BMJ Open

Thread embedding acupuncture for musculoskeletal pain: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015461
Article Type:	Protocol
Date Submitted by the Author:	12-Dec-2016
Complete List of Authors:	Cho, Yeeun; Kyunghee University Korean Medical Hostpital, Acupuncture and Moxibustion Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine Kim, Jihye; Kyunghee University Korean Medicine Hospital, Acupuncture and Moxibustion Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine Lee, Jae Dong; College of Korean Medicine, Kyung Hee University, Department of Acupuncture and Moxibustion
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Thread embedding acupuncture, Randomised controlled trial, Musculoskeletal pain, Systematic review, Meta-analysis

Thread embedding acupuncture for musculoskeletal pain: a systematic review and meta-analysis protocol

*Yeeun Cho[1,2]
Email: kmdyeeun@gmail.com

*Seunghoon Lee[1,3]
Email: kmdoctorlee@gmail.com

Jihye Kim[1,3]
Email: acukjh@hanmail.net

Jung Won Kang[1,3]
Email: doctorkang@naver.com

Jae-Dong Lee[1,3]
Email: ljdacu@gmail.com

* YC and SL contributed equally

[1] Dept. of Acupuncture & Moxibustion Medicine, Kyung Hee University Korean Medicine Hospital, Seoul, South Korea
[2] Dept. of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, South Korea
[3] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

Correspondence to: Jae-Dong Lee, KMD, PhD, Department of Acupuncture and Moxibustion, Kyung Hee University Korean Medicine Hospital, 23 Kyunghee dae-ro, Dongdaemun-gu, 02447, Seoul, South Korea, E-mail: ljdacu@gmail.com Tel: +82-2-9582958 Fax: +82-2-9669366

Total word count: 3,224

ABSTRACT

Introduction: Thread embedding acupuncture (TEA) is a special type of acupuncture that inserts certain medical threads (e.g., catgut or polydioxanone) into subcutaneous tissue at specific points. Although TEA has been widely used for the treatment of musculoskeletal pain in Korean and China, there is a lack of evidence of its efficacy. The aim of this protocol is to evaluate the effectiveness and safety of TEA in the treatment of musculoskeletal pain, by conducting a systematic review and meta-analysis.

Methods and analysis: The following 14 databases will be searched from inception to 10 November 2016: MEDLINE, CENTRAL, EMBASE, CINAHL, AMED, one Chinese database (CNKI) and eight Korean databases (KMBASE, KAMJE, KISS, KNADL, NDSL, OASIS, DBpia and KTKP). The WHO International Clinical Trials Registry Platform (ICTRP) will also be searched to retrieve ongoing and recently completed studies.

All randomised controlled studies in which TEA was used on specific points for musculoskeletal pain will be included and no restrictions on publication status or language will be applied. The risk of bias of each study will be evaluated by the Cochrane risk of bias tool.

Mean difference or standardised mean difference for continuous data and risk ratio for dichotomous data will be calculated with 95% confidence intervals using a random effects model. Additional subgroup and sensitivity analyses will be conducted according to a predefined protocol.

Ethics and dissemination: No ethical issues are predicted. The systematic review will be published in a peer-reviewed journal or conference presentation. These findings will summarize the current evidence of TEA for the treatment of musculoskeletal pain, and may provide guidance for clinicians and patients to select TEA for musculoskeletal pain.

Trial registration number: PROSPERO 2015: CRD42015019046.

Keywords: Thread embedding acupuncture, Randomised controlled trial, Musculoskeletal pain, Systematic review, Meta-analysis

Strengths and limitations of this study

- To the best of our knowledge, this review will be the first systematic review to evaluate the effectiveness and safety of thread embedding acupuncture for musculoskeletal pain.
- Two review authors will select studies, extract data and assess the risk of bias independently.
- This protocol has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement and registered in PROSPERO.
- There might be few studies with low risk of bias, so it might affect the quality of evidence

INTRODUCTION

Musculoskeletal pain is the most frequently reported medical disorder as a single symptom. In the general population, the prevalence of musculoskeletal pain varies from 13.5% to 47%.[1] Musculoskeletal pain leads to limitations in daily activities, loss of work productivity and increased medical costs. Moreover, the quality of life (QoL) of patients with musculoskeletal pain such as chronic whiplash-associated disorders, fibromyalgia[2] and chronic non-specific low back pain[3] is significantly lower than healthy controls.

The most commonly prescribed pharmacological agents for musculoskeletal pain are non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. However, the long-term use of these medications is not recommended because of considerable side-effects, such as gastrointestinal symptoms, weight gain or loss, dizziness.[4] Annually, in the United States, nearly 103,000 hospitalizations and 16,500 deaths are caused by long-term use of NSAIDs.[4] Recently, the U.S. Food and Drug Administration strengthened its warning that NSAIDs can increase the risk of heart attack or stroke.[5] The interest in non-pharmacological treatments for musculoskeletal pain, including complementary and alternative medicine (CAM), has increased because of the deleterious side effects associated with pharmacological agents.

Acupuncture is a common CAM treatment, and many studies demonstrate an effect of acupuncture on musculoskeletal pain. A well-designed meta-analysis, comparing manual- and electroacupuncture with sham and no acupuncture controls, revealed that acupuncture had a greater effect than sham and no acupuncture controls in chronic pain conditions. However, the effect size was small to moderate, and more specific stimulation methods are warranted to determine the effect above the placebo effect.[6]

Thread embedding acupuncture (TEA) is special type of acupuncture that inserts medical threads (e.g., catgut or polydioxanone (PDO)) into subcutaneous tissue at specific points.[7] There are two components involved in TEA, a guide needle and the medical threads. The procedure of TEA is as follow: a medical thread is attached to a guide needle and inserted into the skin of acupuncture points or tender points. The needle is removed after manipulation, and the medical threads is embedded in the tissue. Over three weeks, the embedded thread is gradually softens, decomposes and dissolves in subcutaneous tissue.[8] When compared to acupuncture, TEA may produce a strong and long acting therapeutic effect.

With the availability of safe absorbable medical threads such as PDO, TEA has been widely used for the treatment of musculoskeletal pain in Korea and China. Treatment with TEA includes frozen shoulder,[9] chronic low back pain[10] and osteoarthritis of the knee.[11] However, there is a lack of

evidence on the contribution of TEA in the treatment of musculoskeletal pain. Therefore, this review will evaluate whether TEA is effective and safe for musculoskeletal pain based on pain severity, function, global assessments of participant improvement, QoL, analgesic consumption and adverse events.

OBJECTIVES

This study aims to review the evidence for effectiveness and safety of TEA in the treatment of musculoskeletal pain.

METHODS

Study registration

The protocol for this review was registered prospectively (CRD42015019046; http://www.crd.york.ac.uk/PROSPERO). This protocol has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement. PRISMA-P checklist is presented on online supplementary appendix 1.

Eligibility criteria

Types of studies

Only randomised controlled trials of TEA for musculoskeletal pain will be included in this review. Quasi-randomised controlled studies, observational studies, and experimental studies will be excluded. There will be no restrictions on language or publication status.

Types of participants

Participants with musculoskeletal pain undergoing TEA will be included. Pain induced from headache and systemic illness will not be included.[12] Disease onset and participant age will not be restricted.

