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Transcutaneous electrical acupoint stimulation (TEAS) for cancer-related fatigue: study protocol for a systematic review and meta-analysis

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Abstract

Introduction: Cancer-related fatigue (CRF) is a prevalent symptom in cancer survivors. Since the limitations of current clinical management, like low adherence and adverse events, transcutaneous electrical acupoint stimulation (TEAS) may be a promising therapy for CRF. There have been currently some clinical trials conducted to evaluate the efficacy of TEAS on CRF patients but no systematic review has been conducted. We here design this study to assess the efficacy and safety of TEAS for CRF.

Methods and analysis: CENTRAL, Medline, Embase, ClinicalTrials.gov, World Health Organization International Clinical Trial Registry Platform and two China databases (CNKI and CBM) will be searched from inception to 31 January 2021 without language limitations. The selection of studies, data extraction and assessment of risk of bias will be conducted independently by two review authors. Meta-analysis will be performed using RevMan 5.4.1.

Ethics and dissemination: The results of this systematic review and mate-analysis will be disseminated in a manner of publication on a peer-reviewed journal. The data that will be used will not contain private information of participants so that there is no ethical approval required.

Keywords: Cancer-related fatigue; Transcutaneous electrical acupoint stimulation; Meta-analysis; Protocol.

PROSPERO registration number: CRD42020220282

Strength and limitations of this study

This will be the first systematic review and meta-analysis conducted to evaluate the

efficacy of transcutaneous electrical acupoint stimulation (TEAS) for cancer-related fatigue (CRF).

This study will provide more reliable evidence for TEAS in clinical CRF management in that most of the RCTs on TEAS for CRF have small sample size.

The reliability of this study depends to a large extent on the methodological quality of included studies, and since only English and Chinese datebases will be searched, language bias may not be avoided.

Introduction

Cancer-related fatigue (CRF), defined as a distressing, persistent and subjective sense of tiredness or exhaustion that could not be alleviated by sleep or rest, is a common symptom in cancer survivors[1]and is nearly universal in those receiving anti-cancer treatments[2]. Some epidemiological studies have shown that the prevalence rates of the symptom ranged from 59% to 100%[3]. It inflicts negative impact on many aspects of patients` daily life[4 5], and often causes treatment discontinuation and reduction of overall quality of life even of survival period.

CRF is not just an isolated symptom, but a component of a syndrome including anxiety, depression, insomnia, etc[6]., and is multi-factorial involving anemia, inflammation-mediated changes of cytokines, cellular immunity regulation disorder, oxidative-stress-induced striated muscle dysfunction mediated by cancer or chemotherapeutic agents[4 7 8]. It is often underestimated, under-diagnosed and mal-administrated in clinical practice[9]. Though many interventions including both the pharmacological and the non-pharmacological have been applied in clinical management[10], a meta-analysis has shown that compared with non-pharmaceutical therapy, drugs have yield poorer effects on CRF[11] not to mention its high risk of side-effects. There is still no gold standard for CRF management[12], therefore, an effective and safe treatment for CRF remains an urgent need in clinical practice.

The use of Traditional Chinese medicine (TCM) is prevalent on cancer survivors in China and is accepted worldwide by its efficacy[13]. Acupuncture is an important part of TCM and some clinical trials have shown that acupuncture could provide clinical benefit for patients with CRF[14]. However, as an invasive method, acupuncture would probably be refused by many patients due to the experience of pain resulting in decreased adherence. Transcutaneous electrical acupoint stimulation (TEAS) is a noninvasive alternative to acupuncture, which combines transcutaneous electrical nerve stimulation and acupoints stimulation. It works, in the light of meridian theory, by stimulating acupoints on the surface with low-voltage pulses close to the body`s bioelectricity[15]. At present, this technology has been applied in dealing with varieties of cancer-related symptoms including fatigue, immunosuppression and bone marrow suppression[16-18]. It has been confirmed to be with equal efficacy to acupuncture[19]. Thus,

TEAS may have the same efficacy on CRF management as acupuncture with fewer risks. There have been currently some clinical trials conducted to evaluate the efficacy of TEAS on CRF patients but no systematic review to assess the clinical evidence.

Objective

The aim of this systematic review is to critically access the efficacy and safety of transcutaneous electrical acupoint stimulation (TEAS) for cancer-related fatigue.

