

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Effect of 4 weeks versus 8 weeks of acupuncture for knee osteoarthritis in China: protocol for a randomized controlled trial |
| AUTHORS | Yu, Ying; Liu, Cun-Zhi; Wang, Xue-Zhou; Xi, Ya-Wei; Fu, Yi-Ming; Mi, Bao-Hong; Tu, Jian-Feng |

VERSION 1 – REVIEW

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| REVIEWER | Araya-Quintanilla, Felipe Universidad de Las Americas, 1 Rehabilitation in Health Research Center (CIRES) |
| REVIEW RETURNED | 21-Sep-2023 |

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| GENERAL COMMENTS | <p>Background: They clearly detail the first line of work on pharmacological treatment. However, within the non-pharmacological treatment, before acupuncture, there are various other treatments. For example: exercise, rehabilitation, physiotherapy, etc. This is not clear and there is no information about it before reaching the acupuncture rulings. I suggest including this information. Since acupuncture is a third line treatment.</p> <p>I have important doubts about the justification or necessity of this RCT. There is a lot of information about the short-, medium- and long-term effects of acupuncture at KOA. Additionally, they do not cite more up-to-date substantial evidence, I leave some references:</p> <p>Tian H, Huang L, Sun M, Xu G, He J, Zhou Z, Huang F, Liu Y, Liang F. Acupuncture for Knee Osteoarthritis: A Systematic Review of Randomized Clinical Trials with Meta-Analyses and Trial Sequential Analyses. <i>Biomed Res Int.</i> 2022 Apr 21;2022:6561633.</p> <p>Xin S, Liu J, Yang Z, Li C. Comparative effectiveness of moxibustion and acupuncture for the management of osteoarthritis knee: A systematic review and meta-analysis. <i>Heliyon.</i> 2023 Jul 4;9(7):e17805.</p> <p>Mei F, Yao M, Wang Y, Ma Y, Liu Y, Wu M, Wang Z, Feng L, Hu K, Ma B. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. <i>J Evid Based Med.</i> 2023 Jun;16(2):138-140.</p> <p>Sun N, Tu JF, Lin LL, Li YT, Yang JW, Shi GX, Lao LX, Liu CZ. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. <i>Acupunct Med.</i> 2019 Oct;37(5):261-267. (This study include a dose-response analyses)</p> <p>Lee B, Kim TH, Birch S, Alraek T, Lee HW, Nielsen A, Wieland LS, Lee MS. Comparative effectiveness of acupuncture in sham-controlled trials for knee osteoarthritis: A systematic review and</p> |
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network meta-analysis. *Front Med (Lausanne)*. 2023 Jan 9;9:1061878.
Araya-Quintanilla F, Cuyúl-Vásquez I, Gutiérrez-Espinoza H. Does acupuncture provide pain relief in patients with osteoarthritis knee? An overview of systematic reviews. *J Bodyw Mov Ther*. 2022 Jan;29:117-126.

There is no abbreviation of the word EA
There is no reference of SPIRIT checklist

Methods

Line 14: In the randomization they describe in textual form: "A central stratified block randomized...", technically this is a type of sampling. However, if you want to make a type of randomization of this method, it is necessary to mention which will be the stratum or confounder that remains equally in both groups. This variable is usually chosen on the basis that it affects the prognosis or outcome of the intervention.

This is not clear in the study.

Since the patients belong to the hospital, they are not referred to the physical medicine service, it is perhaps unethical to leave them only with pharmacology without referring them to physiotherapy.

Where will the acupuncture sessions take place then? will it be in another place or in the physiotherapy service but without receiving the physiotherapy?

Sample size

If the MCIDs of the important variables are available, I would make the effort to bet on a 2-point change in the NPRS as an experimental hypothesis. Also, have previous studies to know the variance and SD post acupuncture to bet on that difference with the experimental group. The calculation of sample sizes of response rates is not the most suitable for clinical trials with continuous outcomes.

Statistical analysis

For an analysis of more than 3 times, at least one repeated measures ANOVA should be performed for each group. In this case a basic statistic for independent samples is proposed.

Therefore, this is not correct. In addition, there is no test to analyze the normality of the variables. This subheading is very poor.

There is no figure 1 of the SPIRIT flowchart.

Discussion

Line 24: The sentence " the aims to evaluate the long-term effects of 4 and 8 weeks". 8 weeks for clinical outcomes there are not long term.