Types of interventions

Studies of TEA at specific points (e.g., traditional acupuncture points, ashi points or myofascial trigger points) will be included. Studies that compared TEA to no treatment/waiting list, sham control or active treatment except herbal medicine (e.g., physical therapy, oral medication, surgery, injection or other traditional medical treatments) will be included. When the TEA group received another active treatment, only studies in which participants of all comparison groups received the same active treatment as a co-intervention will be included. Studies that compared general TEA to other types of TEA will be excluded.

Types of outcome measures

Primary outcomes

1. Symptoms of pain which is identified using any pain scales (e.g., numeric rating scale (NRS) or visual analogue scale (VAS))
2. Functional outcome measures (e.g., validated questionnaire or functional scale specific to the presenting condition)
3. Severe adverse events

Secondary outcomes

1. Global assessment of participant improvement (e.g., subjective improvement and proportion of objective measures improvement or overall improvement)
2. QoL assessed using a validated scale (e.g., 36-item Short-Form or Euro-QoL)
3. Analgesic consumption
4. Adverse events related to TEA or any other treatments

Search methods for identification of studies

Electronics searches

The following 14 electronic databases will be searched from inception to 10 November 2016: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), one Chinese database (China National Knowledge Infrastructure (CNKI)) and eight Korean databases (Korean Medical Database (KMBASE), Korean Association of Medical Journal Editors (KAMJE), Korean Studies Information Service System (KISS), Korean National Assembly Digital Library (KNADL), National Digital Science Library (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), Database Periodical Information Academic (DBpia) and Korean Traditional Knowledge Portal (KTKP)). The search terms consisted of two parts: pain (e.g., pain, analgesic, suffering or discomfort) and embedding therapy (e.g., catgut embedding, catgut embedment, needle embedding or thread implantation). The online supplementary appendix 2 shows the detailed search strategies for MEDLINE, CNKI and Korean databases.

Searching other resources

The WHO International Clinical Trials Registry Platform (ICTRP) will be searched to retrieve ongoing and recently completed studies. Relevant publications (e.g., The Acupuncture textbooks and

references within the included studies) will be hand searched.

Data collection and analysis

Selection of studies

Two independent reviewers (YC and SL) will screen the titles and abstracts to assess their suitability for inclusion. Disagreements will be resolved by discussion between the authors.

Data extraction and management

Two independent reviewers (YC and SL) will read the full text of each article and extract data using a data extraction form. The data extraction form includes the author, year, disease, duration, type of treatments, numbers of participants analysed/randomised, numbers of treatments, follow up, outcome measures, results and adverse events. Any disagreements will be resolved by discussion.

Assessment of risk of bias and reporting quality in included studies

Two independent reviewers (YC and SL) will assess the risk of bias based on the Cochrane Collaboration's 'risk of bias' tool. The risk of bias tool covers six domains: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data and selective outcome reporting.[13] The risk of bias for each domain will be rated as 'low risk', 'high risk' or 'unclear risk'.

Measures of treatment effect

The mean difference or standardised mean difference will be used to assess the treatment effect with 95% confidence intervals (CIs) for continuous data (e.g., VAS, NRS or scores of functional outcome measures). Standardised mean difference will be used when calculating the same outcome variables using different scales and methods. The risk ratio will be used to assess the treatment effect with 95% CIs for dichotomous outcomes (e.g., responder or non-responder). Ordinal outcomes (e.g., 'almost cured', 'remarkably effective', 'effective' or 'not effective') in two or more categories will be converted to dichotomous outcomes, such as responder and non-responder.

Dealing with missing data

When there are insufficient data or missing data, the corresponding author will be contacted to request additional information or clarification. If contact is not possible, only the available data will be analysed.

Assessment of heterogeneity

The heterogeneity between different studies will be measured using a visual inspection of the forest plot and Chi-square test with statistical significance. The I^2 statistic will be calculated to assess inconsistencies in the results of the included studies. The I^2 results will be interpreted as follows: unimportant heterogeneity (0% to 40%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%).[13] When the considerable heterogeneity cannot be explained by the diversity in clinical or methodological aspects of the included studies, data cannot be pooled

Assessment of reporting biases

When the numbers of studies used in analysis are sufficient, a funnel plot will be used to detect reporting biases.[13] When there is funnel plot asymmetry, possible factors for the asymmetry (e.g., small-study effects or poor methodological quality) will be identified.

Data synthesis

The meta-analyses will be performed using Review Manager (RevMan) software (version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). A random effects model with 95% CIs will be used to calculate the pooled estimates of effect size because of the predicted substantial heterogeneity between the included studies. When there is considerable heterogeneity ($I^2 > 75\%$) which cannot be explained by the methodological and clinical diversity, the meta-analysis will not be conducted. If quantitative synthesis is not appropriate, summary of the studies will be done in a narrative form. When dichotomous data in studies comparing TEA with two or more controls will be assessed for meta-analysis, data of the TEA group will divided equally and compared individually with control groups to avoid the double counting of data.[14]

Subgroup analysis and investigation of heterogeneity

When the numbers of available studies are sufficient, subgroup analyses will be utilised to interpret the heterogeneity across studies according to the following:

1. Type of thread (e.g., absorbability or size)
2. Type of control (e.g., no treatment/waiting list, sham control or active treatment)
3. Duration of disease (e.g., acute (up to 1 month), subacute (1 to 3 months) or chronic (more than three months))
4. Duration of follow-up (e.g., short-term (within four weeks), medium-term (up to six months) and long-term (more than six months)).

Sensitivity analysis

Sensitivity analyses will be performed when possible to determine whether the results are robust according to the following:

1. Methodological qualities (e.g., whether sequence generation and allocation concealment were adequately conducted)
2. Sample size (e.g., greater or less than 30 participants in each group)
3. Analysis related issues (e.g., cut-off point of ordinal scale to dichotomous scale; 'almost cured, remarkably effective and effective' as a responder versus 'almost cured, remarkably effective' as a responder).

Summary of evidence

Where there are sufficient data, the results of the main outcomes will be summarised in 'Summary of findings' tables using the GRADE approach to evaluate the quality of evidence.[13]

DISCUSSION

The object of this systematic review is to evaluate the effectiveness and safety of TEA for musculoskeletal pain. The first detailed record of the medical application of TEA was in 'Taepyeonghyeminbang (太平惠民方)' published in 982.[15] However, TEA could not had been widely used because of the difficulty of the technique and the absence of proper absorbable materials. With the development of special types of absorbable medical threads such as chromic catgut or PDO, TEA has been more widely used in Korea and China.

Needle insertion during TEA treatment may induce an analgesic effect through mechanism similar to that of manual acupuncture. Mechanism of analgesia with acupuncture include enhanced local circulation,[16 17] segmental effects based on the gate-control theory[16] and extrasegmental effects with descending inhibitory pain control.[18] Moreover, enhanced stimulation induced by an embedded thread might have additional pain relief mechanisms. An animal study demonstrated that TEA produced a regulative effect on nitric oxide (NO),[19] which is an important factor in the processing of persistent neuropathic pain.[20] Another animal study mentioned that the injection of PDO into mice with rheumatoid arthritis has an anti-inflammatory effect by increasing interleukin-10.[21]

This systematic review will provide the current evidence on the effectiveness and safety of TEA for musculoskeletal pain. These findings will provide guidance for clinicians and patients on the use of TEA for musculoskeletal pain. Further clinical research will be designed based on this systematic review.