Methods

The study protocol follows the *Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines (PRISMA-P)*[20] and will be started on 1 January 2021.

Criteria for considering studies for this review

Types of studies

We will only include randomized controlled trials (RCTs) investigating the efficacy of TEAS on cancer-related fatigue. Cross-over trials and quasi-randomized trials will be excluded.

Types of participants

We will include patients of any age or sex who have been diagnosed with CRF. Diagnosis follows *The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Related Fatigue*[21]. If there are no diagnostic criteria documented, it must be diagnosed based on the vital characteristics of CRF (eg, a distressing, persistent and subjective sense of tiredness or exhaustion that could not be alleviated by sleep or rest).

Participants with fatigue caused by other diseases will be excluded such as hepatitis, anemia and hypothyroidism.

Types of interventions

We will include RCTs that evaluate transcutaneous electrical acupoint stimulation (TEAS), and will exclude other invasive or noninvasive methods of acupoints stimulation such as acupuncture, laser stimulation, moxibustion and acupressure. No limitations of treatment duration will be placed.

Control interventions accepted will be: wait-list control, TEAS on corresponding non-acupoints, Other methods of acupoints stimulation (acupuncture, moxibustion, acupressure), Anti-cancer drugs.

We will also exclude studies that compared TEAS with any other complementary and alternative technologies for which the efficacy has not been validated.

Types of outcomes

We will include RCTs that took fatigue as the primary outcome of interest and

evaluated one of the following primary outcomes for at least 4 weeks of TEAS treatment. Measurements for CRF contain questionnaires and diaries based on patients` reports as it is a subjectively experienced symptom.

Primary outcomes

Valid scale-scoring tools quantifying and evaluating patient`s self-reported fatigue such as the revised Piper fatigue scale (FPS)[22] which is wildly used in the assessment of CRF. It contains 22 items and for 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.

Secondary outcomes

The secondary outcomes will, if available, include Quality of life measurement index (QLI), Capacity of daily activities, Exercise duration, Anxiety, Depression, and adverse events. The time for evaluation of outcome measures will depend on the specific report in each included study in that it may be different among studies.

Patients and public involvement

We collected patients` suggestions from China for the design of this study and our findings will be disseminated to Chinese residents through institutions of medical and health service.

Search methods for identification of studies

Electronic searches

Two review authors (YZ, JX) will search 5 English databases and 2 China databases including Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, ClinicalTrials.gov(www.clinicaltrials.gov), World Health Organization International Clinical Trial Registry Platform (www.who.it.trialsearch), China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM). The lists of references of retrieved articles will be searched for potentially eligible trials. Language restriction will not be set to the electronic searches. When a relevant article is found in languages other than English and Chinese, it will be arranged to translation. Terms for search include ‘fatigue’, ‘asthenia’, ‘cancer-related fatigue’, ‘CRF’, ‘cancer’, ‘carcinoma’, ‘tumor’, ‘malignance’, ‘Transcutaneous electrical acupoints stimulation’, ‘TEAS’. The last search update will be done on 31 January 2021.

The search strategy for PubMed is shown in table 1.

Table 1 Search strategy to be used in PubMed

Number	Search items
1	fatigue[MeSH Terms]
2	fatigue
3	cancer-related fatigue
4	cancer
5	carcinoma
6	malignance
7	1 or 2 or 3 or 4 or 5 or 6
8	Transcutaneous electrical acupoint stimulation
9	Transcutaneous acupoint electrical stimulation
10	TEAS
11	transcutaneous electrical acupuncture stimulation
12	transcutaneous electrical acupuncture point stimulation
13	8 or 9 or 10 or 11 or 12
14	Clinical trials[MeSH Terms]
15	randomized[Title/Abstract]
16	randomly[Title/Abstract]
17	trial[Title]
18	14 or 15 or 16 or 17
19	7 and 13 and 18

Searching other sources

The reference lists of all included articles will be checked by the two review authors to retrieve Additional trials. Handsearching will be applied when abstracts are not available online. Unpublished literatures will be searched via conference proceedings. Information unavailable in the articles will be acquired by contacting the authors when it is possible.

Data collection and analysis

Data extraction will proceed in accordance with *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.1[23]. Data analyzing will be conducted using RevMan 5.4.1 (Review Manager 2020).