For RCT protocols, it is necessary to include an item of potential confounders.

I suggest reviewing in detail the SPIRIT structure and guidelines: Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013 Feb 5;158(3):200-7.

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| REVIEWER | Prem, Venkatesan |
| REVIEW RETURNED | 08-Oct-2023 |

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| GENERAL COMMENTS | <p>Introduction: The rationale for the research question is adequate</p> <p>Methods: what is the rationale for dosage of acupuncture 3 times per week for 4 weeks and 8 weeks. Why not have 12 weeks of intervention to have long term effect rather than 8 weeks what is the justification to record outcome measures at 26 weeks as long term effect How blinding of patients in relation to treatment allocation will be maintained In relation to medications, what is the definition of unbearable pain and what will be the dosage of medications and its influence on outcome Will the patients be advised to refrain from exercise How confounding factors such as weight, diet, sleep and psycho social components will be handled Inclusion criteria: including Unilateral and bilateral OA knee, what will be influence on outcome of the study</p> |
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. However, within the non-pharmacological treatment, before acupuncture, there are various other treatments. For example: exercise, rehabilitation, physiotherapy, etc. This is not clear and there is no information about it before reaching the acupuncture rulings. I suggest including this information.

Answers: Thank you for your meaningful suggestions. We have added “Exercise therapy and weight loss have been shown to be effective in KOA1, but sustained maintenance of these methods persists as a challenge² due to depending heavily on patient compliance¹” in the Background section (see Page 6 of 79).

References

1. Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA 2021;325(6):568-78. doi: 10.1001/jama.2020.22171
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393(10182):1745-59. doi: 10.1016/S0140-6736(19)30417-9

2. I have important doubts about the justification or necessity of this RCT. There is a lot of information about the short-, medium- and long-term effects of acupuncture at KOA.

Answers: Thank you for your comments. We agree that there is a lot of trials about the short-, medium- and long-term effects of acupuncture at KOA. However, there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA. For greater clarity of description, we have changed “there is not enough evidence to make a comparison between different acupuncture courses on KOA” to “there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA” in the Background section (see Page 7 of 79). Long-term effect is only the primary outcome and not the innovation of this study. The aim of this trial is to assess the effect of different acupuncture courses (4 weeks vs. 8 weeks) for KOA. To avoid ambiguity, we have removed the “long-term” from the manuscript (see Pages 2, 5, 7 and 8 of 79).

3. Additionally, they do not cite more up-to-date substantial evidence, I leave some references: Tian H, Huang L, Sun M, Xu G, He J, Zhou Z, Huang F, Liu Y, Liang F. Acupuncture for Knee Osteoarthritis: A Systematic Review of Randomized Clinical Trials with Meta-Analyses and Trial Sequential Analyses. *Biomed Res Int*. 2022 Apr 21;2022:6561633.

Xin S, Liu J, Yang Z, Li C. Comparative effectiveness of moxibustion and acupuncture for the management of osteoarthritis knee: A systematic review and meta-analysis. *Heliyon*. 2023 Jul 4;9(7):e17805.

Mei F, Yao M, Wang Y, Ma Y, Liu Y, Wu M, Wang Z, Feng L, Hu K, Ma B. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. *J Evid Based Med*. 2023 Jun;16(2):138-140.

Sun N, Tu JF, Lin LL, Li YT, Yang JW, Shi GX, Lao LX, Liu CZ. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med*. 2019 Oct;37(5):261-267. (This study include a dose-response analyses)

Lee B, Kim TH, Birch S, Alraek T, Lee HW, Nielsen A, Wieland LS, Lee MS. Comparative effectiveness of acupuncture in sham-controlled trials for knee osteoarthritis: A systematic review and network meta-analysis. *Front Med (Lausanne)*. 2023 Jan 9;9:1061878.

Araya-Quintanilla F, Cuyúl-Vásquez I, Gutiérrez-Espinoza H. Does acupuncture provide pain relief in patients with osteoarthritis knee? An overview of systematic reviews. *J Bodyw Mov Ther*. 2022 Jan;29:117-126.