Abbreviations

AMED	The Allied and Complementary Medicine Database
CAM	Complementary and alternative medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CIs	Confidence intervals
CNKI	China National Knowledge Infrastructure
DBpia	Database Periodical Information Academic
ICTRP	The WHO International Clinical Trials Registry Platform
KAMJE	Korean Association of Medical Journal Editors
KISS	Korean Studies Information Service System
KMBASE	Korean Medical Database
KNADL	Korean National Assembly Digital Library
KTKP	Korean Traditional Knowledge Portal
NDSL	National Digital Science Library
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OASIS	Oriental Medicine Advanced Searching Integrated System
PDO	Polydioxanone
PRIMSA-P	Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols
QoL	Quality of life
RevMan	Review Manager
TEA	Thread embedding acupuncture
VAS	Visual analogue scale

Author affiliations

[1] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

[2] Dept. of Acupuncture & Moxibustion Medicine, Kyung Hee Korean Medical Hospital, Seoul, South Korea

Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HI15C0070).

Competing interests

None

Contributors

YC and SL contributed to the development of search strategy. YC and SL will search and select the studies. JDL will act as an arbiter in the selection stage. YC and SL will also read the full text of studies, extract data, assess the risk of bias, and report quality of evidences. YC and SL contributed to the initial drafting. JK and JWK made revisions. YC, SL, JK, JWK and JDL have read and approved the final manuscript for publication.

REFERENCES

1. Cimmino MA, Ferrone C, Cutolo M. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2011;25:173-83.
2. Coppieters I, Ickmans K, Cagnie B, *et al*. Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. *Pain physician* 2015;18:E389-401.
3. Murthy V, Sibbritt DW, Adams J. An integrative review of complementary and alternative medicine use for back pain: a focus on prevalence, reasons for use, influential factors, self-perceived effectiveness, and communication. *Spine J* 2015;15:1870-83.
4. Ussai S, Miceli L, Pisa FE, *et al*. Impact of potential inappropriate NSAIDs use in chronic pain. *Drug Des Devel Ther* 2015;9:2073-7.
5. U.S. Food & Drug Administration. FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm2015 (accessed 11 Nov 2016)
6. Vickers AJ, Cronin AM, Maschino AC, *et al*. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Iintern Med* 2012;172:1444-53.
7. Shin HJ, Lee DJ, Kwon K, *et al*. The success of thread-embedding therapy in generating hair re-growth in mice points to its possibly having a similar effect in humans. *J Pharmacopuncture* 2015;18:20-5.
8. Darpan Bhargava, P. Anantanarayanan, Geetha Prakash, *et al*. Initial inflammatory response of skeletal muscle to commonly used suture materials: An animal model study to evaluate muscle healing after surgical repair - histopathological perspective. *Med Oral Patol Oral Cir Bucal*. 2013;18:e491-6.
9. Jo NY, Rho JD. Effects of embedding therapy on frozen shoulder : a prospective study. *J Korean Med*. 2015;36:1-7.
10. Kim SW, Shin JC. Effects of Korean medical treatment combined with embedding acupuncture on patients with chronic lower back pain : a Retrospective Study. *The Acupuncture* 2016;33:165-71.
11. Lee JH, Yang TJ, Lee DG, *et al*. The effect of needle-embedding therapy on osteoarthritis of the knee combined with Korean medical treatment: report of five cases. *The Acupuncture* 2014;31(4):195-204.
12. Law D, McDonough S, Bleakley C, *et al*. Laser acupuncture for treating musculoskeletal pain: a systematic review with meta-analysis. *J Acupunct Meridian Stud* 2015;8:2-16.
13. GS HJ. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration: Available form www.cochrane-handbookorg 2011.
14. Lee S, Park J, Kim J, *et al*. Acupuncture for postoperative pain in laparoscopic surgery: a systematic review protocol. *BMJ open* 2014;4:1-5.
15. Park YE. *Medicine Wire Injection Therapy*. Seoul: Haenglimseowon 2003:23.
16. White A, Cummings M, Filshie J. *An introduction to western medical acupuncture.* Edinburgh, New York: Churchill Livingstone Elsevier 2008:19-40.
17. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects-reconsideration and a hypothesis. *Acupunct Med* 2002;20:82-99.
18. Silva JR, Silva ML, Prado WA. Analgesia induced by 2- or 100-Hz electroacupuncture in the rat tail-flick test depends on the activation of different descending pain inhibitory mechanisms. *J Pain* 2011;12:51-60.
19. Xie XX, Kou ST, Pu ZH, *et al*. Effects of scalp catgut embedding on SOD, NO, MDA in the rat with Parkinson's disease. *Zhongguo Zhen Jiu* 2007;27:753-6.
20. Schmidtko A. Nitric oxide-mediated pain processing in the spinal cord. *Handb Exp Pharmacol* 2015;227:103-17.
21. Sastry Gollapudi, Chang Sokso, Michael Formica, *et al*. Safety and efficacy of polydioxanone nano-fibers as anti-inflammatory agents. *J Nanomedine Biotherapeutic Discov* 2014;4:1-6.

Online Resource 1 Search strategies

MEDLINE (Ovid Medline)

1. exp Pain

2. exp Pain Management

3. exp Analgesia

4. (pain* or analgesi* or ache* or suffering* or discomfort).mp.

5. 1 or 2 or 3 or 4

6. ((catgut or thread or needle or acupunctur* or acupoint*) adj3 (implantation or embed*)).mp.

7. embedding therapy.mp.

8. 6 or 7

9. 5 and 8

Chinese Database (CNKI)

1. 埋线 OR 埋针 OR 埋藏疗法

2. 痛

3. 随机

4. 1 AND 2 AND 3

Korean Databases (KAMJE, KMBASE, KISS, NDSL, DBpia, KNADL, OASIS and KTKP)

매선 OR 매침 OR 매장요법

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
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	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
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	In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4-5
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	5-6
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	6
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	Appendix 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-9
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)	6-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
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	7

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-7
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	7-8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7-8
	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 I^2 , Kendall's τ)	7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

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Manuscript ID	bmjopen-2016-015461.R1
Article Type:	Protocol
Date Submitted by the Author:	04-May-2017
Complete List of Authors:	Cho, Yeeun; Kyunghee University Korean Medical Hostpital, Acupuncture and Moxibustion Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine Kim, Jihye; Kyunghee University Korean Medicine Hospital, Acupuncture and Moxibustion Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine Lee, Jae Dong; College of Korean Medicine, Kyung Hee University, Department of Acupuncture and Moxibustion
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Complementary medicine, Evidence based practice
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*Yeeun Cho[1,2]
Email: kmdyeeun@gmail.com

*Seunghoon Lee[1,3]
Email: kmdoctorlee@gmail.com

Jihye Kim[1,3]
Email: acukjh@hanmail.net

Jung Won Kang[1,3]
Email: doctorkang@naver.com

Jae-Dong Lee[1,3]
Email: ljdacu@gmail.com

* YC and SL contributed equally

[1] Dept. of Acupuncture & Moxibustion Medicine, Kyung Hee University Korean Medicine Hospital, Seoul, South Korea
[2] Dept. of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, South Korea
[3] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

Correspondence to: Jae-Dong Lee, KMD, PhD, Department of Acupuncture and Moxibustion, Kyung Hee University Korean Medicine Hospital, 23 Kyunghee dae-ro, Dongdaemun-gu, 02447, Seoul, South Korea, E-mail: ljdacu@gmail.com Tel: +82-2-9582958 Fax: +82-2-9669366

Total word count: 3,784

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- There might be few studies with low risk of bias, so it might affect the quality of evidence

INTRODUCTION

Musculoskeletal pain is the most frequently reported medical disorder. In the general population, the prevalence of musculoskeletal pain varies from 40.4% to 69.3%.[1] Musculoskeletal pain leads to limitations in daily activities, loss of work productivity and increased medical costs. Moreover, the quality of life (QoL) of patients with musculoskeletal pain such as chronic whiplash-associated disorders[2] and chronic non-specific low back pain[3] is significantly lower than healthy controls.

