

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Transcutaneous electrical acupoint stimulation (TEAS) for cancer-related fatigue: study protocol for a systematic review and meta-analysis
AUTHORS	Zeng, YiWei; Xia, Jialin; Chen, Zhihan; Tian, Xiaoping; Ren, Yulan

VERSION 1 – REVIEW

REVIEWER	Zick, Suzanna University of Michigan
REVIEW RETURNED	17-Mar-2021

GENERAL COMMENTS	<p>This is a study protocol for a proposed systematic review and meta-analysis of transcutaneous electrical acupoint stimulation (TEAS) for cancer related fatigue (CRF) in both adult and pediatric cancer patients. A major concern of this study is the existence of enough randomized clinical trials that do not have a high risk of biases to conduct this analysis. A quick review in all languages only identified two RCTs in cancer patients. Also, a native English speaker will need to review and make revisions throughout the manuscript. Below are other issues that should be addressed.</p> <p>Abstract Why wasn't Pubmed one of the searched databases in the abstract. The abstract should reflect the manuscript. Please indicate in the abstract that the PRISM methods for systematic trials and meta-analyses being employed. Strengths: this review will not provide more reliable evidence for TEAS in clinical CRF management. Please change to, "systematically assess the evidence for TEAS in CRF management."</p> <p>Introduction Please, distinguish between rates of CRF in cancer patients undergoing treatment as compared to those who have completed treatment. Please, provide a reference for people refusing acupuncture because of pain. I suspect it is more likely needle phobia and or other causes instead of pain. Stating that TEAS is equivalent with acupuncture is not proven for CRF. The reference you supply is for a pilot in irritable bowel syndrome. There has been no comparison study of acupuncture to TEAS in CRF. The justification for using TEAS instead of acupuncture is weak.</p> <p>Primary Outcome Section Unclear if the authors are going to accept any fatigue questionnaire or just the Piper Fatigue Scale. If any fatigue</p>
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	questionnaire, why put in so much information just about the Piper Fatigue Scale? A strength and limitation section should be added to the body of the manuscript.
REVIEWER	Gernier, François Centre François Baclesse Centre de Lutte Contre le Cancer, Clinical Research Departement
REVIEW RETURNED	19-Mar-2021
GENERAL COMMENTS	<p>Thank you for giving me the opportunity to review this study protocol.</p> <p>Cancer-related fatigue is a burden that is still under-addressed by medical teams. Practitioners still lack evidence-based therapeutic solutions that can be offered to patients. It is important to be able to expand the therapies that improve cancer-related fatigue. This review of the literature and metanalysis regarding Transcutaneous electrical acupoint stimulation and cancer-related fatigue would provide additional evidence.</p> <p>The description of the methodology is of good quality, however, some clarifications seem necessary.</p> <p>Page 4 line11: Many fatigue measurement questionnaires exist (such as the Piper fatigue scale described here, but many others exist such as MFI, FactF...), not all fatigue questionnaires have the same psychometric quality. It seems relevant to me to specify that they are those retained or excluded.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1. A major concern of this study is the existence of enough RCTs that do not have a high risk of bias to conduct this analysis.

Response: Thank you for your valuable comments. Your concern reminds us of another possibility. If unfortunately, that is the case, a narrative description of the results will be provided. Therefore, corresponding revision has been made to the Data synthesis Line 203 as follows:

If the meta-analysis is unfeasible, we will provide a narrative description of the results.

2. A native English speaker will need to review and make revisions throughout the manuscript.

Response: Thank you for your valuable comments and instructions. The paper has been carefully and substantially revised to improve the grammar and readability.

3. Why wasn't PubMed one of the searched databases in the abstract. The abstract should reflect the manuscript.

Response: thank you for your valuable comments and instructions. The abstract has been revised substantially as follows:

Abstract

Introduction Cancer-related fatigue (CRF) is a prevalent symptom in cancer survivors. Transcutaneous electrical acupoint stimulation (TEAS) has been reported as a promising therapy for CRF. This protocol is proposed for a systematic review that aims to assess the efficacy and safety of TEAS for CRF.