Answers: Thank you for your suggestions. We have cited 3 papers as the references 26, 28 and 46 in the manuscript as follows: "Acupuncture is widely used in clinical practice to treating KOA, resulting in notable improvements in pain and joint function^{21 25 26}" (see Page 7 of 79); "The effect of acupuncture is inherently intertwined with the treatment course^{22 28}" (see Page 7 of 79) and "Firstly, the nature of the intervention and lack of completely inert sham needles precludes the possibility of blinding both acupuncturists and patients⁴⁶" (see Page 21 of 79).

References

26. Mei F, Yao M, Wang Y, et al. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. *J Evid Based Med* 2023;16(2):138-40. doi: 10.1111/jebm.12532

28. Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37(5):261-67. doi: 10.1136/acupmed-2017-011608

46. Lee B, Kim TH, Birch S, et al. Comparative effectiveness of acupuncture in sham controled trials for knee osteoarthritis: A systematic review and network meta-analysis. *Front Med (Lausanne)* 2022; 9:1061878. doi: 10.3389/fmed.2022.1061878

4. There is no abbreviation of the word EA.

Answers: Sorry for this mistake. The full name of the EA, Electro-acupuncture, has been added (see Page 8 of 79).

5. There is no reference of SPIRIT checklist.

Answers: Thank you for your kind comment. We have added reference of SPIRIT checklist as follows: "The protocol adheres to the principles of the Declaration of Helsinki and will be reported in accordance with the SPIRIT guidelines (additional file 1)³⁹" (see Page 9 of 79).

Reference

39. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583

6. In the randomization they describe in textual form: "A central stratified block randomized...", technically this is a type of sampling. However, if you want to make a type of randomization of this method, it is necessary to mention which will be the stratum or confounder that remains equally in both groups. This variable is usually chosen on the basis that it affects the prognosis or outcome of the intervention. This is not clear in the study.

Answers: Thank you for your kind comments. Given the limited sample size, it is not suitable to set more stratification factors. The stratification factor of this trial is the centre. To avoid ambiguity, we have rewritten the sentence as “This trial will use stratified block randomisation, stratified by centre, with variable block length” (see Page 11 of 79). Despite randomisation, the results may still be influenced by several confounders. Therefore, we have added “Subgroup analysis will be used for potential confounders such as age, gender and weight, and affected knee” in the Data analysis section (see Page 19 of 79).

7. Since the patients belong to the hospital, they are not referred to the physical medicine service, it is perhaps unethical to leave them only with pharmacology without referring them to physiotherapy. Where will the acupuncture sessions take place then? will it be in another place or in the physiotherapy service but without receiving the physiotherapy?

Answers: Thank you for your valuable suggestions. The patients in both intervention and control groups in this trial will receive acupuncture therapy, which belongs to physiotherapy (see Pages 11-14 of 79). We will not leave patients only with pharmacology. Moreover, according to the previous trial carried out by our team, about one third of patients had received other physiotherapy at some point in the past but had little benefit¹. The acupuncture will be provided at the department of acupuncture in hospital. The patients will be advised to maintain their lifestyle and not to receive other physiotherapy for reducing confounding factors. And the protocol has been approved by the Medical Ethical Committee of Beijing University of Chinese Medicine (2023BZYL0506) (see Page 20 of 79).

Reference

1. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol*. 2021;73(3):448-458.

8. If the MCIDs of the important variables are available, I would make the effort to bet on a 2-point change in the NPRS as an experimental hypothesis. Also, have previous studies to know the variance and SD post acupuncture to bet on that difference with the experimental group. The calculation of sample sizes of response rates is not the most suitable for clinical trials with continuous outcomes.

Answers: Thank you for your valuable suggestions. The concept of MCII was introduced to present the effect of intervention at the individual level. Calculating sample sizes based on the difference in variance and standard deviation between groups is desirable, however an alternative method exists. An advisable design using MCII is based on a “responder analysis,” namely, comparing the proportion of patients with each intervention who experience a change greater than MCII. This type of data presentation can provide patients and policy makers with more straightforward information that allows them to decide whether a treatment should be used. The response rate at week 26 is the primary outcome in this trial and sample size is calculated based on this primary outcome. This method was also used in our previous research¹ and other KOA study².

References

1. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584

2. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354(8):795-808. doi: 10.1056/NEJMoa052771

9. For an analysis of more than 3 times, at least one repeated measures ANOVA should be performed for each group. In this case a basic statistic for independent samples is proposed. Therefore, this is not correct. There is no test to analyze the normality of the variables. This subheading is very poor.

