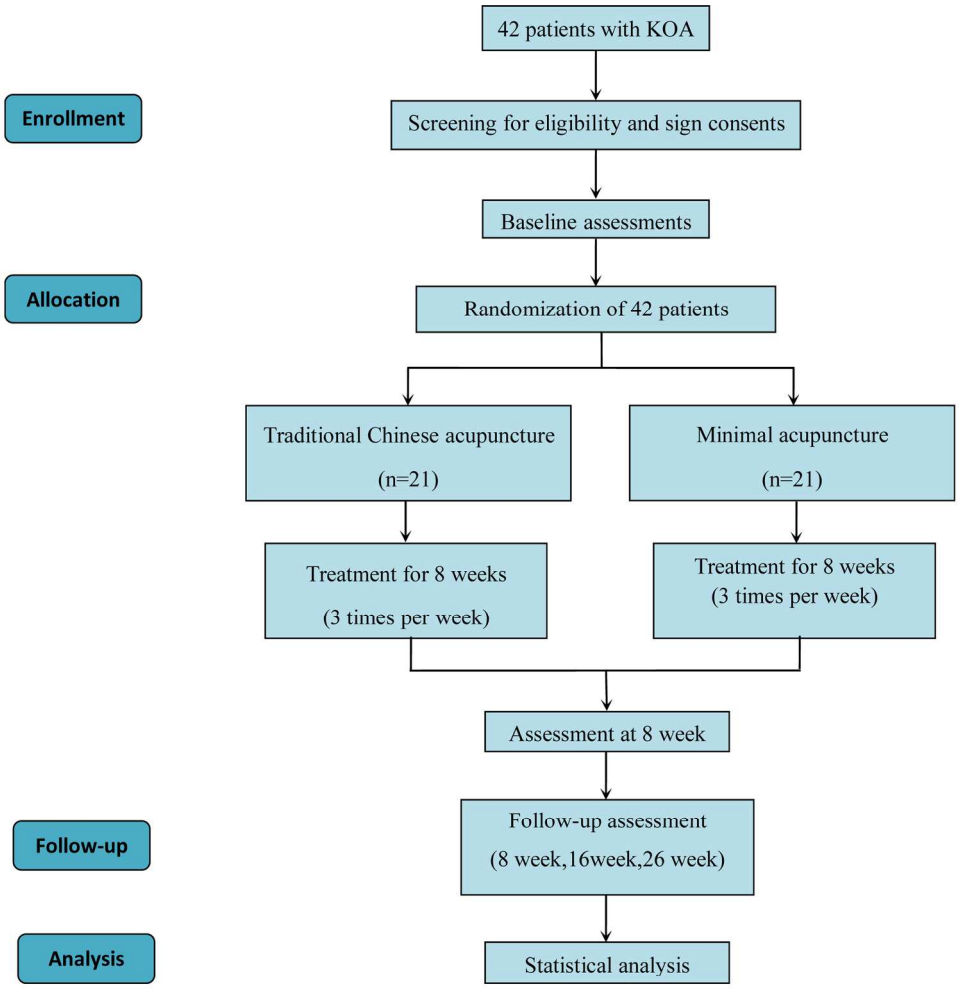

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Traditional Chinese acupuncture vs minimal acupuncture for mild to moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial

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Primary Subject Heading:	Complementary medicine
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Keywords:	Knee Osteoarthritis, Acupuncture, Clinical trials < THERAPEUTICS, PAIN MANAGEMENT

Traditional Chinese acupuncture vs minimal acupuncture for mild to moderate knee osteoarthritis: a protocol for a randomised, controlled pilot trial

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Keywords: knee osteoarthritis; acupuncture; clinical trials ; pain management;

minimal acupuncture

Word count: 11917words.

ABSTRACT

Introduction: Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders. Acupuncture is a popular form of complementary and alternative medicine for musculoskeletal conditions, although the evidence is inconclusive. Our objective is to evaluate the efficacy of Traditional Chinese acupuncture for pain relief and function improvement in mild to moderate knee osteoarthritis (TCAKOA) participants.