Selection of studies

Two review authors (YZ, JX) will screen out identified abstracts from the literature search. RCTs evaluating the efficacy of TEAS for patients with cancer-related fatigue will be included. We will retrieve full texts of all remaining articles and the same two

review authors will independently screen all the full-text articles according to the inclusion criteria. Disagreements will be settled by discussion, and when agreement cannot be reached, the third review author (YR) will make the final decision. The PRISMA flow diagram of selection process is presented in figure 1.

Data extraction and management

We will design a data extraction form by which two authors (YZ, JX) will independently extract the data from eligible studies. It includes the following information: author, year of publication, participants, number of participants undergone randomization, randomization method, allocation concealment method, blinding method, interventions, analytic set, number of participants analyzed, outcome measures, adverse events and follow-up. Discrepancies will be resolved through discussion or, if necessary, by the third author (YR). For unclear information, we will contact the first or corresponding author to ask for further details.

Assessment of risk of bias in included studies

Two reviewer authors will independently assess the risk of bias for each RCTs included using Cochrane Collaboration's risk of bias tool[24] which contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. In each domain the risk of bias will be classified as 'low risk' of bias, 'high risk' of bias or 'unclear risk' of bias. disagreement will be resolved by discussion or consensus with the third author.

Data analysis

Data synthesis

The process will be performed using RevMan 5.4.1 (Review Manager 2020). Trials that have the same outcome measures in similar populations will be combined to estimate pooled effect. Risk (RR) will be used as pooled statistics for dichotomous data. For numeric variables, standardized mean difference (SMD) will be used as pooled statistics considering that out primary outcome is scoring scale. If the RR or SMD are not available, we will try to re-calculate them by using the reported data including the median, p values and confidence intervals (CIs).

Hypothesis test will apply inverse variance method for numeric data and the Mantel-Haenszel method for dichotomous data, and is considered statistically significant when $p<0.05$.

Assessment of heterogeneity

Heterogeneity will be assessed using the χ^2 test and I^2 statistics. When there is no

significant heterogeneity ($I^2 < 50\%$ and $p > 0.1$), the fixed effect model will be applied. If significant heterogeneity is found ($80\% > I^2 > 50\%$ and $p < 0.1$), the random effect model will be applied.

Subgroup analysis and sensitivity analysis

Subgroup analysis will be performed based on the primary and secondary outcome measures to detect possible causes of heterogeneity. The following subgroups will be investigated respectively: different types of control (wait-list, TEAS on non-acupoints, acupuncture, drugs), treatment duration, severity of symptoms at baseline.

Sensitivity analysis will be performed to confirm the robustness and the stability of the evidence. We will remove studies of 'high risk' of bias or studies of 'unclear risk' of bias and reanalyze the remaining data. If sensitivity does not substantially reverse the results, it will make the results more reliable.

Assessment of publication bias

Publication bias will be analyzed using funnel plots if there are more than 10 articles included. A symmetrically distributed funnel plots indicates that there is no publication bias. If less than 10 articles are included, Egger and Begg tests will be applied.

Summary of evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be applied to evaluate the quality of evidence for outcomes. Based on the methodology of study design, GRADE approach classified the quality of evidence as 'high', 'moderate', 'low', and 'very low'. The quality level can be downgraded by concerns about risk of bias, indirectness of evidence, heterogeneity, precision of effect and publication bias in each study.

Ethics and dissemination

The results of this systematic review and mate-analysis will be disseminated in a manner of publication on a peer-reviewed journal. The data that will be used will not contain private information of participants so that there is no ethical approval required.

Contributors YZ and JX designed this study. YR is the guarantor for the article. The manuscript of this protocol was drafted by YZ and revised by YR and JX. The research strategy was developed by all review authors. YZ and JX will independently carry out the search, selection and identification of studies and the data extraction. YZ will perform the data synthesis and analysis. YR will be served as the third author for settlement of disagreement. YR and ZC will be the adviser for methodology. All authors have approved the publication of the protocol.

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Competing interest None declared.

Patient consent Not required.

Ethics approval Not required.

