

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prospective comparison of acupuncture with sham acupuncture to determine impact on sedation and analgesia in mechanically ventilated critically ill patients (PASSION study): protocol for a randomized controlled trial
AUTHORS	Zhang, Yuzhuo; Yang, Guang; Wei, Jinyi; Chen, Fangliang; Zhang, Min-Zhou; Mao, Shuai

VERSION 1 – REVIEW

REVIEWER	Josielli Comachio The University of Sydney Faculty of Medicine and Health
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	<p>Thank you for the opportunity to review this interesting manuscript. I have a few comments that I list below:</p> <p>Please add the aim of the study in the abstract session.</p> <ul style="list-style-type: none">- Can you provide a reason (references) for the acupoints chosen?- It would be more transparent to show all the different search strategies for all databases in an appendix and not only one search strategy.- Please specify how missing data will be handled. Which formulas will be used? How will missing data (e.g. standard deviations) be imputed?-- Can you please be more clear regarding hospital ICU admission and which kind of "diseases" the patients have or you expect to treat?
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REVIEWER	Frank Kiwanuka University of Eastern Finland, Department of Nursing Science
REVIEW RETURNED	17-Jan-2022

GENERAL COMMENTS	<p>It is an interesting protocol as it presents a design of an RCT comparing acupuncture, sham acupuncture, and their impact on sedation and analgesia in mechanically ventilated critically ill patients. However, some revisions are needed as follows:</p> <p>The authors need to pay particular attention and closely proofread and check the use of English throughout the manuscript.</p> <p>On page 14, line 38 to 47, the authors mention that "An interruptive sedation strategy was used by bedside nurses, and sedation levels and pain intensity were assessed with the Richmond Agitation Sedation Scale (RASS)^{15 16}, the Behavioral Pain Scale (BPS), or the Numeric Rating Scale (NRS) ^{17 18} every 4 h in objective to adapt sedatives and analgesics to avoid overuse. Have these tools</p>
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	<p>procedures already been used or conducted? If not, the tense of the sentence needs to be corrected.</p> <p>On page 23, line you mention that "adequate measures will be taken to put other people in a masked state. what are those measures? The study could benefit from formulating these measures at the protocol phase.</p>
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REVIEWER	Eyal Ben-Arie China Medical University
REVIEW RETURNED	18-Jan-2022

GENERAL COMMENTS	<p>Thank you for the opportunity to review this article. I think this is a promising and important investigation that can improve our knowledge of acupuncture effectiveness for patients under mechanical ventilation.</p> <p>I have a few suggestions that can improve the study and will not mislead the reader.</p> <p>Abstract: Page - line 7: please add ICU and 28 days mortality to the outcomes</p> <p>Introduction: Page 7 Line 57 – I think this statement should be revised. There are previous studies that investigated the use of acupuncture reports on reducing excessive sedation and analgesia, and the duration of mechanical ventilation, such as: Li Y, Li Y, Zhang WC. [Effects of acupuncture in Siguan points on man-machine counteraction in respiratory failure patients during mechanical ventilation]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006;26(10):930-2. Tsay SL, Wang JC, Lin KC, Chung UL. Effects of acupressure therapy for patients having prolonged mechanical ventilation support. Journal of advanced nursing. 2005;52(2):142-50. AminiSaman J, Mohammadi S, Karimpour H, Hemmatpour B, Sharifi H, Kawyannejad R. Transcutaneous Electrical Nerve Stimulation at the Acupuncture Points to Relieve Pain of Patients Under Mechanical Ventilation: A Randomized Controlled Study. J Acupunct Meridian Stud. 2018;11(5):290-5. Page 8 – line 4 : Please make sure this sentence is correct. See the following as an example: AminiSaman J, Mohammadi S, Karimpour H, Hemmatpour B, Sharifi H, Kawyannejad R. Transcutaneous Electrical Nerve Stimulation at the Acupuncture Points to Relieve Pain of Patients Under Mechanical Ventilation: A Randomized Controlled Study. J Acupunct Meridian Stud. 2018 Oct;11(5):290-295. doi: 10.1016/j.jams.2018.06.008. Epub 2018 Jul 20. PMID: 30036691. I also know of a few study protocols that will investigate the use of sham acupuncture as well for those patients. Page 8 – line 15 : Please explain the term “PASSION study”</p> <p>Methods: Page 13 line 55 : For the SAC group I would recommend adding an illustration of the sham points.</p> <p>Discussion: Page 21 figure 2,3 : Please mention the high level of heterogeneity in the analysis.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

---Please add the aim of the study in the abstract session.