Methods/analysis: 42 patients will be recruited who have been diagnosed with mild to moderate KOA and randomly allocated in equal proportions to traditional Chinese acupuncture (TCA) or minimal acupuncture (MA). They will receive acupuncture for 24 sessions over eight weeks. The primary endpoint is success rate, which will be calculated according to a change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores at 8 weeks. Secondary endpoints include pain and function measurement, global change, the quality of life, and the use of NSAID (Celebrex, Pfizer) at 8 weeks, 16 weeks and 26 weeks.

Ethics and dissemination: Ethical approval of this study has been granted by the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (Permission number:2016BL-010-02). We will obtain Written informed consent from all participants. Outcomes of the trial will be disseminated through peer-reviewed publications.

Trial registration numbers: ISRCTN14016893

BACKGROUND

Knee Osteoarthritis (KOA) is one of the most common musculoskeletal disorders,[1] which features as a protracted course of disease. A systematic review shows that the prevalence of KOA is 27.3% in women, and 21.0% in men.[2] A cross-sectional study with 9512 participants aged 50 years or older shows that the prevalence of radiographic KOA was 43.8% in women, and 21.1% in men in South Korea.[3] KOA is one of the leading cause of pain and global disability.

The objective of treating KOA is the alleviation of pain and improving quality of life. Five guidelines[4-7] have evaluated treatment effects on key outcomes of KOA (including pain, function, and disability). Pharmacologic agents, comprising non-opioid/opioid oral, non-steroidal anti-inflammatory drugs (NSAIDs) oral, intra-articular steroid, topical analgesics, and hyaluronate injections are normally utilized, but may be associated with significant adverse reactions (such as peptic ulcer, hypertension, and renal damage).[6 8 9] Guidelines emphasize the potential role of non-pharmacologic treatment, such as aerobic exercise, electrical nerve stimulation (TENS), acupuncture in the treatment. Effective

alternatives to pharmacological are therefore desirable.

Traditional Chinese acupuncture (TCA) is a popular form of complementary and alternative medicine. In 2005, Germany Witt and colleagues showed that 8 weeks of the semi-standardized acupuncture treatment had significantly alleviated the patient's pain and dysfunction contrasted to the minimal acupuncture treatment and no treatment condition.[10] A meta-analysis showed that acupuncture could be considered as an effective physical treatment for KOA.[11] However, in the October 2014 publication of JAMA, Dr. Hinman et al conducted a Zelen design clinical trial to investigate acupuncture for patients suffering from chronic knee pain. The investigation declared that acupuncture did not convey more advantages compared to sham or better function in sufferers with mild or harsh chronic knee pain.[12] However, flaws may exist in the trial design, statistics, interpretation of the results.[13-27] First of all, participants aged ≥ 50 years with moderate to severe chronic knee pain have been recruited. These inclusion criteria may be more suitable for arthroscopic or joint replacement therapy according to the guidance.[1 4] Secondly, acupuncture intervention is 8–12 sessions in total. The dosage for acupuncture is far from sufficient.[15 17] Thirdly, the team registered trial as studying laser acupuncture, instead of traditional acupuncture.[28] Researchers had changed the main aim selectively.[15 27] At present, there is a controversy over whether the acupuncture has benefit for KOA.[1 4] Therefore, our aim is to investigate the intensive TCA for participants with mild to moderate KOA.

MATERIALS AND METHODS

Study design

The study proposes a two-arm, randomised, clinical pilot trial. We will enroll patients from Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University, Beijing Friendship Hospital and Beijing Jishuitan Hospital. The trial has been registered with ISRCTN at Current Controlled Trials (ISRCTN14016893). Some recruitment strategies include radio and print advertisements through the local web sites and community center as well as recruiters with general practitioners. The intervention includes 24 sessions of acupuncture and 3 times follow-up (figure 1, table 1).