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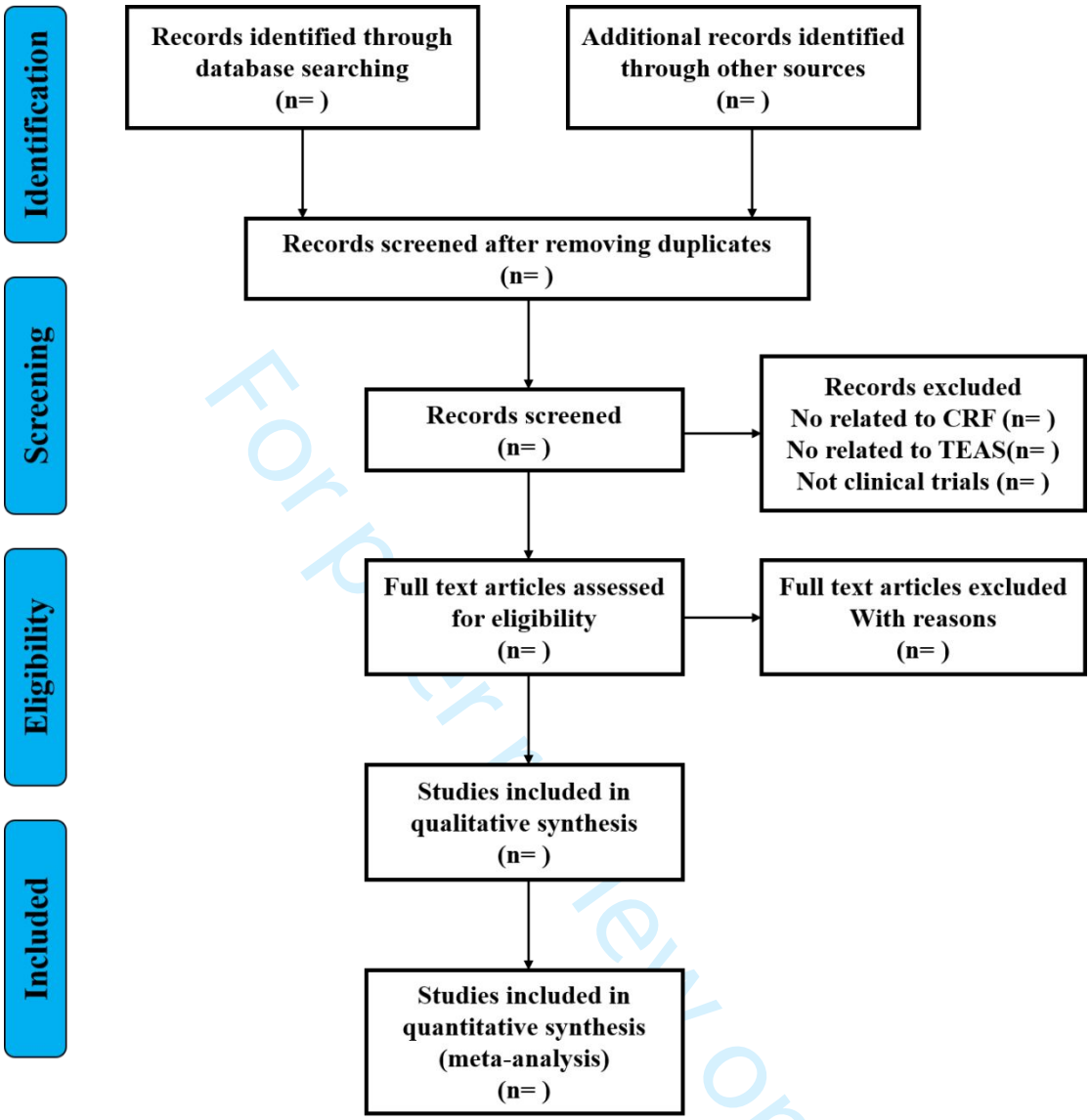
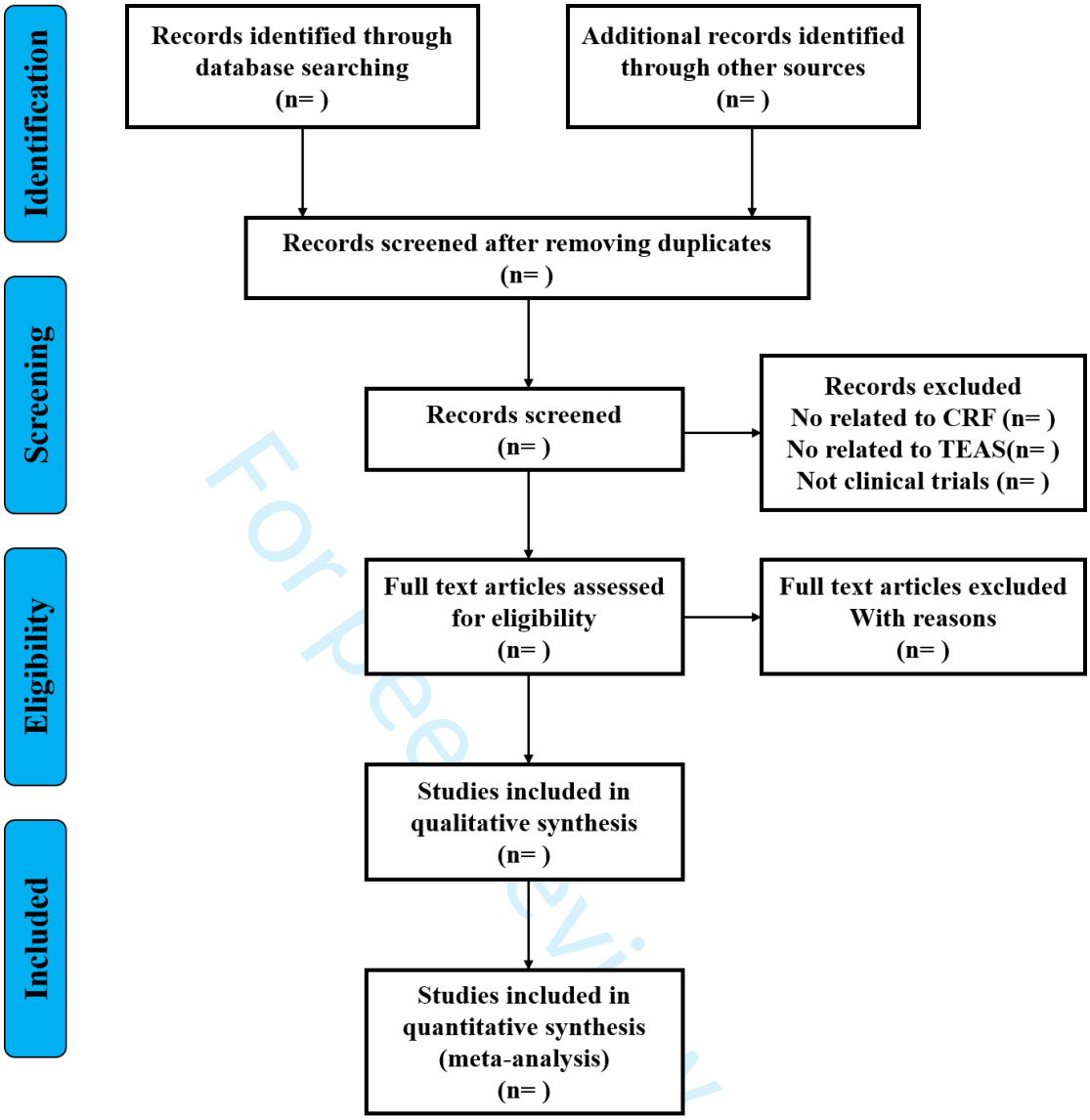
Figure 1 Flow diagram of the study selection process. CRF, cancer-related fatigue; TEAS, transcutaneous electrical acupoint stimulation.