Answers: Thank you for your suggestions. We have added “NRS and WOMAC scores at multiple time points will be compared using a mixed-effects model with repeated measure as sensitivity analysis” (see Pages 18 and 19 of 79) and a normality test for the measurement data in the Data analysis section as follows: “Measurement data will be tested for normality. For those conforming to a normal

distribution, the mean and standard deviation will be calculated. For those that do not, median (interquartile range) will be calculated” (see Page 18 of 79) and “If measurement data conforms to a normal distribution, it will use t-test analysis. While it does not conform to normal distribution, it will be subjected to Mann-Whitney test” (see Page 18 of 79).

10. There is no figure 1 of the SPIRIT flowchart.

Answers: Thank you for your suggestion. We have changed Table 1 into Figure 1.

11. Line 24: The sentence “the aims to evaluate the long-term effects of 4 and 8 weeks”. 8 weeks for clinical outcomes there are not long term.

Answers: We are sorry for this unclear description. Initially, we deemed that assessing outcomes at 26-week follow-up was long-term effect. However, following a comprehensive review of existing literature, we recognised the existence of varying definitions for the term “long-term effect”. To avoid controversy, the term of “long-term effect” has been deleted (see Page 21 of 79).

12. For RCT protocols, it is necessary to include an item of potential confounders.

Answers: Thank you for this meaningful suggestion. Admittedly, several confounding factors exist for KOA, which may impact the results, despite randomisation. Therefore, we have added “Subgroup analysis will be used for potential confounders such as age, gender and weight, and affected knee” in the Data analysis section (see Page 19 of 79).

13. I suggest reviewing in detail the SPIRIT structure and guidelines: Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* 2013 Feb 5;158(3):200-7.

Answers: Thank you for your kind suggestion. We have carefully read and cited this literature.

According to SPIRIT 2013 and your advice, we have made three changes in the manuscript: (1) adding the description of exercise therapy and weight loss in Background section (see Page 5), (2) changing Table 1 into Figure 1, (3) adding an explanation of why a DMC is not needed as follows: “The trial has a low risk of safety and is not designed for interim analyses. Therefore, Data Monitoring Committee will not be established” (see Page 19 of 79).

14. Unfortunately my judgment towards the study is not favorable for publication due to the lack of methodological rigor, statistical analysis proposal and lack of substantiation of the study.

Answers: Thank you for your comment. In this trial, the random number sequence and treatment plans will be placed inside corresponding the numbered opaque envelopes. And various researchers will be responsible for the generation of the random number sequence, allocation concealment, patients’ recruitment, acupuncture treatment and outcome measure assessment to control bias. In randomised controlled trials of acupuncture, it is common that acupuncturists are not blinded. However, acupuncturists will receive training on how to minimize bias by interacting less with patients. This trial aims to determine the effectiveness of different acupuncture courses, rather than assessing their efficacy. Thus, patients will not be blinded. In this study, data analysts and outcome assessors will be blinded.

We do have shortcomings in our statistical analyses. As per your previous comments, we have added normality test, a mixed-effects model with repeated measure analysis as sensitivity analysis and subgroup analysis in Data analysis section as follows: “Measurement data will be tested for normality. For those conforming to a normal distribution, the mean and standard deviation will be calculated. For those that do not, median (interquartile range) will be calculated” (see Page 18 of 79). “If measurement data conforms to a normal distribution, it will undergo t-test analysis. While it does not conform to normal distribution, it will be subjected to Mann-Whitney test” (see Page 18 of 79). “NRS and WOMAC scores at multiple time points will be compared using a mixed-effects model with

repeated measure as sensitivity analysis” (see Pages 18 and 19 of 79). “Subgroup analysis will be used for potential confounders such as age, gender and weight, and affected knee” (see Page 19 of 79).

No disease-modifying pharmaceutical agents have been approved, and current KOA treatments are mainly used to treat symptoms. All guidelines emphasize the importance of non-pharmacological treatments. Acupuncture has been shown to have effect and safety in KOA patients¹. The effect of acupuncture is inherently intertwined with the treatment course^{2 3}. The latest clinical practice guideline suggested acupuncture for 4–8 weeks on KOA⁴. However, there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA. In order to fill the gaps in the field., we conduct this trial to evaluate the effect of 4 weeks versus 8 weeks of acupuncture on KOA.