Methods and analysis CENTRAL, PubMed, Medline, EMBASE, Chinese National Knowledge

Infrastructure, VIP, Wanfang database, Chinese Biomedical Literature Database, Chinese Clinical Trial Registry System ClinicalTrials.gov, and World Health Organization International Clinical Trial Registry Platform will be searched from inception to 31 January 2021 without language limitations. The eligible randomized controlled trials (RCTs) will be included. The primary outcomes include changes in the revised Piper fatigue scale, the Brief fatigue inventory, the Multidimensional fatigue inventory, and the Functional assessment of chronic illness therapy-fatigue. The secondary outcomes are the quality-of-life measurement index, the Hamilton anxiety scale, the Hamilton depression scale, and adverse events. The selection of studies, data extraction, and assessment of risk of bias will be conducted independently by two reviewers. Data synthesis will be performed using RevMan 5.4.1. The quality of evidence will be evaluated with the Grading of Recommendations, Assessment, Development and Evaluation system. This study will strictly adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.

Ethics and dissemination Ethical approval is not required as this is a systematic review and meta-analysis based on previously published studies involving no private information of patients. The results of this study will be disseminated in a peer-reviewed journal.

PROSPERO registration number CRD42020220282

4. Indicate in the abstract that the PRISM methods for systematic trials and meta-analyses being employed.

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Abstract Line 37 as follows: This study will strictly adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.

5. Strengths: This review will not provide more reliable evidence for TEAS in clinical CRF management. Please change to, "systematically assess the evidence for TEAS in CRF management."

Response: thank you for your valuable comments and instructions. We have made corresponding revisions throughout the MS.

6. Distinguish between rates of CRF in cancer patients undergoing treatment as compared to those who have completed treatment.

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Introduction Line 61 as follows:

Cancer-related fatigue (CRF), a common symptom in cancer survivors, is defined as a distressing, persistent, and subjective sense of tiredness or exhaustion that cannot be alleviated by sleep or rest.¹ It is almost universal in those patients receiving anti-cancer treatments and affects nearly 65% of cancer survivors.²⁻⁴ Approximately 62% to 85% of cancer patients who undergo active treatments experience CRF.⁵

7. Provide a reference for people refusing acupuncture because of pain. I suspect it is more likely needle phobia and or other causes instead of pain.

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Introduction Line 80 as follows:

Transcutaneous electrical acupoint stimulation (TEAS) combines transcutaneous electrical nerve stimulation with acupoint stimulation and is a non-invasive alternative to acupuncture. Under the guidance of meridian theory, this technique stimulates acupoints on the surface with low-voltage pulses close to the body's bioelectricity and has been reported to relieve the varieties of cancer-related symptoms, including fatigue, immunosuppression, and bone marrow suppression.¹⁸⁻²¹ In addition, compared with the traditional manual acupuncture that requires qualified acupuncturists or TCM clinicians to perform, TEAS can be implemented by nursing staff or patients themselves after training making it more accessible.²² Moreover, this non-invasive therapeutic approach is pain-free and more acceptable for patients with

needle phobia.²³

8. Stating that TEAS is equivalent with acupuncture is not proven for CRF. The reference you supply is for a pilot in irritable bowel syndrome. There has been no comparison study of acupuncture to TEAS in CRF.

