PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Application of electroacupuncture for postoperative pain management after total knee arthroplasty: a study protocol for a single-blinded, randomised placebo-controlled trial
AUTHORS	Zhong, Sheng; Huang, Hai; Xie, Jun; Zhao, Ling; Song, Xiu-ling; Chen, Yue-lai; Xiao, Lian-bo

VERSION 1 - REVIEW

REVIEWER	Gangmi Kim Clinical Professor, Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Republic of Korea
REVIEW RETURNED	15-Sep-2018

GENERAL COMMENTS	The study topic is proper because evidence to support or refute the use of acupuncture as a complemantary medicine in treating pain is not sufficient up to now. The study design is appropriate to answer the research question as well. The major concern is that some ideas of traditional Chinese medicine are presented in the text without any references. Or some statements are presented with wrong references. 1. In line 90-91 (“According to the theories of Traditional Chinese Medicine, acupuncture can help dredge the meridians and correct imbalance of flow of energy.”), a reference of a scientific article should be provided for this statement to be published on the medical journal. Otherwise, deletion of the sentence is strongly recommended. 2. In line 93, reference No. 6 and 7 do not support that acupunture is effective for pain. The authors concluded either the benefits of acupuncture do not meet thresholds for clinical relevance or evidence is not sufficient. 3. In line 94, reference No. 8 does not support electroacupuncture is beneficial for postoperative pain. It showed low or very low certainty that electrotherapy and acupuncture improve pain. Minor concerns: 1. Please specify the dates of the study in the manuscript. 2. In line 73-74, please elaborate on this sentence. What is the placebo effect in this study? Please describe it specifically. And who are affected by the placebo?

	3. In line 96-99, a brief summary of the reference No. 10 to 13 would help the readers to understand your hypothesis and the design of this study for prove that hypothesis. 4. In line 114, could you please provide a brief table or a diagram of the ERAS program for this study? Do you routinely apply ERAS program for TKA patients in your institution or apply the ERAS for this study especially? The readers may want to know if the ERAS program is a routine in TKA. 5. In line 149, why No. 4 is ineligible criteria? 6. In line 151-173 (study interventions), first, could you explain the anatomical locations of the three acupoints in medical terms with a reference? Second, please explain the reason why those three acupoints were selected with a reference. Third, GB4, ST36, and SP9 are located on knee according to Figure 3. Is there any risk of surgical site infection? Because those three points are close to operation wound. 7. In line 159, please provide an explanation for De-qi sensation for readers of medical journal. 8. In line 173, it is questionable if the reference No. 15 is appropriate to support the sham-EA method is effective, because participant blinding was performed only in two of the 12 centers. 9. In line 203, please provide a definition or the description of the HSS score with a reference for it. A supplemental Table would be helpful for readers. 10. In line 208-210, please present a reference for the sentence. 11. In line 212, please present a reference for HAMA and a supplemental Table for readers' convenience. 12. In line 218-220, could you provide the detail of functional index-emesis as supplement for readers' convenience? 13. In line 262-263, please provide references for the statement. 14. In line 263-267, -2.26 should be corrected as -22.6. 15. Because acute postoperative pain is highly associated with persistent post-surgical pain, as written in the manuscript, controlling pain and suppressing it under a target level before discharge is important. How much do you plan to control postoperative pain before discharge? Do you have any specific discharge criteria? 16. Discussion needs to be revised. Overall, it is obscure and unclear what authors' idea is and what do you want to discuss with the readers. 17. Please check Table 1. if it is correctly edited.

