

BMJ Open Appraising the safety and reporting quality of thread-embedding acupuncture: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Thread-embedding acupuncture (TEA) is a special type of acupuncture treatment in which medical threads are inserted into subcutaneous tissues or muscles at therapeutic points. TEA is a medical practice that combines acupuncture and medical threads. As such, it is necessary to evaluate the safety of TEA. This systematic review and meta-analysis aimed to assess the safety of TEA and reporting quality of studies regarding TEA.

Methods and analysis The systematic review will be conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. Searching strategies will be systemically conducted using the following databases from their inception date to September 2022: MEDLINE, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), CiNii, J-STAGE, Korean Medical Database, Korean Studies Information Service System (KISS), ScienceON and Oriental Medicine Advanced Searching Integrated System (OASIS). The search strategies will be adjusted for each database as appropriate. The risk of bias will be assessed using the McMaster tool to identify the quality of harm assessment and reporting in study reports (McHarm). A meta-analysis will be used to synthesise the frequency and incidence of adverse events.

Ethics and dissemination No ethical approval and consent is required for this systematic review. The results of this systematic review will be disseminated through peer-reviewed publications and conference presentations.
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INTRODUCTION

Acupuncture is an effective and safe treatment that has been used for a long time, mainly in East Asia. Recently, new methods of acupuncture, such as electroacupuncture, auricular acupuncture and pharmacopuncture, have been used for the treatment of various diseases.^{1 2} Thread-embedding acupuncture (TEA) is a special type of acupuncture that involves inserting medical thread into subcutaneous tissues or muscles

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.
- ⇒ This study will be the first systematic review evaluating the safety and reporting quality of thread-embedding acupuncture (TEA) without any language restrictions.
- ⇒ We will conduct a comprehensive search in all the Core database and the main domestic databases for the key east Asia countries in which TEA is actively conducted.
- ⇒ The potential limitations include a possibility that adverse events were not reported or were selectively reported in the published articles and different quality of the identified studies.

at therapeutic points. As such, TEA is a form of medical practice that combines acupuncture and medical threads.³ In East Asia, the acupuncture retention method is used to provide continuous stimulation to address stubborn chronic diseases, and the thread is dipped in the drug and embedded in the acupoint.^{4 5} Currently, TEA is mainly used in clinical practice in Korean medicine and traditional Chinese medicine. These forms of TEA differ in terms of the target diseases and the purpose of treatment.⁶ Typically, threads made of catgut or polydioxanone (PDO) are used for TEA. Threads must be made of degradable materials with non-toxic by-products that decompose after use.⁷ PDO is a synthetic, absorbable and colourless polyester that was first manufactured in the early 1980s, which has been commonly used for the manufacturing of biodegradable medical materials.⁸

TEA is well known as an effective treatment method, especially in East Asia for musculoskeletal diseases, such as herniated

intervertebral disc and osteoarthritis and internal diseases such as abdominal obesity, non-alcoholic fatty liver disease and gastro-oesophageal reflux disease.^{9–13}

Acupuncture has generally been known as a safe treatment method with minimal risk of adverse events (AEs) to patients. The York Acupuncture Safety Study conducted in 2001 analysed 34 407 cases of the acupuncture treatment. They reported 10 920 mild transient reactions following acupuncture treatment, mainly bruising, pain and bleeding. No serious AEs (SAEs) were reported.¹⁴ In a large-scale prospective study of 229 300 patients who received acupuncture treatment, 19 726 patients reported experiencing at least one AE and 4963 patients reported an AE that required treatment. The common AEs reported were bleeding, hematoma, pain and vegetative symptoms like vertigo, nausea and sweating. Only two cases (0.001%) of pneumothorax, an SAE, were reported. Among them, one patient required hospital treatment and the other required clinical observation only.¹⁵

TEA is a subtype of acupuncture treatment. There are differences between TEA and traditional acupuncture treatment. As such, it is necessary to evaluate the safety of TEA. This systematic review (SR) and meta-analysis aimed to assess the safety of TEA and reporting quality of the available studies regarding TEA.

MATERIALS AND METHODS

Study design

We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.^{16–17} The PRISMA-P checklist of this protocol is attached as an online supplemental file 1.¹⁸ This SR protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. This study is planned to be performed from September to December 2022.

Eligibility criteria

The following inclusion and exclusion criteria will be applied. The review question is: whether TEA is safe compared with other treatments. The PICO, which consists of participants/populations, interventions, comparator group and outcomes, is often used to refine the review question. The PICO of this protocol is as follows.

Type of participants/populations

The participants/populations will include all patients treated with TEA at least once. There will be no restrictions on the participant's age, sex, race or underlying diseases.

Type of interventions

The intervention in this SR will be TEA. We will include studies in which TEA is used alone or in combination with other treatment.