Table 1 Time to visit and data collection

	Baseline	Treatment phase		Follow-up phase	
	−1 day	0 day	8 weeks	16 weeks	26 weeks

Patients					
Informed consent	×				
Sign informed Consent		×			
Medical history	×				
Physical examination	×				
Randomization		×			
Intervention		24 sessions of TCA			
TCA group (n=21)					
Comparisons		24 sessions of MA			
MA group (n=21)					
Outcomes					
WOMAC		×	×	×	×
KOOS		×	×	×	×
VAS		×	×	×	×
SF-12		×	×	×	×
The use of NSAID			×	×	×
Participant safety					
Adverse events		×	×	×	×

Inclusion criteria

1. Age 45-75 years (either sex).

2. Chronic knee pain for the last 6 months.

3. Morning stiffness ≤ 30 minutes.

Criteria above are consistent with the National Institute for Health and Clinical Excellence (NICE) Guidelines 2014 Edition.[4]

4. Radiologic confirmation of KOA (Kellgren–Lawrence grade Ⅱ or Ⅲ[29]).

Exclusion criteria

1. Recent acupuncture.

2. Other sickness impact the knee.

3. On surgical operation list.

4. Neurologic as well as psychiatric diseases.

5. Severe coagulopathy.

6. Breastfeeding or pregnancy.

7. Not fitting to take the NSAID (Celebrex, Pfizer) provided.

For bilaterally eligible knees, the most symptomatic side will be evaluated in the course of the study.

Randomisation and allocation concealment

Eligible patients will be randomly assigned to TCA group or MA group in a ratio of 1:1 through central automated allocation procedures. An independent statistician generates randomisation sequence by using the SAS version 9.1.3 statistical package (SAS Institute, Cary, NC, USA). Acupuncturists will not involve in the process of randomisation.

The research assistants who collect data, the statisticians who assess outcomes and make statistical analysis will be blinded to group assignment. Participants will not be disclosed information regarding the allocation. Administrators will not be blinded because of the nature of intervention.

Interventions

The acupuncture protocol follows the CONSORT[30] and STRICTA[31]. All acupuncturists have Chinese medicine practitioner licenses, and they have been qualified for at least ten years. All acupuncturists will receive training in the application of minimal acupuncture. Celebrex will give to participants if their pain intensity ≥ 80 on a 10-cm VAS.[32]

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These points are composed of 10 local points (*ST34, ST35, ST 36, EX-LE2, EX-LE5, GB33, GB34, SP9, SP10, LV8*) and 11 distal points (*GB31, GB36, GB39, GB 41, ST 40, ST41, LR3, BL60, SP6, KI3, LI4*) (figure 2). Physicians can choose 5-6 local points and 3-4 distal points. Needles will be making an optimum insertion into the skin. Acupuncturists are instructed to achieve "De Qi" and needles will be stimulated manually at least 10 seconds.

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confidence intervals.

Ethics and dissemination

The protocol has been registered to ClinicalTrials. gov registry. Any revisions about the protocol will be documented in the ClinicalTrials. gov registry. Written informed consent will be obtained from all participants. The patients will be given adequate time to raise questions and to consider whether or not to involve in the study. We are going to publish the results of this trial in a peer-reviewed clinical journal to have widespread dissemination.

DISCUSSION

KOA is a common public health problem and a leading cause of disability. The results of this pilot study are going to concentrate on patients suffering from mild to moderate KOA and will investigate whether acupuncture can be a practicable and efficient therapy.