The most commonly prescribed pharmacological agents for musculoskeletal pain are non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. However, the long-term use of these medications is not recommended because of considerable side-effects, such as weight gain or loss, gastrointestinal symptoms and dizziness.[4] The 2009 Korean hospital outpatient analysis reported that the prevalence of ulcer complications was increased from 11.3% to 47.2% as the number of prescribed days of NSAIDs was increased.[5] Recently, the U.S. Food and Drug Administration strengthened its warning that NSAIDs can increase the risk of heart attack or stroke.[6] The interest in non-pharmacological treatments for musculoskeletal pain, including complementary and alternative medicine (CAM), may have increased because of the deleterious side effects associated with pharmacological agents.[7] In particular, CAM such as manual therapy, yoga, physical therapy and meditation, is known to have chronic pain-relief effect and recommended as treatment for pain.[8]

Acupuncture is a common CAM treatment, and many studies demonstrate an effect of acupuncture on musculoskeletal pain such as shoulder impingement syndrome,[9] acute lumbar sprain[10] and chronic neck pain.[11] A well-designed meta-analysis, comparing manual- and electroacupuncture with sham and no acupuncture controls, revealed that acupuncture had a better effect than sham and no acupuncture controls in chronic pain conditions. However, the effect size was small to moderate, and more specific stimulation methods are warranted to determine the effect above the placebo effect.[12]

Thread embedding acupuncture (TEA) is special type of acupuncture that inserts medical threads (e.g., catgut or polydioxanone (PDO)) into subcutaneous tissue or muscles at specific points (e.g., traditional acupuncture points or tender points).[13] There are two components involved in TEA, a guide needle and the medical threads. TEA involves the insertion of a medical thread, which is attached to a guide needle, into the skin overlying specific acupuncture or tender points. The needle is removed after insertion and the medical threads remain embedded in the subcutaneous tissue or muscle. The embedded thread gradually softens, decomposes and dissolves with times in the subcutaneous tissue or muscle.[14] The complete absorption times differ depending on the types of threads. The absorption of PDO is known to be slow during first 3 months,[15] and proceed until 180 to 210 days.[14] When compared to acupuncture, TEA may produce a strong and long acting therapeutic effect. One Chinese

randomised controlled trial (RCT) confirmed that TEA had better effect compared to acupuncture in reducing pain of patients with lumbar intervertebral disc herniation.[16]

With the availability of safe absorbable medical threads such as PDO, TEA has been widely used for the treatment of musculoskeletal pain in Korea, China and Taiwan. Treatment with TEA includes frozen shoulder,[17] chronic low back pain[18] and osteoarthritis of the knee.[19] However, there is a lack of evidence on the contribution of TEA in the treatment of musculoskeletal pain. Therefore, this review will evaluate whether TEA is effective and safe compared to other treatments for the treatment of musculoskeletal pain based on pain severity, function, global assessments of participant improvement, QoL, analgesic consumption and adverse events.

OBJECTIVES

This study aims to review the evidence for effectiveness and safety of TEA compared to other techniques in the treatment of musculoskeletal pain.

Research questions based on the PICOS approach

- Population: patients with musculoskeletal pain
- Intervention: TEA
- Comparison: no treatment/waiting list, sham control or active treatment (e.g., physical therapy, oral medication, surgery, injection or other traditional medical treatments), except herbal medicine
- Outcome: pain severity, function, global assessments of participant improvement, QoL, analgesic consumption and adverse events
- Study design: RCTs

Details were described as below.

METHODS

Study registration

The protocol for this review was registered prospectively (CRD42015019046; http://www.crd.york.ac.uk/PROSPERO). This protocol has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement. PRISMA-P checklist is presented in the online supplementary appendix 1.

Eligibility criteria

Types of studies

Only RCTs of TEA for musculoskeletal pain will be included in this review. Quasi-randomised controlled studies, observational studies, and experimental studies will be excluded. There will be no restrictions on language. And only published studies will be included.

Types of participants

Participants with musculoskeletal pain undergoing TEA will be included. Pain induced from headache and systemic illness will not be included.[20] Disease onset and participant age will not be restricted.

Types of interventions and comparisons

Studies about the effect of TEA at specific points (e.g., traditional acupuncture points or tender points) will be included. Studies in which the effect of TEA was compared to no treatment/waiting list, sham control or active treatment (e.g., physical therapy, oral medication, surgery, injection or other traditional medical treatments) will be included. Studies in which the effect of TEA was compared to herbal medicine will be excluded. In case the TEA group received another active treatment, only studies in which participants of all comparison groups received the same active treatment as a co-intervention will be included. Studies that compared general TEA to other types of TEA will be excluded.

Types of outcome measures

Primary outcome measures

1. Symptoms of pain which is identified using any pain scales (e.g., numeric rating scale (NRS) or visual analogue scale (VAS))
2. Functional outcome measures (e.g., validated questionnaire or functional scale specific to the musculoskeletal disease such as range of motion (ROM))
3. Severe adverse events related to the treatment

Secondary outcome measures

1. Global assessment of participant improvement (e.g., subjective improvement and proportion of overall improvement)
2. QoL assessed using a validated scale (e.g., 36-item Short-Form or Euro-QoL)
3. Analgesic consumption
4. Adverse events related to TEA or any other treatments

Search methods for identification of studies

Electronics searches

The following 16 electronic databases will be searched from inception to 14 May 2017: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), three Chinese databases (China National Knowledge Infrastructure (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP) and the Wanfang database) and eight Korean databases (Korean Medical Database (KMBASE), Korean Association of Medical Journal Editors (KAMJE), Korean Studies Information Service System (KISS), Korean National Assembly Digital Library (KNADL), National Digital Science Library (NDSL), Oriental Medicine Advanced Searching Integrated System (OASIS), Database Periodical Information Academic (DBpia) and Korean Traditional Knowledge Portal (KTKP)). The search terms consisted of two parts: pain (e.g., pain, analgesic, suffering or discomfort) and embedding therapy (e.g., catgut embedding, catgut embedment, needle embedding or thread implantation). The online supplementary appendix 2 shows the detailed search strategies for MEDLINE, CNKI and Korean databases.

Searching other resources

The WHO International Clinical Trials Registry Platform (ICTRP) will be searched to retrieve recently completed studies. Relevant publications (e.g., The Acupuncture textbooks and references within the included studies) will be hand searched.

Data collection and analysis

Selection of studies

Two independent reviewers (YC and SL) will screen the titles and abstracts to assess their suitability for inclusion. YC and SL will read the full text of remained studies and select included studies for this review. Disagreements will be resolved by discussion between the authors.