REVIEWER	Barbara Shay University of Manitoba Canada
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	Page 1 line 28 when is the study planned? What dates Page 1 line 39 not major flaws although there are only 2 groups. It is not completely clear if they are comparing the outcomes for two treatment groups, there is no acupuncture only and no sham-acupuncture groups. Has this been proven already? Page 7 line 111 how are the patients be recruited? Page 7 line 118- is the difference in the VAS clinically meaningful? Will you be able to tell the difference between sham and verum EA with only -1.14 difference in VAS? Page 8 line 144 What is the purpose of having an ASA grade? Page 9 line 159 and 169 does the electrical device have a brand name and manufacturer? Line 160 define tolerable intensity (is it as strong as tolerated?) Page 10 line 176- how long is the PCA administered post-op? Line 181 discontinuing criteria (1) does not make sense to me (2) what kinds of changes would make it inappropriate for acupuncture post op. (4) what kinds of adverse reactions would indicate discontinuance? What do you mean by rapid deterioration? Line 192, who records the VAS, ?the patient? The assessor? Do they put a mark on the VAS?This is not clear. Line 194 no pain not symptoms Line 194-195 it seems you are saying this twice; additional dose of PCA… Line 197, what is the typical Length of stay for post-op TKR? How will the additional use of analgesics be collected? Does the patient come back after 2 weeks with their case report form? Line 209 you need a reference for according to previous reports, EA has the potential to promote functional rehabilitation. What do you mean functional rehab, is this related to swelling? Line 223 are needle sticking and breaking common adverse effects? Do you mean hematoma or a surface bruise? Line 243 244- no idea what you mean by calculating the differences in the enumeration data??? Line 261. Postoperative pain after TKA is mostly caused by post-op functional exercise. Really? Need a reference??? Lines 267-269- I don't understand why you are discussing a single EA treatment without multimodal analgesia here…. Fig 2 shows that the needles are 2 different lengths? Is this correct? Could someone be able to tell it is the sham needle? A few problems with written English…. Page 4 line 44 relieve Page 4 line 46 people first "patients with OA" Keywords: delete "the" study protocol Page 5 line 65 relieve Line 103 what is an effective electroacupuncture blind method? Line 108 what is a parallel RCT? There are some abbreviations that are not standard… Page 6 line 89 enhanced recovery after surgery (ERAS)?

	Page 12 line 236 237 FAS, PPS and SS I have never heard of these abbreviations.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Dear Prof. Kim:

Thank you very much for your kind comments and suggestions. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We appreciate for your warm work earnestly and hope that the corrections will meet with approval. Revised portions are marked in the manuscript. The main corrections in the paper and the response to your comments are as following:

COMMENT	RESPONSE
1. In line 90-91 ("According to the theories of Traditional Chinese Medicine, acupuncture can help dredge the meridians and correct imbalance of flow of energy."), a reference of a scientific article should be provided for this statement to be published on the medical journal. Otherwise, deletion of the sentence is strongly recommended.	We have deleted this sentence according to your recommendation.
2. In line 93, reference No. 6 and 7 do not support that acupuncture is effective for pain. The authors concluded either the benefits of acupuncture do not meet thresholds for clinical relevance or evidence is not sufficient.	Thank you for raising this major question. It is because of the uncertainty of the efficacy of acupuncture or electroacupuncture that we conducted this randomized controlled trial. We have revised this section and updated the references.
3. In line 94, reference No. 8 does not support electroacupuncture is beneficial for postoperative pain. It showed low or very low certainty that electrotherapy and acupuncture improve pain.	Drug-free interventions are the direction of our efforts, we are precise because of the clinical observation of the effectiveness of electroacupuncture. Evidence-based medicine has also confirmed that electrotherapy and acupuncture may be effective against postoperative pain, and we conducted this study. We have revised the discussion in this section.
4. Please specify the dates of the study in the manuscript.	We planned to begin recruiting patients from June 2018.
5. In line 73-74, please elaborate on this sentence. What is the placebo effect in this study? Please describe it specifically. And who are affected by the placebo?	The acupuncturists cannot be blinded in the study, so the bias cannot be avoided. We have corrected the inappropriate expression.