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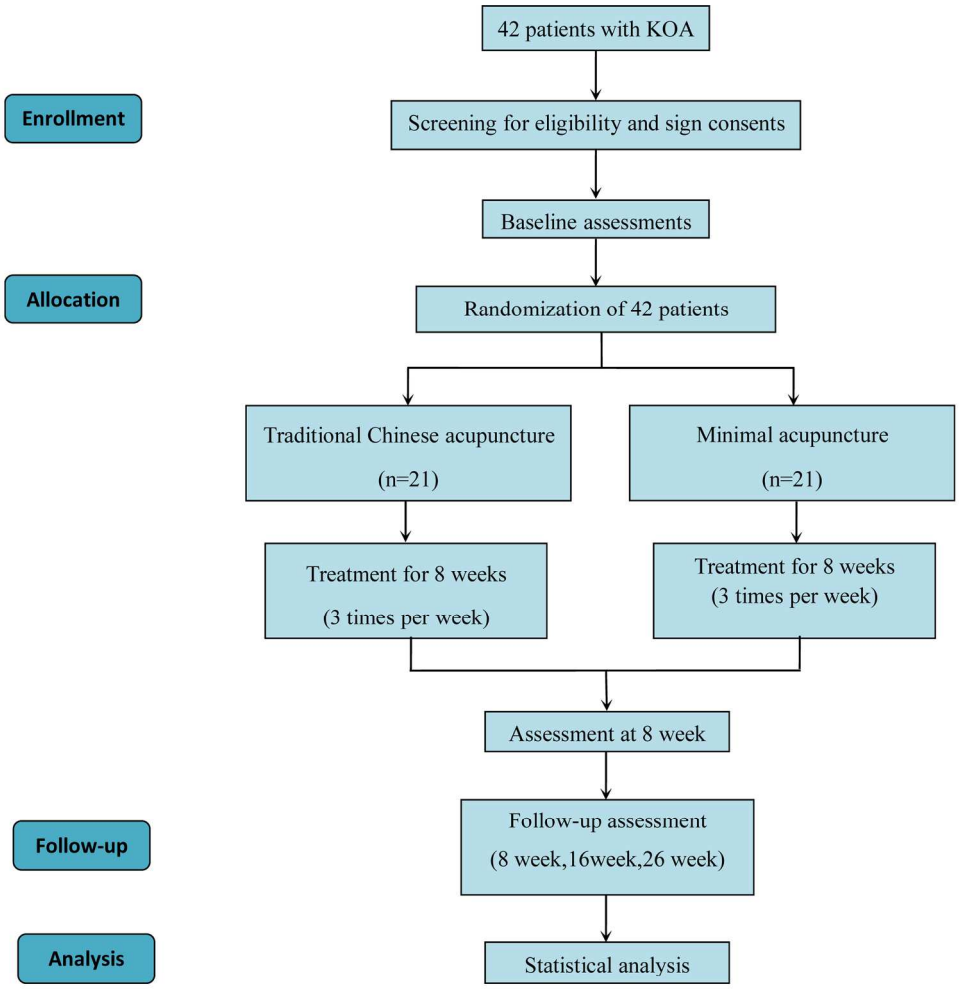

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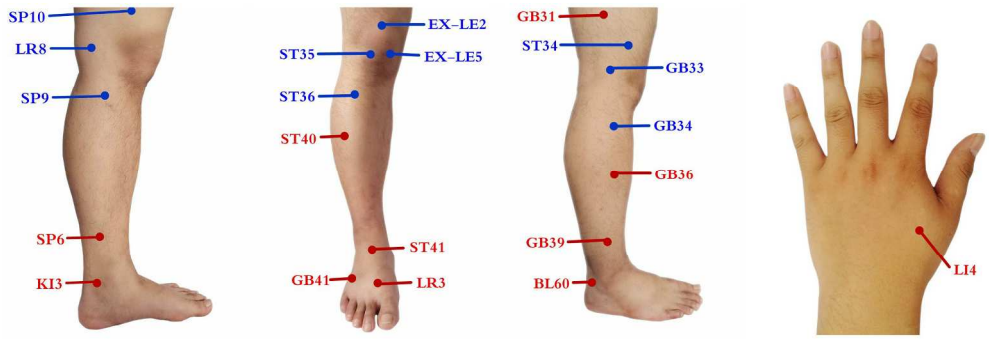

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