Reply 1: Thank you for your valuable comments. To meet the journal formatting requirements of this journal, we add the aim of our study at the end of the Introduction in the abstract session (page 2, line 35 to 38). The specific modifications are as follows:

Therefore, we present a protocol to investigate whether acupuncture, used for sedation and analgesia, can reduce the duration of mechanical ventilation, save medical resources, and reduce the mortality of critically ill patients receiving mechanical ventilation.

---Can you provide a reason (references) for the acupoints chosen?

Reply 2: This comment is valuable and enable us to greatly improve the quality of our manuscript. We have added the reasons for the acupoints chosen in the discussion section (page 16, line 384 to 386). The specific modifications are as follows:

In addition, previous studies have shown that Yintang (EX-HN3) and Shenmen (HT7) have good sedative effects, Hegu (LI4) and Taichong (LR3) have analgesic advantages, while Baihui (DU20) appears both sedative and analgesic effects.⁴³⁻⁴⁷

---It would be more transparent to show all the different search strategies for all databases in an appendix and not only one search strategy.

Reply 3: Thank you for your constructive comments, which really helped us improve the manuscript. We have added search strategies in the appendix. The specific modifications are as follows:

Two authors independently searched PubMed, EMBASE and Web of science databases from inception to December 1st, 2021, to identify potentially eligible studies. Eligible studies were randomized controlled trials comparing treatments for acupuncture against placebo. The following search terms were used: acupuncture, analgesic, sedation. Twenty-one RCTs were included in the qualitative analysis.

Analgesia: (((("Acupuncture Therapy"[Mesh]) OR (Acupuncture Treatment[Title/Abstract] OR Acupuncture Treatments[Title/Abstract] OR Treatment, Acupuncture[Title/Abstract] OR Therapy, Acupuncture[Title/Abstract] OR Pharmacopuncture Treatment[Title/Abstract] OR Treatment, Pharmacopuncture[Title/Abstract] OR Pharmacopuncture Therapy[Title/Abstract] OR Therapy, Pharmacopuncture[Title/Abstract] OR Acupotomy[Title/Abstract] OR Acupotomies[Title/Abstract]))) AND (((("Conscious Sedation"[Mesh]) OR (Sedation, Moderate[Title/Abstract] OR Moderate Sedation[Title/Abstract] OR Sedation, Conscious[Title/Abstract])) OR (Sedation[Title/Abstract])) OR (sedative[Title/Abstract]))

Sedation: ((("Acupuncture Therapy"[Mesh]) OR (Acupuncture Treatment[Title/Abstract] OR Acupuncture Treatments[Title/Abstract] OR Treatment, Acupuncture[Title/Abstract] OR Therapy, Acupuncture[Title/Abstract] OR Pharmacopuncture Treatment[Title/Abstract] OR Treatment, Pharmacopuncture[Title/Abstract] OR Pharmacopuncture Therapy[Title/Abstract] OR Therapy, Pharmacopuncture[Title/Abstract] OR Acupotomy[Title/Abstract] OR Acupotomies[Title/Abstract]))) AND ((("Analgesics"[Mesh]) OR (Anodynes[Title/Abstract] OR Analgesic Drugs[Title/Abstract] OR Drugs, Analgesic[Title/Abstract] OR Analgesic[Title/Abstract] OR Analgesic Agents[Title/Abstract] OR Agents, Analgesic[Title/Abstract] OR Antinociceptive Agents[Title/Abstract] OR Agents, Antinociceptive[Title/Abstract]))

---Please specify how missing data will be handled. Which formulas will be used? How will missing data (eg. standard deviations) be imputed?

Reply 4: Thank you for this suggestion. As we mentioned in the statistical analysis of methods section, missing data will be handled according to the principle of multiple imputation (page 14, line 337 to 338). Specifically, we will use Markov Chain Monte Carlo (MCMC) method with 5-10 iterations for multiple imputation.

--- Can you please be more clear regarding hospital ICU admission and which kind of "diseases" the patients have or you expect to treat?

Reply 5: Thanks very much for the time and effort that you have put into reviewing this manuscript. In this study, all of the mechanically ventilated critically ill patients in the three ICUs are the potential subjects. They may suffer from severe pneumonia, severe asthma, acute respiratory distress syndrome, or just undergo cardiac surgery, acute abdominal surgery, and so on. Thus, all patients who meet the inclusion criteria but not the exclusion criteria in the ICUs are eligible to participate in this study.