Data extraction and management

Two independent reviewers (YC and SL) will read the full text of each article and extract data using a data extraction form. The data extraction form includes the author, year, disease, duration, type of treatments, numbers of participants analysed/randomised, numbers of treatments, follow up, outcome measures, results and adverse events. Any disagreements will be resolved by discussion.

Assessment of risk of bias and reporting quality in included studies

Two independent reviewers (YC and SL) will assess the risk of bias based on the Cochrane

Collaboration's 'risk of bias' tool. The risk of bias tool covers six domains: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data and selective outcome reporting.[21] The risk of bias for each domain will be rated as 'low risk', 'high risk' or 'unclear risk'.

Measures of treatment effect

The mean difference or standardised mean difference will be used to assess the treatment effect with 95% confidence intervals (CIs) for continuous data (e.g., VAS, NRS or scores of functional outcome measures). Standardised mean difference will be used when calculating the same outcome variables using different scales and methods. The risk ratio will be used to assess the treatment effect with 95% CIs for dichotomous outcomes (e.g., responder or non-responder). Ordinal outcomes (e.g., 'almost cured', 'remarkably effective', 'effective' or 'not effective') in two or more categories will be converted to dichotomous outcomes, such as responder and non-responder.

Dealing with missing data

When there are insufficient data or missing data, the corresponding author will be contacted to request additional information or clarification. If contact is not possible, only the available data will be analysed.

Assessment of heterogeneity

The heterogeneity between different studies will be measured using a visual inspection of the forest plot and Chi-square test with statistical significance. The I^2 statistic will be calculated to assess inconsistencies in the results of the included studies. The I^2 results will be interpreted as follows: unimportant heterogeneity (0% to 40%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%).[21] When the considerable heterogeneity cannot be explained by the diversity in clinical or methodological aspects of the included studies, data will not be pooled

Assessment of reporting biases

When the numbers of studies used in analysis are sufficient, a funnel plot will be used to detect reporting biases.[21] When there is funnel plot asymmetry, possible factors for the asymmetry (e.g., small-study effects or poor methodological quality) will be identified.

Data synthesis

The meta-analyses will be performed using Review Manager (RevMan) software (version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). A random effects model or fixed effect model with 95% CIs will be used to calculate the pooled estimates of effect size. When there is considerable heterogeneity ($I^2 > 75\%$) which cannot be explained by the methodological and clinical diversity, the meta-analysis will not be conducted. If quantitative synthesis is not appropriate, summary of the studies will be done in a narrative form. When dichotomous data in studies comparing TEA with two or more controls will be assessed for meta-analysis, data of the TEA group will divided equally and compared individually with control groups to avoid the double counting of data.[22]

Subgroup analysis and investigation of heterogeneity

When the numbers of available studies are sufficient, subgroup analyses will be utilised to interpret the heterogeneity across studies according to the following:

1. Type of thread (e.g., absorbability or size)
2. Type of control (e.g., no treatment/waiting list, sham control or active treatment)
3. Duration of disease (e.g., acute (up to 1 month), subacute (1 to 3 months) or chronic (more than three months))
4. Duration of follow-up (e.g., short-term (within four weeks), medium-term (up to six months) and long-term (more than six months)).

Sensitivity analysis

Sensitivity analyses will be performed when possible to determine whether the results are robust according to the following:

1. Methodological quality (e.g., whether sequence generation and allocation concealment were adequately conducted)
2. Sample size (e.g., greater or less than 30 participants in each group)
3. Analysis related issues (e.g., cut-off point of ordinal scale to dichotomous scale; 'almost cured, remarkably effective and effective' as a responder versus 'almost cured, remarkably effective' as a responder).

Summary of evidence

In case there are sufficient data, the results of the main outcomes will be summarised in 'Summary of findings' tables using the GRADE approach to evaluate the quality of evidence.[21]

DISCUSSION

The aim of this systematic review is to evaluate the effectiveness and safety of TEA for the treatment of musculoskeletal pain. The first detailed record of the medical application of TEA was in 'Taepyeonghyeminbang (太平惠民方)' published in 982.[23] However, TEA could not had been widely used because of the difficulty of the technique and the absence of proper absorbable materials. With the development of special types of absorbable medical threads such as chromic catgut or PDO, TEA has been more widely used in Korea, China and Taiwan.

Needle insertion during TEA treatment may induce an analgesic effect through mechanism similar to that of manual acupuncture. Mechanism of analgesia with acupuncture include enhanced local circulation,[24 25] segmental effects based on the gate-control theory[24] and extrasegmental effects with descending inhibitory pain control.[26] Moreover, enhanced stimulation induced by an embedded thread might have additional pain relief mechanisms. An animal study demonstrated that TEA produced a regulative effect on nitric oxide (NO),[27] which is an important factor in the processing of persistent neuropathic pain.[28] Another animal study mentioned that the injection of PDO into mice with rheumatoid arthritis has an anti-inflammatory effect by increasing interleukin-10.[29]

This systematic review will provide the current evidence on the effectiveness and safety of TEA for musculoskeletal pain. These findings will provide guidance for clinicians and patients on the use of TEA for musculoskeletal pain. Moreover, these results are also available to health care professionals in Western countries who are unfamiliar with the use of TEA. Further clinical research will be designed based on this systematic review.

Abbreviations

AMED	The Allied and Complementary Medicine Database
CAM	Complementary and alternative medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CIs	Confidence intervals
CNKI	China National Knowledge Infrastructure
DBpia	Database Periodical Information Academic
ICTRP	The WHO International Clinical Trials Registry Platform
KAMJE	Korean Association of Medical Journal Editors
KISS	Korean Studies Information Service System
KMBASE	Korean Medical Database
KNADL	Korean National Assembly Digital Library
KTKP	Korean Traditional Knowledge Portal
NDSL	National Digital Science Library
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OASIS	Oriental Medicine Advanced Searching Integrated System
PDO	Polydioxanone
PRIMSA-P	Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols
QoL	Quality of life
RCT	Randomised controlled trial
RevMan	Review Manager
ROM	Range of motion
TEA	Thread embedding acupuncture
VAS	Visual analogue scale
VIP	The Chongqing VIP Chinese Science and Technology Periodical Database

Author affiliations

[1] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

[2] Dept. of Acupuncture & Moxibustion Medicine, Kyung Hee Korean Medical Hospital, Seoul, South Korea

Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HI15C0070).

Competing interests

None

Contributors

YC and SL contributed to the development of search strategy. YC and SL will search and select the studies. JDL will act as an arbiter in the selection stage. YC and SL will also read the full text of studies, extract data, assess the risk of bias, and report quality of evidences. YC and SL contributed to the initial drafting. JK and JWK made revisions. YC, SL, JK, JWK and JDL have read and approved the final manuscript for publication.