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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	5

		obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	5-6
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

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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

Keywords Cancer-related fatigue; transcutaneous electrical acupoint stimulation; meta-analysis; protocol

Strength and limitations of this study

- 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.
- The study will review quantitative data systematically from multiple databases to assess the efficacy and safety of TEAS for patients with CRF.
- This study follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- Potential poor methodological quality, publication bias, and small sample size of the included studies may be the limitations of the study.

Introduction

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] CRF is not just an isolated symptom, but associates with anxiety, depression, and insomnia.[6] It is a

multifactorial condition involving anemia, inflammation-mediated changes of cytokines, cellular immunity dysregulation, and oxidative-stress-induced striated muscle dysfunction mediated by cancer or chemotherapeutic agents.[7-9] It inflicts a negative impact on patients' quality of daily life and may cause treatment discontinuation and survival reduction. [8 10] However, it has often been underestimated, underdiagnosed, and insufficiently treated.[11] Though both pharmacological and non-pharmacological interventions have been applied in clinical management, a meta-analysis has shown that compared with non-pharmaceutical therapy, the efficacy of drugs on CRF is inferior with an increased risk of side effects.[12 13] The gold standard for CRF management is still unavailable.[14] Hence, an effective and safe treatment option remains an urgent need for patients with CRF.