6. In line 96-99, a brief summary of the reference No. 10 to 13 would help the readers to understand your hypothesis and the design of this study for prove that hypothesis.	We have added a summary and revised this part.
7. In line 114, could you please provide a brief table or a diagram of the ERAS program for this study? Do you routinely apply ERAS program for TKA patients in your institution or apply the ERAS for this study especially? The readers may want to know if the ERAS program is a routine in TKA.	We have added a table of ERAS program for this study, this program is routinely applied in our hospital.
8. In line 149, why No. 4 is ineligible criteria?	Patients with high ASA grades have a greater risk of surgery and are not recommended to participate in our trials based on experimental ethical considerations.
9. In line 151-173 (study interventions), first, could you explain the anatomical locations of the three acupoints in medical terms with a reference? Second, please explain the reason why those three acupoints were selected with a reference. Third, GB34, ST36, and SP9 are located on knee according to Figure 3. Is there any risk of surgical site infection? Because those three points are close to operation wound.	(1) ST32: On the anterolateral aspect of the thigh, on the line connecting the lateral end of the base of the patella with the anterior superior iliac spine, 6 B-cun superior to the base of the patella. ST36: On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 cun inferior to ST35. ST36 is located on the tibialis anterior muscle. SP9: On the tibial aspect of the leg, in the depression between the border of the medial condyle of the tibia and the medial border of the tibia. GB34: On the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula.[1] (2) Many studies on ST36 shows that it has analgesic effect after TKA and it has been used clinically for a long time.[2] Similarly, GB34, ST32, and SP9 are also used for analgesia after TKA before.[3,4] Depending on the theory of Traditional Chinese Medicine and clinical experience, we selected those acupoints for this study. (3) Although the 3 acupoints are located on knee, the needles do not penetrate into the joint cavity and we tested during the operation. We have applied it in clinical practice for several years and there was no infection associated with EA. 1. World Health Organization. Regional Office for the Western Pacific. WHO standard acupuncture point locations in the Western Pacific Region. Manila : World Health Organization, Western Pacific Region 2008.

	2. Zhang R, Lao L, Ren K, et al. Mechanisms of acupuncture-electroacupuncture on persistent pain. 2014. doi:10.1097/ALN.0000000000000101 3. Ntritsou V, Mavrommatis C, Kostoglou C, et al. Effect of perioperative electroacupuncture as an adjunctive therapy on postoperative analgesia with tramadol and ketamine in prostatectomy: a randomised sham-controlled single-blind trial. Acupunct Med 2014;32:215–22. doi:10.1136/acupmed-2013-010498 4. Mikashima Y, Takagi T, Tomatsu T, et al. Efficacy of acupuncture during post-acute phase of rehabilitation after total knee arthroplasty. J Tradit Chinese Med = Chung i tsa chih ying wen pan 2012;32:545–8.
10. In line 159, please provide an explanation for De-qi sensation for readers of medical journal.	De-qi sensation is a sensation mediated by sensory afferent nerves. It is generally characterised by soreness, numbness, heaviness, distension, and aching in the deep tissues surrounding the inserted needle. 1. Lundeberg T. To be or not to be: the needling sensation (de qi) in acupuncture. Acupunct Med 2013;31:129–31. doi:10.1136/acupmed-2013-010384
11. In line 173, it is questionable if the reference No. 15 is appropriate to support the sham-EA method is effective, because participant blinding was performed only in two of the 12 centers.	The participant blinding was performed in 12 centres. In the article (reference No. 15), they randomly selected 2 hospitals to test if the participants can distinguish the EA or sham-EA and the purpose is to prove the effectiveness. One of the authors (YLC) participated in that trial and he guides us to perform the method.
12. In line 203, please provide a definition or the description of the HSS score with a reference for it. A supplemental Table would be helpful for readers.	We have added the supplemental Table.
13. In line 208-210, please present a reference for the sentence.	We removed this sentence from here, and the relevant discussion we put in the Introduction section.
14. In line 212, please present a reference for HAMA and a supplemental Table for readers' convenience.	We have added the supplemental Table.

15. In line 218-220, could you provide the detail of functional index-emesis as supplement for readers' convenience?	We have added the supplemental Table.
16. In line 262-263, please provide references for the statement.	We have revised this part and added the references.
17. In line 263-267, -2.26 should be corrected as -22.6.	It may be our description mistake. We wanted to use a uniform standard to describe the VAS score (from 0 to 10), which consistent with previous descriptions.
18. Because acute postoperative pain is highly associated with persistent post-surgical pain, as written in the manuscript, controlling pain and suppressing it under a target level before discharge is important. How much do you plan to control postoperative pain before discharge? Do you have any specific discharge criteria?	The discharge criteria for the patients without special deformity is consists of three parts. (1) The VAS score is less than 3 at rest; (2) At least 90 degrees of flexion and functional muscle power; (3) Independent mobility with a suitable walking aid and safe on climbing stairs with support.
19. Discussion needs to be revised. Overall, it is obscure and unclear what authors' idea is and what do you want to discuss with the readers.	We have revised the part of Discussion.
20. Please check Table 1. if it is correctly edited.	We are sorry for the mistake, and we have corrected the table.