REFERENCES

1. Abdulmonem A, Hanan, A, Elaf A, *et al*. The prevalence of musculoskeletal pain & its associated factors among female Saudi school teachers. *Pak J Med sci* 2014;30:1191-6.
2. Coppieters I, Ickmans K, Cagnie B, *et al*. Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. *Pain physician* 2015;18:E389-401.
3. Murthy V, Sibbritt DW, Adams J. An integrative review of complementary and alternative medicine use for back pain: a focus on prevalence, reasons for use, influential factors, self-perceived effectiveness, and communication. *Spine J* 2015;15:1870-83.
4. Ussai S, Miceli L, Pisa FE, *et al*. Impact of potential inappropriate NSAIDs use in chronic pain. *Drug Des Devel Ther* 2015;9:2073-7.
5. Cho J, Lee E, Shin WG. Evaluation of NSAID usage and appropraiteness for prevention of NSAID-related ulcer complications. *Kor J Clin Pharm* 2012;22:211-19.
6. U.S. Food & Drug Administration. FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm2015 (accessed 11 Nov 2016)
7. Ventola CL. Current Issues Regarding Complementary and Alternative Medicine (CAM) in the United States: Part 1: The Widespread Use of CAM and the Need for Better-Informed Health Care Professionals to Provide Patient Counseling. *PT* 2010;35:461-8.
8. Bauer BA, Tilburt, J. C., Sood, A., *et al*. Complementary and alternative medicine therapies for chronic pain. *Chin J Integr Med* 2016;22:403-11.
9. Rueda Garrido, J.C., Vas, J, Lopez, D.R. Acupuncture treatment of shoulder impingement syndrome: A randomized controlled trial. *Complementary Ther Med* 2016;25:92-7.
10. Lin R, Zhu, N., Liu, J., *et al*. Acupuncture-movement therapy for acute lumbar sprain: a randomized controlled clinical trial. *J Tradit Chin Med* 2016;36:19-25.
11. MacPherson H, Tilbrook, H., Richmond, S., *et al*. Alexander Technique Lessons or Acupuncture Sessions for Persons With Chronic Neck Pain: A Randomized Trial. *Ann Intern Med* 2015;163:653-62.
12. Vickers AJ, Cronin AM, Maschino AC, *et al*. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med* 2012;172:1444-53.
13. Shin HJ, Lee DJ, Kwon K, *et al*. The success of thread-embedding therapy in generating hair re-growth in mice points to its possibly having a similar effect in humans. *J Pharmacopuncture* 2015;18:20-5.
14. Darpan Bhargava, P., Anantanarayanan, Geetha Prakash, *et al*. Initial inflammatory response of skeletal muscle to commonly used suture materials: An animal model study to evaluate muscle healing after surgical repair - histopathological perspective. *Med Oral Patol Oral Cir Bucal* 2013;18:e491-6.
15. Molea G, Schonauer, F., Bifulco, G., *et al*. Comparative study on biocompatibility and absorption times of three absorbable monofilament suture materials (Polydioxanone, Poliglecaprone 25, Glycomer 631). *Br J Plast Surg* 2000;53:137-41.
16. Jaing Y, Cheng J, Ding M, *et al*. Clinical observation of lumbar disc herniation treated with material modified embedding. *J Tradit Chin Med* 2015;42:846-47.
17. Jo NY, Roh JD. Effects of embedding therapy on frozen shoulder : a prospective study. *J Korean Med* 2015;36:1-7.
18. Kim SW, Shin JC. Effects of Korean medical treatment combined with embedding acupuncture on patients with chronic lower back pain : a Retrospective Study. *The Acupuncture* 2016;33:165-71.
19. Lee JH, Yang TJ, Lee DG, *et al*. The effect of needle-embedding therapy on osteoarthritis of the knee combined with Korean medical treatment: report of five cases. *The Acupuncture* 2014;31:195-204.
20. Law D, McDonough S, Bleakley C, *et al*. Laser acupuncture for treating musculoskeletal pain: a systematic review with meta-analysis. *J Acupunct Meridian Stud* 2015;8:2-16.
21. GS HJ. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration: Available form www.cochrane-handbook.org* 2011.
22. Lee S, Park J, Kim J, *et al*. Acupuncture for postoperative pain in laparoscopic surgery: a systematic review protocol. *BMJ open* 2014;4:1-5.
23. Park YE. *Medicine Wire Injection Therapy*. Seoul: Haenglimseowon, 2003:23.
24. White A, Cummings M, Filshie J. *An introduction to western medical acupuncture.* Edinburgh, New York: Churchill Livingstone Elsevier 2008:19-40.
25. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects-reconsideration and a hypothesis. *Acupunct Med* 2002;20:82-99.

26. Silva JR, Silva ML, Prado WA. Analgesia induced by 2- or 100-Hz electroacupuncture in the rat tail-flick test depends on the activation of different descending pain inhibitory mechanisms. *J Pain* 2011;12:51-60.
27. Xie XX, Kou ST, Pu ZH, *et al*. Effects of scalp catgut embedding on SOD, NO, MDA in the rat with Parkinson's disease. *Zhongguo Zhen Jiu* 2007;27:753-6.
28. Schmidtko A. Nitric oxide-mediated pain processing in the spinal cord. *Handb Exp Pharmacol* 2015;227:103-17.
29. Sastry Gollapudi, Chang Sokso, Michael Formica, *et al*. Safety and efficacy of polydioxanone nano-fibers as anti-inflammatory agents. J *Nanomedicine Biotherapeutic Discov* 2014;4:1-6.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
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	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
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	In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
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	5-6
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	7
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	Appendix 2 Qualification of searchers : YC and SL, who has received a professional education in the field of search and made search strategies several times in the past, will conduct searching.
Study records: Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
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)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8
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	7-8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

Online Resource 1 Search strategies

MEDLINE (Ovid Medline)

Patient	1. exp Pain
	2. exp Pain Management
	3. exp Analgesia
	4. (pain* or analgesi* or ache* or suffering* or discomfort).mp.
	5. 1 or 2 or 3 or 4
Intervention	6. ((catgut or thread or needle or acupunctur* or acupoint*) adj3 (implantation or embed*)).mp.
	7. embedding therapy.mp.
	8. 6 or 7
	9. 5 and 8

Chinese Database (CNKI)

Intervention (meaning: TEA)	1. 埋线 OR 埋针 OR 埋藏疗法
Patient (meaning: pain)	2. 痛
Study design (meaning: randomised)	3. 随机
	4. 1 AND 2 AND 3

Korean Databases (KAMJE, KMBASE, KISS, NDSL, DBpia, KNADL, OASIS and KTKP)

Intervention (meaning: TEA)	1. 매선 OR 매침 OR 매장요법
Patient (meaning: pain)	2. 통증 OR 진통
	3. 1 AND 2

URLs of databases

MEDLINE	http://gateway.ovid.com/autologin
CENTRAL	http://www.thecochranelibrary.com/
EMBASE	https://www.embase.com
CINAHL	http://search.ebscohost.com/login.asp?profile=ehost&defaultdb=rzh
AMED	http://gateway.ovid.com/autologin
CNKI	www.cnki.net
VIP	www.cqvip.com
The Wanfang database	www.wanfangdata.com
KMBASE	http://kmbase.medric.or.kr/
KAMJE	https://kamje.or.kr/
KISS	http://kiss.kstudy.com/
KNADL	http://www.nanet.go.kr/
NDSL	http://www.ndsl.kr/index.do
OASIS	https://oasis.kiom.re.kr/
DBpia	http://www.dbpia.co.kr/
KTKP	http://www.koreantk.com
ICTRP	http://apps.who.int/trialsearch/