Traditional Chinese medicine (TCM) has been widely used among cancer survivors in China and gradually accepted worldwide by its efficacy in recent years.[15] As an integral part of TCM, acupuncture is being adopted by cancer patients for a wide range of cancer-related symptoms, and some clinical trials have shown that acupuncture can provide clinical benefits for patients with CRF.[16 17] 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]

In recent years, an increasing body of clinical trials has been carried out to evaluate the efficacy and safety of TEAS on CRF patients, and the results have indicated it might be a promising therapeutic intervention. However, currently no systematic review has been reported to assess the clinical evidence. This study will include and systematically synthesize the eligible randomized clinical trials (RCTs) without language restrictions. To the best of our knowledge, this meta-analysis is the first attempt to assess the available evidence of TEAS for the treatment of CRF. Hopefully, this study may yield helpful information for the people concerned.

Objective

This systematic review aims to critically assess the efficacy and safety of TEAS for CRF.

Methods

The study protocol will follow the *Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines (PRISMA-P).*[24 25]

Criteria for including studies for this review

Types of studies

We will only include randomized controlled trials (RCTs) investigating the efficacy and safety of TEAS on CRF. Cross-over trials and quasi-randomized trials will be excluded.

Types of participants

We will include patients with CRF of any age or sex who have been diagnosed by any recognized diagnostic criteria (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Related Fatigue) or based on the vital characteristics of CRF (e.g., a distressing, persistent, and subjective sense of tiredness or exhaustion that could not be alleviated by sleep or rest). Participants with fatigue caused by other diseases will be excluded, such as hepatitis, anemia, and hypothyroidism.

Types of interventions

We will include RCTs that utilize TEAS with or without conventional medicine and exclude other invasive or noninvasive acupoint stimulation methods, such as acupuncture, laser stimulation, moxibustion, and acupressure. No limitations will be placed on the duration of treatment.

Types of comparator(s)/control

Control interventions will be wait-list control, TEAS on corresponding non-acupoints, other methods of acupoint stimulation (e.g., acupuncture, moxibustion, and acupressure), and the same conventional anti-cancer drugs as the interventional group. We will also exclude studies that compare TEAS with any other complementary and alternative therapies.

Types of outcome measures

Primary outcomes

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).

Secondary outcomes

The secondary outcomes will include the quality-of-life measurement index (QLI), the anxiety and depression levels measured by qualified scales such as the Hamilton anxiety scale (HAMA) and the Hamilton depression scale (HAMD), and adverse events.

Patients and public involvement

No patient involved.

Search methods for identification of studies

Electronic searches

Two reviewers (YWZ, JLX) will independently search Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), VIP, Wanfang database, Chinese Biomedical Literature Database (CBM), ClinicalTrials.gov(www.clinicaltrials.gov), and World Health Organization International Clinical Trial Registry Platform (www.who.it.trialsearch) from inception to 31 January 2021. The lists of references of retrieved articles will be searched for identifying potentially eligible trials. Language restriction will not be imposed on the electronic searches. We will use the following terms in a combination for the search: fatigue, asthenia, cancer-related fatigue, CRF, cancer, carcinoma, tumor, malignancy, Transcutaneous electrical acupoints stimulation, and TEAS. The search strategy for PubMed is shown in table 1.

Searching other sources

The two reviewers will check the reference lists of all included articles to retrieve additional trials. Manual searching will be applied when abstracts are not available online. Unpublished literature will be searched via conference proceedings. Information unavailable in the articles will be acquired by contacting the authors when it is possible.