References

1. Mei F, Yao M, Wang Y, et al. Acupuncture for knee osteoarthritis: A systematic review and meta-analysis. *J Evid Based Med* 2023;16(2):138-40. doi: 10.1111/jebm.12532
2. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc* 2013;88(10):1141-6. doi: 10.1016/j.mayocp.2013.06.009
3. Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37(5):261-67. doi: 10.1136/acupmed-2017-011608
4. Luo X, Liu J, Li Q, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. *J Evid Based Med* 2023;16(2):237-45. doi: 10.1111/jebm.12526

Reviewer 2:

1. Introduction:

The rationale for the research question is adequate.

Answer: Thank you very much for endorsing our work.

2. what is the rationale for dosage of acupuncture 3 times per week for 4 weeks and 8 weeks.

Answers: Thank you for your comment. The effect of acupuncture is associated with dose, including frequency and courses¹. Our previous trial revealed that acupuncture 3 times per week immediately improved knee pain and dysfunction and had longer lasting effect². Both 4-week and 8-week courses of acupuncture treatment for KOA have been reported to be effective^{3 4}. 4–8 weeks of acupuncture for KOA is recommended by the latest clinical practice guideline⁵. However, there is a paucity of evidence about head-to-head comparison of diverse acupuncture courses, with regards to their effect in treating KOA. In order to fill the gaps in the field, we conduct this trial to evaluate the effect of 4 weeks versus 8 weeks of acupuncture for KOA. We have also modified the Background section for clarity of presentation (see Page 8 of 79).

References

1. Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37(5):261-67. doi: 10.1136/acupmed-2017-011608
2. Lin LL, Tu JF, Wang LQ, et al. Acupuncture of different treatment frequencies in knee osteoarthritis: a pilot randomised controlled trial. *Pain* 2020;161(11):2532-38. doi: 10.1097/j.pain.0000000000001940
3. Liu J, Li Y, Li L, et al. Effects of acupuncture at acupoints with lower versus higher pain threshold for knee osteoarthritis: a multicenter randomized controlled trial. *Chin Med* 2022;17(1):67. doi: 10.1186/s13020-022-00626-3
4. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584
5. Luo X, Liu J, Li Q, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. *J Evid Based Med* 2023;16(2):237-45. doi: 10.1111/jebm.12526

3. Why not have 12 weeks of intervention to have long term effect rather than 8 weeks?

Answers: Thank you for your comment. The guideline recommended 4-8 weeks of acupuncture for KOA, compared to 12 weeks¹. However, it is unclear which course of acupuncture is more effective, 8 weeks or 4 weeks for KOA. We conduct this trial to evaluate the effect of 4 weeks versus 8 weeks of acupuncture for KOA. Admittedly, we do not compare multiple treatment courses and it has been indicated within the Limitations section “the trial only compared two common treatment courses of acupuncture, 4 weeks and 8 weeks, without any comparison to other courses” (see Page 22 of 79). We have also modified the Background section for clarity of presentation (see Page 8 of 79).

Reference

1. Luo X, Liu J, Li Q, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. *J Evid Based Med* 2023;16(2):237-45. doi: 10.1111/jebm.12526

4. What is the justification to record outcome measures at 26 weeks as long-term effect?

Answers: Thank you for your comment. After conducting an extensive literature review, it became apparent that the definition of long-term effect varies. To avoid controversy, we have removed the “long-term” from the manuscript (see Pages 2, 5, 7 and 8 of 79).

5. How blinding of patients in relation to treatment allocation will be maintained?

Answers: Sorry for unclear description. We have amended the Blinding section as “In consideration of the nature of the intervention, the acupuncturist and patients will not be blinded. The outcome assessor and data analyst will be blinded to group assignments. The allocation will remain undisclosed to outcome assessor and data analyst until the completion of the statistical analysis” (see Page 11 of 79).

6. In relation to medications, what is the definition of unbearable pain and what will be the dosage of medications and its influence on outcome?

Answers: Thank you for your comment. As the tolerance of pain varies among individuals, the definition of unbearable pain is challenging. Thus, there is no definition of unbearable pain in this trial. The protocol mentioned “Diclofenac Sodium Enteric-coated Tablets will be dispensed in sets of 6 tablets, with instructions for patients to ingest one orally three times daily” (see Page 12 of 79). We have supplemented “25 mg per tablet” (see Page 12 of 79). Medication usage can influence outcomes, so it will be used as a secondary outcome (see Page 17 of 79).