BMJ Open

Thread embedding acupuncture for musculoskeletal pain: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015461.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Jun-2017
Complete List of Authors:	Cho, Yeeun; Kyunghee University Korean Medical Hostpital, Acupuncture and Moxibustion Lee, Seunghoon; Kyung Hee University Korean Medicine Hospital, Dept. of Acupuncture & Moxibustion Medicine Kim, Jihye; Kyunghee University Korean Medicine Hospital, Acupuncture and Moxibustion Kang, Jung Won; Kyung Hee University, Acupuncture & Moxibustion Medicine Lee, Jae Dong; College of Korean Medicine, Kyung Hee University, Department of Acupuncture and Moxibustion
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Complementary medicine, Evidence based practice
Keywords:	Thread embedding acupuncture, Randomised controlled trial, Musculoskeletal pain, Systematic review, Meta-analysis

Thread embedding acupuncture for musculoskeletal pain: a systematic review and meta-analysis protocol

*Yeeun Cho[1,2]
Email: kmdyeeun@gmail.com

*Seunghoon Lee[1,3]
Email: kmdoctorlee@gmail.com

Jihye Kim[1,3]
Email: acukjh@hanmail.net

Jung Won Kang[1,3]
Email: doctorkang@naver.com

Jae-Dong Lee[1,3]
Email: ljdacu@gmail.com

* YC and SL contributed equally

[1] Dept. of Acupuncture & Moxibustion, Kyung Hee University Korean Medicine Hospital, Seoul, South Korea
[2] Dept. of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, South Korea
[3] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

Correspondence to: Jae-Dong Lee, KMD, PhD, Department of Acupuncture and Moxibustion, Kyung Hee University Korean Medicine Hospital, 23 Kyunghee dae-ro, Dongdaemun-gu, 02447, Seoul, South Korea, E-mail: ljdacu@gmail.com Tel: +82-2-9582958 Fax: +82-2-9669366

Total word count: 3,885

ABSTRACT

Introduction: Thread embedding acupuncture (TEA) is a special type of acupuncture that inserts certain medical threads (e.g., catgut or polydioxanone) into subcutaneous tissue or muscles at specific points. Although TEA has been widely used for the treatment of musculoskeletal pain in Korea, China, and Taiwan, evidence regarding its efficacy is lacking. The aim of this protocol is to evaluate the effectiveness and safety of TEA in the treatment of musculoskeletal pain, by conducting a systematic review and meta-analysis.

Methods and analysis: The following 16 databases will be searched from their inception to 14 May 2017: MEDLINE, CENTRAL, EMBASE, CINAHL, AMED, three Chinese database (CNKI, VIP, and the Wanfang database) and eight Korean databases (KMBASE, KAMJE, KISS, KNADL, NDSL, OASIS, DBpia, and KTKP). The World Health Organisation International Clinical Trials Registry Platform (ICTRP) will also be searched to retrieve the recently completed studies.

All randomised controlled studies in which TEA was used on specific points for the treatment of musculoskeletal pain will be included and no restrictions on language will be applied. The risk of bias of each study will be evaluated by the Cochrane risk of bias tool.

Mean difference or standardised mean difference for continuous data and risk ratio for dichotomous data will be calculated with 95% confidence intervals using a random effects model or a fixed effects model. Additional subgroup and sensitivity analyses will be conducted according to a predefined protocol.

Ethics and dissemination: No ethical issues are predicted. The systematic review will be published in a peer-reviewed journal or conference presentation. These findings will summarise the current evidence of TEA for the treatment of musculoskeletal pain and may provide guidance for clinicians and patients to select TEA for musculoskeletal pain.

Trial registration number: PROSPERO 2015: CRD42015019046.

Keywords: Thread embedding acupuncture, Randomised controlled trial, Musculoskeletal pain, Systematic review, Meta-analysis

Strengths and limitations of this study

● To the best of our knowledge, this review will be the first systematic review to evaluate the effectiveness and safety of thread embedding acupuncture for musculoskeletal pain.

● Two review authors will select the studies, extract data, and assess the risk of bias independently.

● This protocol has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement and registered in PROSPERO.

● There might be few studies with a low risk of bias; hence, they might affect the quality of the evidence

INTRODUCTION

Musculoskeletal pain is the most frequently reported medical disorder. In the general population, the prevalence of musculoskeletal pain varies from 40.4% to 69.3%.[1] Musculoskeletal pain leads to limitations in daily activities, loss of work productivity, and increased medical costs. Moreover, the quality of life (QoL) of patients with musculoskeletal pain, such as chronic whiplash-associated disorders,[2] and chronic non-specific low back pain,[3] is significantly lower than that of healthy controls. The most commonly prescribed pharmacological agents for musculoskeletal pain are non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. However, the long-term use of these medications is not recommended because of considerable side-effects, such as weight gain or loss, gastrointestinal symptoms, and dizziness.[4] A Korean hospital outpatient analysis in 2009 showed that the prevalence of ulcer complications increased from 11.3% to 47.2% as the number of prescribed days of NSAIDs increased.[5] Recently, the U.S. Food and Drug Administration strengthened its warning that NSAIDs can increase the risk of heart attack or stroke.[6] The interest in non-pharmacological treatments for musculoskeletal pain, including complementary and alternative medicine (CAM), may have increased because of the deleterious side effects associated with pharmacological agents.[7] In particular, CAM modalities, such as manual therapy, yoga, physical therapy, and meditation, are known to have chronic pain-relief effects and are recommended as treatment modalities for pain.[8]

Acupuncture is a common CAM treatment modality, and many studies have demonstrated the effect of acupuncture on musculoskeletal pain, such as shoulder impingement syndrome,[9] acute lumbar sprain,[10] and chronic neck pain.[11] A well-designed meta-analysis that compared manual- and electroacupuncture with sham and no acupuncture controls revealed that acupuncture had a better effect than sham and no acupuncture controls in chronic pain conditions. However, the effect size was small to moderate, and more specific stimulation methods are warranted to determine the effect above the placebo effect.[12]

Thread embedding acupuncture (TEA) is special type of acupuncture that inserts medical threads (e.g., catgut or polydioxanone [PDO]) into subcutaneous tissue or muscles at specific points (e.g., traditional acupuncture points or tender points).[13] There are two components involved in TEA, a guide needle and the medical threads. TEA involves the insertion of a medical thread, which is attached to a guide needle, into the skin overlying specific acupuncture or tender points. The needle is removed after insertion and the medical threads remain embedded in the subcutaneous tissue or muscle. The embedded thread gradually softens, decomposes, and dissolves with time in the subcutaneous tissue or muscle.[14] The complete absorption times differ with the types of threads. The absorption of PDO is

known to be slow during first 3 months[15] and proceeds until 180 to 210 days.[14] When compared with acupuncture, TEA may produce a strong and long-lasting therapeutic effect. One Chinese randomised controlled trial (RCT) confirmed that TEA had a better effect than acupuncture in reducing the pain of patients with lumbar intervertebral disc herniation.[16]

With the availability of safe absorbable medical threads such as PDO, TEA has been widely used for the treatment of musculoskeletal pain in Korea, China, and Taiwan. Treatments with TEA include frozen shoulder,[17] chronic low back pain,[18] and osteoarthritis of the knee.[19] However, there is a lack of evidence on the contribution of TEA in the treatment of musculoskeletal pain. Therefore, this review will evaluate whether TEA is effective and safe compared to other treatments for the treatment of musculoskeletal pain, based on the pain severity, function, global assessments of participant improvement, QoL, analgesic consumption, and adverse events.