Table 1 Search strategy to be used in PubMed

Search Line	Search items
#1	fatigue [MeSH Terms]

#2	fatigue
#3	cancer-related fatigue
#4	cancer
#5	carcinoma
#6	malignance
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	transcutaneous electrical acupoint stimulation
#9	transcutaneous acupoint electrical stimulation
#10	TEAS
#11	transcutaneous electrical acupuncture stimulation
#12	transcutaneous electrical acupuncture point stimulation
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#7 AND #13
#15	Clinical trials [MeSH Terms]
#16	Randomized [Title/Abstract]
#17	Randomly [Title/Abstract]
#18	Trial [Title]
#19	#15 OR #16 OR #17 OR #18
#20	#7 AND #14 AND #19

Data collection and analysis

Data extraction will be performed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, version 6.1.[27] Data analysis will be conducted using RevMan 5.4.1 (Review Manager 2020).

Selection of studies

Two reviewers (YWZ, JLX) will independently perform abstract screening. RCTs evaluating the efficacy of TEAS for patients with CRF will be included. We will retrieve the full texts of all remaining articles and independently screen all the full-text articles according to the inclusion criteria. Disagreements will be settled by discussion, and when an agreement cannot be reached, the third review author (YLR) will make the final decision. The PRISMA flow diagram of the selection process is presented in figure 1.

Data extraction and management

We will design a data extraction form and two authors (YWZ, JLX) will independently extract the data from the eligible studies. It includes the following information: reference ID, author, year of publication, participant characteristics (e.g., age, gender, duration and severity of the disease), sample size, randomization method, allocation

concealment method, blinding method, interventions, analytic set, number of participants analyzed, outcome measures, adverse events, and follow-up. Discrepancies will be resolved through discussion or by the third reviewer (YLR). For unclear information, we will contact the first or corresponding author.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias for each RCTs included using Cochrane Collaboration's risk of bias tool, which contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. In each domain, the risk of bias will be classified as 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias.[28] Disagreement will be resolved by discussion or consensus with the third author.

Data analysis

Data synthesis

The process will be performed using RevMan 5.4.1 (Review Manager 2020). Trials that have the same outcome measures in similar populations will be combined to estimate the pooled effect. For dichotomous data, a risk ratio (RR) with 95% confidence intervals (CIs) will be used as pooled statistics. For numeric variables, standardized mean difference (SMD) with 95% CIs will be used considering that the primary outcome is the scoring scale. If the RR or SMD is not available, we will try to re-calculate them using the reported data, including the median, p values, and confidence intervals (CIs). The hypothesis test will apply the inverse variance method for numeric data and the Mantel-Haenszel method for dichotomous data. A p-value less than 0.05 ($p<0.05$) is statistically significant. If the meta-analysis is unfeasible, we will provide a narrative description of the results.

Assessment of heterogeneity

Heterogeneity will be assessed using the χ^2 test and I^2 statistics. When there is no significant heterogeneity ($I^2<50\%$ and $p>0.1$), the fixed-effect model will be applied. The random-effects model will be applied for significant heterogeneity ($80\%>I^2>50\%$ and $p<0.1$).

Subgroup analysis and sensitivity analysis

Subgroup analysis will be performed based on the primary and secondary outcome measures to detect possible causes of heterogeneity. The following subgroups will be investigated respectively: different types of the control (e.g., wait-list, TEAS on non-acupoints, acupuncture, and drugs), treatment duration, and the severity of symptoms at baseline. A sensitivity analysis will be performed to evaluate the robustness and

stability of the evidence, analyses will be limited to studies with a low risk of bias, and one study will be iteratively removed at a time.

Assessment of publication bias

Publication bias will be analyzed using funnel plots if there are more than ten studies included. A symmetrically distributed funnel plot indicates that there is no publication bias. If less than ten articles are included, Egger and Begg tests will be applied.

Summary of evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be applied to classify the quality of evidence as 'high', 'moderate', 'low', and 'very low' in the domain of the risk of bias (methodological quality), indirectness of evidence, heterogeneity, precision of effect, and publication bias in each study.

Ethics and dissemination

The results of this systematic review and mate-analysis will be disseminated in a peer-reviewed journal. No ethical approval is required since this study will not contain any private information of participants.

Contributors YWZ, JLX, XPT, and YLR designed this study. XPT and YLR are the guarantors for the study. The manuscript of this protocol was drafted by YWZ and revised by YLR and XPT. All reviewers developed the research strategy. YWZ and JLX will independently carry out the search, selection and identification of studies and the data extraction. YWZ and XPT will perform the data synthesis and analysis. YLR will be served as the third reviewer for settlement of disagreement. YLR and ZHC will be the adviser for methodology. All authors have approved the publication of this protocol.