Table 1 Search strategy for the PubMed

Number	Search terms
#1	thread embedding acupuncture
#2	thread embedding
#3	catgut embedding
#4	OR #1–3
#5	safety
#6	safe
#7	adverse event
#8	adverse reaction
#9	adverse effect
#10	side effect
#11	complication
#12	risk
#13	harm
#14	OR #5–14
#15	#4 AND #14

Type of comparator groups

The comparator group will include patients who did not undergo TEA. Placebo, sham control, waiting list and any other active controls, including conventional treatments, will be included.

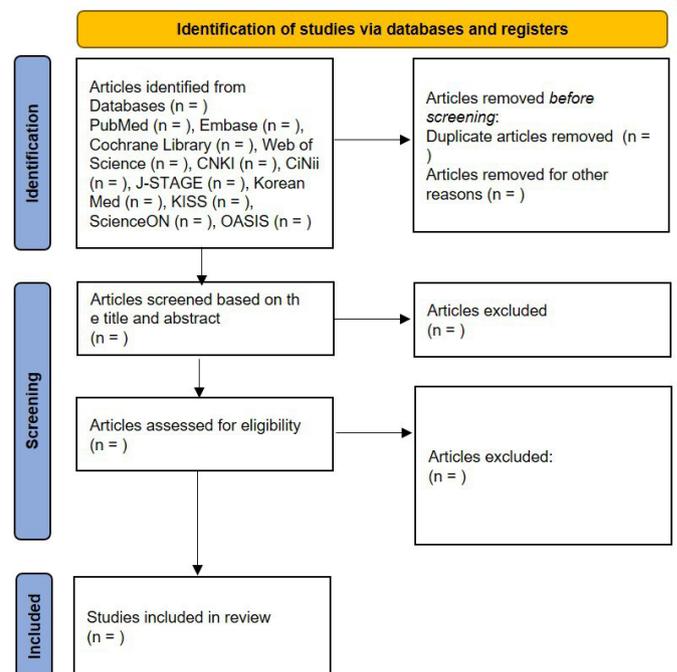


Figure 1 PRISMA flow diagram. CNKI, China National Knowledge Infrastructure; KISS, Korean Studies Information Service System; OASIS, Oriental Medicine Advanced Searching Integrated System; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Outcome measures

The primary outcomes will be the incidence (or frequency) and the types of AEs associated with TEA. The secondary outcomes will be severity, causality and follow-up information. In this SR, there is no predefined AE of special interest because the fact that around 80% of AE-associated studies do not have target-specific AEs, which were extracted from AE data in comprehensive studies.¹⁹

Type of studies

The types of studies in this SR will be all clinical trials, and observational studies including cross-sectional studies, cohort studies, longitudinal studies, case–control studies or case studies in which TEA represented at least one of the independent variables. Case reports or case series can help identify rare and previously unknown AEs. However, these will not be included in the meta-analysis because these studies do not contain denominator information that can be used to estimate the ratio or proportion. Case reports or case series will not be excluded as they may contain new information about a study that is not reported elsewhere including in the original article. Review articles and animal experiments will be excluded.

Search strategy

The following databases will be systemically searched from their inception date to September 2022: MEDLINE (via PubMed), Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), CiNii, J-STAGE, Korean Medical Database, Korean Studies Information Service System (KISS), ScienceON and Oriental Medicine Advanced Searching Integrated System (OASIS). There will be no language restriction, and the searches will be performed according to the language of each database.

We will conduct the search by combining multiple free texts including Medical Subject Headings terms related to TEA with Boolean operators. The free texts will include thread embedding, TEA and catgut embedding. AE, adverse effect, adverse reaction, side effect, complication, harm and risk will also be included as search terms. The search strategy will be adjusted for each database as appropriate. An example of the search strategy is presented in [table 1](#).

Study selection

After searching by intervention, two reviewers (Y Woo and B-I Kwon) will independently perform the screening procedure. Duplicate studies will be excluded first. Subsequently, studies will be excluded based on the screening of titles and abstracts. The two reviewers will independently review the full texts of the remaining articles to confirm inclusion or exclusion using predetermined criteria. Reasons for exclusion will be documented. Any disagreements between the two reviewers will be resolved through discussions. If the two reviewers fail to reach a consensus, a third reviewer (J-H Kim) will make the final decision. [Figure 1](#) shows the article identification and screening flow used in this study.

Data extraction

The data collected will include the authors' names, the title of the article, year of publication, study design, country of publication and the number of participants (including age, sex, race), diseases originally treated, study period, thread type used for TEA and concomitant treatment. In addition, the number of AE cases, type of AEs, AE coding or terminology system (eg, COSTART, WHO-ART, MedDRA), severity of AEs (mild, moderate, severe), the seriousness of AEs (eg, death, life-threatening, hospitalisation, disability or permanent

Table 2 McMaster tool for assessing quality of harms assessment and reporting in study reports (McHarm)