7. Will the patients be advised to refrain from exercise?

Answers: Thank you for your comment. Exercise is indeed an influencing factor, and we have recommended that patients maintain their previous lifestyle to reduce the influence of confounding factors (see Page 9 of 79).

8. How confounding factors such as weight, diet, sleep and psycho social components will be handled?

Answers: Thank you for your comment. In this trial, participants will be randomized to ensure balanced distribution of known and unknown confounding factors between the two groups. And we have added “Subgroup analysis will be used for potential confounders such as age, gender and weight” in Data analysis section (see Page 19 of 79). Besides, in term of diet, sleep and psycho social components, we advise patients to maintain their existing lifestyle (see Page 9 of 79).

9. Inclusion criteria: including Unilateral and bilateral OA knee, what will be influence on outcome of the study?

Answers: Thank you for your comment. Inclusion of patients with unilateral and bilateral OA knee is intended to increase the external validity of the findings, which is a common method^{1 2}. Furthermore, we defined the evaluation side according to previous studies^{3 4}. And we have added subgroup analysis according to affected knee in the Data section (see Page 19 of 79).

References

1. Deyle GD, Allen CS, Allison SC, et al. Physical Therapy versus Glucocorticoid Injection for Osteoarthritis of the Knee. *N Engl J Med* 2020;382(15):1420-29. doi: 10.1056/NEJMoa1905877
2. Harris R, Strotmeyer ES, Sharma L, et al. The Association Between Severity of Radiographic Knee OA and Recurrent Falls in Middle and Older Aged Adults: The Osteoarthritis Initiative. *J Gerontol A Biol Sci Med Sci* 2023;78(1):97-103. doi: 10.1093/gerona/glac050
3. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet*. 2005;366:136–143. doi: 10.1016/S0140-6736(05)66871-7
4. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584

VERSION 2 – REVIEW

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|-------------------------|--|
| REVIEWER | Araya-Quintanilla, Felipe Universidad de Las Americas, 1 Rehabilitation in Health Research Center (CIRES) |
| REVIEW RETURNED | 09-Nov-2023 |
| GENERAL COMMENTS | need changes |

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Dr. Felipe Araya-Quintanilla, Universidad de Las Americas, Universidad SEK

Comments to the Author:

need changes

Answers: Thank you for your comment. According to your previous comments, we have revised the manuscript as follows:

1.However, within the non-pharmacological treatment, before acupuncture, there are various other treatments. For example: exercise, rehabilitation, physiotherapy, etc. This is not clear and there is no information about it before reaching the acupuncture rulings. I suggest including this information.

Answers: Thank you for your comment. We have added “Cognitive behavioral therapy may reduce pain of KOA patients, however, evidence is limited⁸.” in the Background section (see Pages 5 and 22 of 65).

Reference

8. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol* 2020;72(2):220-33. doi: 10.1002/art.41142

8. If the MCIDs of the important variables are available, I would make the effort to bet on a 2-point change in the NPRS as an experimental hypothesis. Also, have previous studies to know the variance and SD post acupuncture to bet on that difference with the experimental group. The calculation of sample sizes of response rates is not the most suitable for clinical trials with continuous outcomes.

Answers: Thank you for your valuable suggestions. In addition to the previous reply to you and original sample size based on primary outcome (response rates), we calculated the sample size based on mean and standard deviation of NRS scores and WOMAC function scores. Drawing upon our team's prior research¹, the mean NRS scores at week 26 for the 4-week and 8-week groups will be 4.2 and 3.0, respectively. The standard deviation will be 1.8. To provide 80% power at a two-tailed α level of 0.05, 47 patients each group are needed utilizing PASS 15.05 software and accounting for 20% dropout. The mean WOMAC function scores at week 26 for both groups will be 14.0 and 10.0 with a standard deviation of 7.0. Accounting for 20% dropout, 63 patients each group are needed to provide 80% power at a two-tailed α level of 0.05. Both 47 and 63 are less than the original sample size of 74 each group, which suggests that our sample size is powerful to test the differences of NRS and WOMAC function scores between 4-week group and 8-week group.

Reference

1. Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol* 2021;73(3):448-58. doi: 10.1002/art.41584