A. Inclusion criteria	B. Exclusion criteria
1. Aged 18 years or over and under 80 years;	1. Skin lesions near the acupuncture points;
2. Required mechanical ventilation >24 hours;	2. Coagulopathy (bleeding time >4 min, thrombocytes <50,000/ μ l);
3. Continuous intravenous administration of sedative and analgesic medications;	3. Hypohepatia with Childs-Pugh class B or C;
4. Willingness to provide informed consent prior to enrollment;	4. Second- or third-degree atrioventricular block;
5. Be able to comply with all follow-up evaluations (in investigator's opinion).	5. Severe dementia;
	6. Psychiatric disorder;
	7. Neurological disease;
	8. Active seizures;
	9. Alcohol or drug abuse;
	10. Benzodiazepine dependency;
	11. Moribund state with the planned withdrawal of life support;
	12. Family or physician refusal;
	13. Pregnancy or lactation;
	14. Currently participated in any other investigational therapeutic or device trial.

Reviewer: 2

---The authors need to pay particular attention and closely proofread and check the use of English throughout the manuscript.

Reply 1: Thanks for your constructive comments and suggestions. We have now worked on both language and readability. We really hope that the flow and language levels have been substantially improved.

---On page 14, line 38 to 47, the authors mention that "An interruptive sedation strategy was used by bedside nurses, and sedation levels and pain intensity were assessed with the Richmond Agitation Sedation Scale (RASS)^{15 16}, the Behavioral Pain Scale (BPS), or the Numeric Rating Scale (NRS) 17 18 every 4 h in objective to adapt sedatives and analgesics to avoid overuse. Have these tools procedures already been used or conducted? If not, the tense of the sentence needs to be corrected.

Reply 2: These tools procedures have not been used or conducted, and we apologize for this language issue. We have revised the tense of this sentence into the future tense in the methods session (page 10, line 217 to 221). The specific modifications are as follows:

An interruptive sedation strategy will be adopted by bedside nurses, and sedation levels and pain intensity will be assessed with the Richmond Agitation Sedation Scale (RASS)^{20 21}, the Behavioral Pain Scale (BPS), or the Numeric Rating Scale (NRS)^{22 23} every 4 h in order to adapt sedatives and analgesics to avoid overuse.

---On page 23, line you mention that "adequate measures will be taken to put other people in a masked state. what are those measures? The study could benefit from formulating these measures at the protocol phase

Reply 3: Thanks very much for the time and effort that you have put into reviewing this manuscript. We apologize for this unclear statement. We have revised this statement in the discussion session (page 17, line 415 to 417). The specific modifications are as follows:

However, adequate measures will be taken to put the patients and medical team members of the other two groups in a masked state. For example...

As we mentioned in randomization and blinding of the methods session, allocation of participants will be concealed in sealed envelopes and known by the study coordinator and acupuncturists who will not be involved in outcome assessment and be required to sign a confidentiality agreement about patient allocation. All patients will be treated in a single treatment room. In both AC and SAC groups, patients, bedside nurses, and physicians will be blinded to which acupuncture method the patients would receive. The data collectors and the biostatisticians will also be masked from the treatment assignment.

Reviewer: 3

--please add ICU and 28 days mortality to the outcomes.

Reply 1: We are grateful for the suggestion. We have added ICU and 28 days mortality to the outcomes in the abstract session (page 2, line 52 to 54). The specific modifications are as follows:

Additional outcomes include the prevalence and days of delirium in ICU, mortality in ICU and within 28 days after randomization, and the number of ventilator free days in 28 days.

---Page 7 Line 57 – I think this statement should be revised. There are previous studies that investigated the use of acupuncture reports on reducing excessive sedation and analgesia, and the duration of mechanical ventilation, such as:Li Y, Li Y, Zhang WC. [Effects of acupuncture in Siguan points on man-machine counteraction in respiratory failure patients during mechanical ventilation]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006;26(10):930-2. Tsay SL, Wang JC, Lin KC, Chung UL. Effects of acupressure therapy for patients having prolonged mechanical ventilation support. Journal of advanced nursing. 2005;52(2):142-50. AminiSaman J, Mohammadi S, Karimpour H, Hemmatpour B, Sharifi H, Kawyannejad R. Transcutaneous Electrical Nerve Stimulation at the Acupuncture Points to Relieve Pain of Patients Under Mechanical Ventilation: A Randomized Controlled Study. J Acupunct Meridian Stud. 2018;11(5):290-5.

Reply 2: Thank you for underlining this deficiency. We have revised this statement in the Introduction session (page 5, line 94 to 97). The specific modifications are as follows:

Moreover, some studies have investigated the use of acupuncture on reducing sedative and analgesic drug demands, and the duration of mechanical ventilation, while improving patients' experience during mechanical ventilation. ¹²⁻¹⁵

---Page 8 – line 4 : Please make sure this sentence is correct. See the following as an example: AminiSaman J, Mohammadi S, Karimpour H, Hemmatpour B, Sharifi H, Kawyannejad R. Transcutaneous Electrical Nerve Stimulation at the Acupuncture Points to Relieve Pain of Patients Under Mechanical Ventilation: A Randomized Controlled Study. J Acupunct Meridian Stud. 2018 Oct;11(5):290-295. doi: 10.1016/j.jams.2018.06.008. Epub 2018 Jul 20. PMID: 30036691.I also know of a few study protocols that will investigate the use of sham acupuncture as well for those patients.