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Competing interest None declared.

Patient consent Not required.

Ethics approval Not required.

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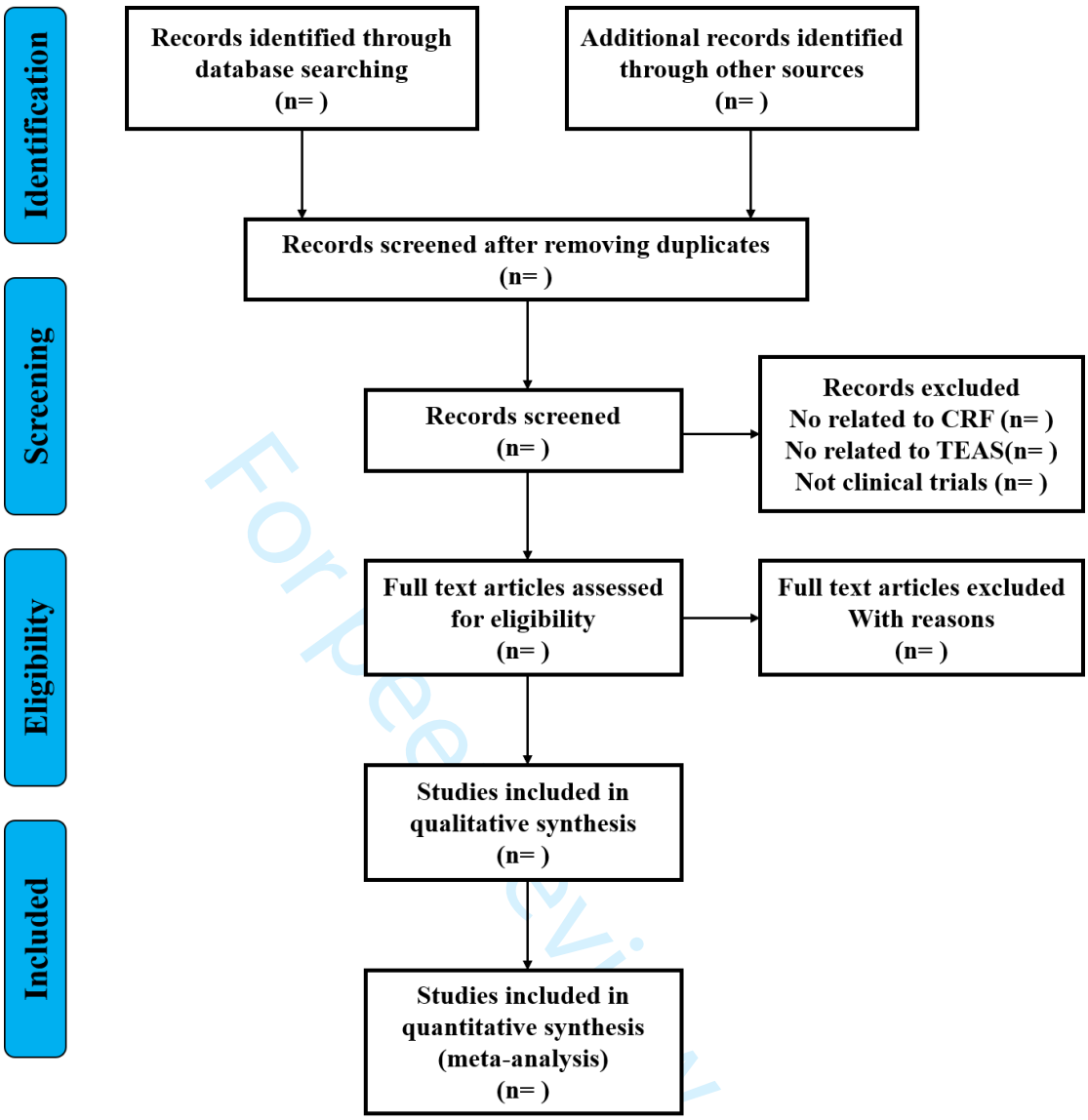
Figure 1 Flow diagram of the study selection process. CRF, cancer-related fatigue; TEAS, transcutaneous electrical acupoint stimulation.



Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	8
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	8
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2-3

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3-5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	5-6

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4-5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	7
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	8

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8