Once again, thank you very much for your comments and suggestions. We look forward to your information about my revised papers and thank you for your good comments.

Yours sincerely,

Sheng Zhong

Reviewer 2

Dear Prof. Shay:

Thank you very much for your kind comments and suggestions. We have tried our best to revise and improve the manuscript and made many changes in the manuscript according to your good comments. The suggestions are helpful and revised portions are marked in the manuscript. We have studied comments carefully and have made the correction which we hope meet with approval. The main corrections in the paper and the response to your comments are as following:

COMMENT	RESPONSE
1. Page 1 line 28 when is the study planned? What dates	The study was planned from December 2017 to April 2018 and we began subjects from June 2018.

2. Page 1 line 39 not major flaws although there are only 2 groups. It is not completely clear if they are comparing the outcomes for two treatment groups, there is no acupuncture only and no sham-acupuncture groups. Has this been proven already?	From clinical observations, we found that electroacupuncture is superior to manual acupuncture because of its sustained stimulation effect. So we decided to design a randomized controlled single-blind trial to verify its validity. The purpose of this study is to confirm the efficacy of electroacupuncture in postoperative analgesia. We will evaluate the efficacy of manual acupuncture in future studies.
3. Page 7 line 111 how are the patients be recruited?	We recruited from patients who were preparing for unilateral total knee arthroplasty in the inpatient ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital.
4. Page 7 line 118- is the difference in the VAS clinically meaningful? Will you be able to tell the difference between sham and verum EA with only -1.14 difference in VAS?	We don't think there is only a difference of -1.14 between EA and Sham. The -1.14 difference in the VAS score seems not clinically meaningful and it is used to calculate the sample size of this study. We use a smaller mean difference to obtain a larger sample size to ensure the statistical power is enough.
5. Page 8 line 144 What is the purpose of having an ASA grade?	Patients with high ASA grades have a greater risk of surgery and are not recommended to participate in our trials based on experimental ethical considerations.
6. Page 9 line 159 and 169 does the electrical device have a brand name and manufacturer?	The electrical stimulation device is Hwato SDZ-V, produced by Suzhou Medical Appliance Factory, Suzhou, China.
7. Page 10 line 176- how long is the PCA administered post-op?	PCA is administered 48 hours post-op.
8. Line 181 discontinuing criteria (1) does not make sense to me (2) what kinds of changes would make it inappropriate for acupuncture post op. (4) what kinds of adverse reactions would indicate discontinuance? What do you mean by rapid deterioration?	(1) Some patients have not received acupuncture treatment before, and they may not endure the discomfort of acupuncture after surgery, or fainting during acupuncture treatment, this part of patients will not follow the protocol with postoperative acupuncture treatment. (2) Severe physiological and pathological changes such as anaesthesia accidents, cardiac-cerebrovascular accidents, nerve or vascular injury during surgery. (3) We refer to the severe complications related to surgery, such as deep vein thrombosis, pulmonary embolism and severe allergic reactions.

	We have revised this part.
9. Line 192, who records the VAS, ?the patient? The assessor? Do they put a mark on the VAS?This is not clear.	The VAS score is assessed by the patients and they will put a mark on the visual analogue scale, then assessors record it.
10. Line 194 no pain not symptoms	We have corrected the word as your suggestion.
11. Line 194-195 it seems you are saying this twice; additional dose of PCA…	We have removed the duplicate expression.
12. Line 197, what is the typical Length of stay for post-op TKR? How will the additional use of analgesics be collected? Does the patient come back after 2 weeks with their case report form?	The patient will be transferred to the rehabilitation ward for 2 weeks of rehabilitation after surgery. We can collect the additional use of analgesics within 2 weeks.
13. Line 209 you need a reference for according to previous reports, EA has the potential to promote functional rehabilitation. What do you mean functional rehab, is this related to swelling?	We removed this sentence from here, and the relevant discussion we put in the Introduction section.
14. Line 223 are needle sticking and breaking common adverse effects? Do you mean hematoma or a surface bruise?	We have corrected the inappropriate expression.
15. Line 243 244- no idea what you mean by calculating the differences in the enumeration data???	We are sorry for the wrong expression. It is the count data actually.
16. Line 261. Postoperative pain after TKA is mostly caused by post-op functional exercise. Really? Need a reference???	It may our wrong expression. For total knee replacement surgery, the principle of gap balance is rather tight, not loose. There are often patients who have residual knee flexion deformity (about 5 degrees) after surgery. And we encourage patients to try knee flexion and extension exercises and use CPM machines to help them. Patients are more painful during exercise than at rest after TKA. Compared with TKA, the pain during functional exercise after THA will be significantly lighter. We have revised this part and corrected the wrong expressions. 1. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2:e000435. doi:10.1136/bmjopen-2011-000435