Response: thank you very much for your valuable comments. The inappropriate reference has been deleted, and corresponding revision has been made to the Introduction Line 80 as follows:

Transcutaneous electrical acupoint stimulation (TEAS) combines transcutaneous electrical nerve stimulation with acupoint stimulation and is a non-invasive alternative to acupuncture. Under the guidance of meridian theory, this technique stimulates acupoints on the surface with low-voltage pulses close to the body's bioelectricity and has been reported to relieve the varieties of cancer-related symptoms, including fatigue, immunosuppression, and bone marrow suppression.¹⁸⁻²¹ In addition, compared with the traditional manual acupuncture that requires qualified acupuncturists or TCM clinicians to perform, TEAS can be implemented by nursing staff or patients themselves after training making it more accessible.²² Moreover, this non-invasive therapeutic approach is pain-free and more acceptable for patients with needle phobia.²³

9. The justification for using TEAS instead of acupuncture is weak.

Response: thank you for your valuable comments. To make it sound more rational to use TEAS, we have made corresponding revisions as follows:

Under the guidance of meridian theory, TEAS stimulates acupoints on the surface with low-voltage pulses close to the body's bioelectricity and has been reported to relieve the varieties of cancer-related symptoms, including fatigue, immunosuppression, and bone marrow suppression.¹⁸⁻²¹ In addition, compared with the traditional manual acupuncture that requires qualified acupuncturists or TCM clinicians to perform, TEAS can be implemented by nursing staff or patients themselves after training making it more accessible.²² Moreover, this non-invasive therapeutic approach is pain-free and more acceptable for patients with needle phobia.²³

10. Unclear if the authors are going to accept any fatigue questionnaire or just the Piper Fatigue Scale. If any fatigue questionnaire, why put in so much information just about the Piper Fatigue Scale?

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Primary outcomes Line 132 as follows:

The primary outcomes include changes in the revised Piper fatigue scale (PFS-R).²⁶ It is a well-recognized and commonly used multidimensional measure in the CRF research field and contains 22 items and four subscales with a total score of 10, and each score section represents the corresponding severity of fatigue (0 for none, 1-3 for mild, 4-6 for moderate, and 7-10 for severe fatigue). CRF scores measured with other tools will also be included such as the Brief fatigue inventory (BFI), the Multidimensional fatigue inventory (MFI), and the Functional assessment of chronic illness therapy-fatigue (FACIT-F).

11. A strength and limitation section should be added to the body of the manuscript.

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Strength and limitations of this study Line 49 as follows:

Strength and limitations of this study

λ To the best of our knowledge, this study will be the first systematic review and meta-analysis to evaluate the efficacy and safety of TEAS for CRF.

λ The study will review quantitative data systematically from multiple databases to assess the efficacy and safety of TEAS for patients with CRF.

λ This study follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.

λ Potential poor methodological quality, publication bias, and small sample size of the included studies may be the limitations of the study.

Reviewer #2:

1. Page 4 line11: Many fatigue measurement questionnaires exist (such as the Piper fatigue scale described here, but many others exist such as MFI, FactF...), not all fatigue questionnaires have the same psychometric quality. It seems relevant to me to specify that they are those retained or excluded.

Response: thank you for your valuable comments and instructions. Corresponding revision has been made to the Primary outcomes Line 132 as follows:

The primary outcomes include changes in the revised Piper fatigue scale (PFS-R).²⁶ It is a well-recognized and commonly used multidimensional measure in the CRF research field and contains 22 items and four subscales with a total score of 10, and each score section represents the corresponding severity of fatigue (0 for none, 1-3 for mild, 4-6 for moderate, and 7-10 for severe fatigue). CRF scores measured with other tools will also be included such as the Brief fatigue inventory (BFI), the Multidimensional fatigue inventory (MFI), and the Functional assessment of chronic illness therapy-fatigue (FACIT-F).

VERSION 2 – REVIEW

REVIEWER	Gernier, François Centre François Baclesse Centre de Lutte Contre le Cancer, Clinical Research Departement
REVIEW RETURNED	08-Aug-2021

GENERAL COMMENTS	Given the articles that will be used, a review by a biostatistician seems relevant to me in order to assess the relevance of a meta-analysis, which would enrich the level of evidence to be provided
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