Reply 3: It is true as professor said this sentence is not correct. We have removed this sentence and pointed out the inconsistent findings on the sedative and analgesic effects of acupuncture, as well as the limited studies on the sedative and analgesic effects of acupuncture in all critically ill patients who need mechanical ventilation in ICU (page 5, line 97 to 100). The specific modifications are as follows:

However, there are still a few discrepant research findings on the sedative and analgesic effects of acupuncture.^{16 17} And studies investigating both the sedative and analgesic effects of acupuncture among all critically ill patients needing mechanical ventilation in ICU are limited.

Page 8 – line 15 : Please explain the term “PASSION study”

Reply 4: In our study, “PASSION” is extracted from the letters in the title as follows:

Prospective comparison of **A**cupuncture with **S**ham acupuncture to determine impact on **S**edati**O**n and analgesia in mechanically ve**N**tilated critically ill patients. — P-A-S-S-I-O-N

Page 13 line 55: For the SAC group I would recommend adding an illustration of the sham points

Reply 5: We are grateful for the suggestion. We have added an illustration of the sham points in the methods session. The specific modifications are as follows:

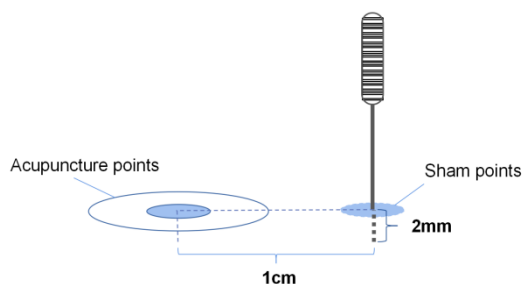


Figure 2. Illustration of the sham points

Page 21 figure 2,3 : Please mention the high level of heterogeneity in the analysis.

Reply 6: Thank you for your constructive comments, which really helped us improve the manuscript. We have revised the meta-analysis, followed by analysis of the heterogeneity (page 15-16, line 369 to 383). The specific modifications are as follows:

According to the meta-analysis of acupuncture on pain relief, visual analog scale (VAS) pain scores in the AC group is lower than that in the NAC group [MD=-11.13, 95%CI(-13.59,-8.68), Z=8.9, P<0.00001], Figure 3A.36-50 However, there is a substantial heterogeneity of results in these trials (I² = 70%). As shown in Figure 3B, heterogeneity decreases (I² = 14%) when the studies by Xian Wang and Zheng Lihong are excluded, and the AC group consistently shows a greater pain relief compared to NAC group [MD=-10.92, 95%CI(-12.93,-8.91), Z=10.66, P<0.00001]. Meanwhile, acupuncture, without adverse effects, has been shown to exert sedation effects in various medical conditions. As it shown in the meta-analysis, with a high heterogeneity(I² = 95%), the bispectral index (BIS) value in the AC group is also lower than that in the NAC group [MD=-5.82,95%CI (-9.36, -2.27), Z=3.22, P=0.001], Figure 4A.51-56 As shown in Figure 4B, heterogeneity decreases (I² = 0%) when the studies by J. Fleckenstein and Jiheng Chen are excluded, and the AC group consistently shows a better sedative effect compared to NAC group [MD=-3.18,95%CI(-5.53,-0.84),Z=2.66, P<0.008].

Once again, thank you very much for your comments and suggestions that allowed us to prepare a current version of this manuscript containing the important new data. We hope that our corrections and responses will now gain your approval.

VERSION 2 – REVIEW

REVIEWER	Frank Kiwanuka University of Eastern Finland, Department of Nursing Science
REVIEW RETURNED	28-May-2022
GENERAL COMMENTS	Thank you for your good work in revising your manuscript. The purpose of the article is to investigate whether acupuncture, used for sedation and analgesia, can reduce the duration of mechanical ventilation, save medical resources, and reduce the mortality of critically ill patients receiving mechanical ventilation

	<p>The trial is interesting and has the potential to reduce excessive sedation and analgesia for mechanically ventilated patients. Thus, the strength of the manuscript is the topic and the limitations consist mainly of non-blinding.</p> <p>More details have been provided as such, it is possible that a different researcher can be able to read your article and replicate and get similar results.</p> <p>No further comments to the article at the moment</p>
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REVIEWER	Eyal Ben-Arie China Medical University
REVIEW RETURNED	17-May-2022

GENERAL COMMENTS	The authors answered all of my questions.
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