Question	
1	Were the harms predefined using standardised or precise definitions?
2	Were serious events precisely defined?
3	Were severe events precisely defined?
4	Were the number of deaths in each study group specified or were the reason(s) for not specifying them given?
5	Was the mode of harm collection specified as active?
6	Was the mode of harm collection specified as passive?
7	Did the study specify who collected the harms?
8	Did the study specify the training or background of who ascertained the harms?
9	Did the study specify the timing and frequency of collection of the harms?
10	Did the author(s) use standard scale(s) or checklist(s) for harms collection?
11	Did the authors specify if the harms reported encompass all the events collected or a selected sample?
12	Was the number of participants that withdrew or were lost to follow-up specified for each study group?
13	Was the total number of participants affected by harms specified for each study arm?
14	Did the author(s) specify the number for each type of harmful event for each study group?
15	Did the author(s) specify the type of analyses undertaken for harms data?



damage, congenital anomaly/birth defect) and suspected causality (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable) will be documented.^{20–22}

Risk of bias (quality) assessment

The risk-of-bias (RoB 2) tool for Randomized clinical trials (RCTs) and ROBINS-I tool for non-randomised studies are recommended as the RoB tools. However, these are not suitable when considered outcome is AE. AEs will be extracted post hoc from included trials in an exploratory approach. As such, it may not be possible to list cointerventions or confounders in the protocol. This is particularly important if new or unexpected AEs that have not been prespecified as outcomes of interest in the trials are identified, and where monitoring and reporting may be potentially inadequate.¹⁷ In this SR, the RoB will be assessed using the McMaster tool for assessing the quality of harm assessment and reporting in study reports (McHarm), as shown in table 2.²³

Two reviewers (Y Woo and DH Lee) will independently assess the RoB using Mcharm. The answers to each question are 'yes (implying a less risk of bias)', 'no (implying a high risk of bias)' and 'unsure'. Any disagreement between the two reviewers will be resolved through discussion. If the two reviewers fail to reach a consensus, a third reviewer (J-H Kim) will make the final decision.

Data synthesis and meta-analysis

If a quantitative synthesis is appropriate, we will conduct a meta-analysis, but if not, we will conduct a narrative analysis. The frequency and incidence of AEs will be calculated as relative risk (RR). We will use the Review Manager (REVMAN) software for Windows to calculate the RR and to perform a meta-analysis (V.5.3; Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). The I^2 statistic (significance level=0.1) will be used to measure heterogeneity.²⁴ An I^2 score of 0 (zero) will be considered as no heterogeneity, whereas a score of more than zero but less than 25% will be considered low heterogeneity. Moreover, the I^2 score ranging 0%~40% may not be important; 30%~60% reveals moderate heterogeneity; 50%~90% substantial heterogeneity and 75%~100% considerable heterogeneity. A random-effect model or fixed-effect model with a 95% CI will be used to calculate the pooled estimates of the effect size. A meta-analysis will be performed using fixed-effect model if the I^2 value is 50% or less. If the I^2 value is higher than 50%, a random-effect model will be used for data pooling. For missing data, we will contact the original author whenever possible and conduct sensitivity analyses with high-quality studies only. All discrepancies will be resolved by discussion with a third reviewer. In cases of high heterogeneity, we will perform subgroup analyses. Subgroup analyses will be performed using such as the target disease, implanted thread type and operating conditions (administrative site and depth, etc).

Patient and public involvement

Patients or members of the public were not involved in the design of this study.

DISCUSSION

Some previous SR studies on the safety of TEA have been published and concluded that TEA is a safe treatment. Huang reviewed 620 AE cases and 28 types of AEs related to TEA in 45 RCTs and 16 case reports. The most common AEs were induration, bleeding, ecchymosis, redness, swelling, fever and pain. The rarest AEs were epilepsy, irregular menstruation, skin ulcer, thread malabsorption and fat liquefaction, with one case per each AE. Only five cases of SAEs (three necrosis, one multiple skin ulcer and one suppuration) have been reported. All reported cases of SAEs recovered after symptomatic treatment with no sequelae.²⁵ Martins reviewed 1278 AE cases and product problems related to PDO implants in 49 clinical trials and 104 scientific publications. In the study, commonly reported AEs were surgical site infections, foreign body reactions, inflammatory reactions, postoperative pain and fever, but no deaths were reported.²⁶

These two previous studies did not include the Cochrane library as a search database. Only articles published in English and Chinese were included, and no meta-analysis was performed on the safety of TEA. In this protocol, the Cochrane library will be included as a search database, and all the published articles without any language restrictions will be reviewed. Considering that Korea and China are the key countries in which TEA is actively conducted, articles written in Korean would be able to provide substantial additional resources and information to assess the safety of TEA for the following reasons. First of all, while TEA is mainly used for internal or gynaecological diseases in China, there are many TEA treatments for musculoskeletal disorders or plastic surgeries in Korea.^{27 28} Moreover, the type of threads used in China and Korea is different. Therefore, to ensure that the safety data can be collected more comprehensively, articles written in Korean will be considered.⁶ Articles searched by previous studies were published up to January 2020. In recent years, more TEA-associated studies have been conducted; therefore, it is very meaningful to search for newer articles. In this way, AEs from articles not included in the previous studies may be considered.

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