17. Lines 267-269- I don't understand why you are discussing a single EA treatment without multimodal analgesia here…	We have revised the part of Discussion.
18. Fig 2 shows that the needles are 2 different lengths? Is this correct? Could someone be able to tell it is the sham needle?	The patients are in a supine position when undergoing acupuncture treatment, they cannot see the needles, only acupuncturists know the type of needles. After the needles are inserted into the adhesive pads, the appearance of two groups is the same.
19. Page 12 line 236 237 FAS, PPS and SS I have never heard of these abbreviations.	These abbreviations are derived from Biostatistics. An intention-to-treat (ITT) analysis of the results of an experiment is based on the initial treatment assignment and not on the treatment eventually received. According to ICH E9 "STATISTICAL PRINCIPLES FOR CLINICAL TRIALS", Full Analysis Set (FAS) is identical to the Intention-to-Treat (ITT) population. The per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias. For safety analyses, the safety set is used; for efficacy analyses, full analysis set is used. These are supported by the CONSORT statement. 1. Shah PB. Intention-to-treat and per-protocol analysis. CMAJ 2011;183:696; author reply 696. doi:10.1503/cmaj.111-2033 2. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res 2011;2:109–12. doi:10.4103/2229-3485.83221
20. A few problems with written English…. Page 4 line 44 relieve Page 4 line 46 people first "patients with OA" Keywords: delete "the" study protocol Page 5 line 65 relieve	We have corrected the wrong expressions.
21. Line 103 what is an effective electroacupuncture blind method?	We have corrected the wrong expression.
22. Line 108 what is a parallel RCT?	We have corrected the wrong expression and abbreviations.
23. There are some abbreviations that are not standard…	ERAS is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. Involving

Page 6 line 89 enhanced recovery after surgery (ERAS)?	several medical professions to re-examine its traditional practices and replacing them with evidence-based best practices. 1. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery. JAMA Surg 2017;152:292. doi:10.1001/jamasurg.2016.4952 2. Soffin EM, YaDeau JT. Enhanced recovery after surgery for primary hip and knee arthroplasty: a review of the evidence. Br J Anaesth 2016;117:iii62-iii72. doi:10.1093/bja/aew362

VERSION 2 – REVIEW

REVIEWER	Barbara Shay University of Manitoba Canada
REVIEW RETURNED	11-Dec-2018

GENERAL COMMENTS	nice revision, generally looks good.... line 120 please tell me how and who will recruit patients? will all those who are admitted for TKR approached? line 286 "adequately characterize" the placebo effect line 289 clinically "relevant" line 299 we will recommend EA...if the results indicate effectiveness over placebo.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Dear Prof. Shay:

Thank you again for your kind comments and suggestions. We are very happy that the previous revision can get your affirmation. We have revised the manuscript in the manuscript according to your good comments. The suggestions are helpful and revised portions are marked in the manuscript.

COMMENT	RESPONSE
1. line 120 please tell me how and who will recruit patients? will all those who are admitted for TKR approached?	Sheng Zhong (SZ) and Hai Huang (HH) will recruit patients who meet the inclusion criteria in the hospital and introduce the patient to the trial process, possible benefits and risks to obtain their informed consent. At present, about 90% of patients will agree to accept this trial.

2. line 286 "adequately characterize" the placebo effect line 289 clinically "relevant" line 299 we will recommend EA...if the results indicate effectiveness over placebo.	We have corrected the wrong expressions.