OBJECTIVES

This study aims to review the evidence for effectiveness and safety of TEA, compared to other techniques in the treatment of musculoskeletal pain.

Research questions based on the PICOS approach

- Population: patients with musculoskeletal pain
- Intervention: TEA
- Comparison: no treatment/waiting list, sham control, or active treatment (e.g., physical therapy, oral medication, surgery, injection, or other traditional medical treatments), except for herbal medicine
- Outcome: pain severity, function, global assessments of participant improvement, QoL, analgesic consumption, and adverse events
- Study design: RCTs

The details are described below.

METHODS AND ANALYSIS

Study registration

The protocol for this review was registered prospectively (CRD42015019046; http://www.crd.york.ac.uk/PROSPERO). This protocol was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement. The PRISMA-P checklist is presented in the online supplementary appendix 1.

Eligibility criteria

Types of studies

Only RCTs of TEA for musculoskeletal pain will be included in this review. Quasi-randomised controlled studies, observational studies, and experimental studies will be excluded. There will be no restrictions regarding the language that the studies are published in. And only published studies will be included.

Types of participants

Participants with musculoskeletal pain undergoing TEA will be included. Pain induced from headache and systemic illness will not be included.[20] There will not be any restrictions based on disease onset and age of the participants.

Types of interventions and comparisons

Studies about the effect of TEA at specific points (e.g., traditional acupuncture points or tender points) will be included. Studies in which the effects of TEA was compared to no treatment/waiting list, sham control, or active treatment (e.g., physical therapy, oral medication, surgery, injection, or other traditional medical treatments) will be included. Studies in which the effects of TEA were compared to herbal medicine will be excluded. In case the participants of the TEA group received another active treatment, only studies in which the participants of all comparison groups received the same active treatment as a co-intervention will be included. Studies that compared general TEA with other types of TEA will be excluded.

Types of outcome measures

Primary outcome measures

1. Symptoms of pain that are identified using any pain scales (e.g., numeric rating scale [NRS] or visual analogue scale [VAS])
2. Functional outcome measures (e.g., validated questionnaire or functional scale specific to the musculoskeletal disease, such as the range of motion [ROM])
3. Severe adverse events related to the treatment

Secondary outcome measures

1. Global assessment of participant improvement (e.g., subjective improvement and proportion of overall improvement)
2. QoL assessed using a validated scale (e.g., 36-item Short-Form or Euro-QoL)

3. Analgesic consumption
4. Adverse events related to TEA or any other treatments

Search methods for identification of studies

Electronics searches

The following 16 electronic databases will be searched from their inception to 14 May 2017: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED), three Chinese databases (China National Knowledge Infrastructure [CNKI], the Chongqing VIP Chinese Science and Technology Periodical Database [VIP], and the Wanfang database) and eight Korean databases (Korean Medical Database [KMBASE], Korean Association of Medical Journal Editors [KAMJE], Korean Studies Information Service System [KISS], Korean National Assembly Digital Library [KNADL], National Digital Science Library [NDSL], Oriental Medicine Advanced Searching Integrated System [OASIS], Database Periodical Information Academic [DBpia], and Korean Traditional Knowledge Portal [KTKP]). The search terms consisted of two parts: pain (e.g., pain, analgesic, suffering, or discomfort) and embedding therapy (e.g., catgut embedding, catgut embedment, needle embedding, or thread implantation). The online supplementary appendix 2 shows the detailed search strategies for MEDLINE, CNKI, and Korean databases.

Searching other resources

The World Health Organisation International Clinical Trials Registry Platform (ICTRP) will be searched to retrieve recently completed studies. Relevant publications (e.g., textbooks on acupuncture and the references within the included studies) will be manually searched.

Data collection and analysis

Selection of studies

Two independent reviewers (YC and SL) will screen the titles and abstracts to assess their suitability for inclusion. YC and SL will read the full texts of the suitable studies and perform further selection based on the inclusion criteria. Disagreements will be resolved by discussion between the authors.

Data extraction and management

Two independent reviewers (YC and SL) will read the full texts of each article and extract the data using a data extraction form. The data extraction form includes the author, year, disease, duration, type of treatments, numbers of participants analysed/randomised, numbers of treatments, follow up,

outcome measures, results and adverse events. Any disagreements will be resolved by discussion.

Assessment of risk of bias and reporting quality in included studies

Two independent reviewers (YC and SL) will assess the risk of bias based on the Cochrane Collaboration's 'risk of bias' tool. The risk of bias tool covers six domains: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting.[21] The risk of bias for each domain will be rated as 'low risk', 'high risk', or 'unclear risk'.

Measures of treatment effect

The mean difference or standardised mean difference will be used to assess the treatment effect with 95% confidence intervals (CIs) for continuous data (e.g., VAS, NRS, or scores of functional outcome measures). Standardised mean difference will be used when calculating the same outcome variables using different scales and methods. The risk ratio will be used to assess the treatment effect with 95% CIs for dichotomous outcomes (e.g., responder or non-responder). Ordinal outcomes (e.g., 'almost cured', 'remarkably effective', 'effective', or 'not effective') in two or more categories will be converted to dichotomous outcomes, such as responder and non-responder.

Dealing with missing data

When there are insufficient data or missing data, the corresponding author will be contacted to request additional information or clarification. If the corresponding author cannot be contacted, the available data alone will be analysed.

Assessment of heterogeneity

The heterogeneity between different studies will be measured using a visual inspection of the forest plot and Chi-square test with statistical significance. The I^2 statistic will be calculated to assess inconsistencies in the results of the included studies. The I^2 results will be interpreted as follows: unimportant heterogeneity (0% to 40%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%), and considerable heterogeneity (75% to 100%).[21] When considerable heterogeneity cannot be explained by the diversity in clinical or methodological aspects of the included studies, the data will not be pooled

Assessment of reporting biases

If the numbers of studies used in the analyses are sufficient, funnel plots will be used to detect

reporting biases.[21] When there is a funnel plot asymmetry, possible factors for the asymmetry (e.g., small-study effects or poor methodological quality) will be identified.

Data synthesis

The meta-analyses will be performed using the Review Manager (RevMan) software (version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). A random effects model or a fixed effect model with 95% CIs will be used to calculate the pooled estimates of effect size. When there is considerable heterogeneity ($I^2 > 75\%$) that cannot be explained by the methodological and clinical diversity, the meta-analysis will not be conducted. If the quantitative synthesis is not appropriate, the summary of the studies will be done in a narrative form. When dichotomous data in studies comparing TEA with two or more controls will be assessed for meta-analysis, the data of the TEA group will divided equally and compared individually with control groups to avoid double counting.[22]

Subgroup analysis and investigation of heterogeneity

When the numbers of available studies are sufficient, subgroup analyses will be utilised to interpret the heterogeneity across studies according to the following:

1. Type of thread (e.g., absorbability or size)
2. Type of control (e.g., no treatment/waiting list, sham control, or active treatment)
3. Duration of disease (e.g., acute [up to 1 month], subacute [1 to 3 months], or chronic [more than three months])
4. Duration of follow-up (e.g., short-term [within four weeks], medium-term [up to six months], and long-term [more than six months]).

Sensitivity analysis

Sensitivity analyses will be performed when possible to determine whether the results are robust according to the following:

1. Methodological quality (e.g., whether sequence generation and allocation concealment were adequately conducted)
2. Sample size (e.g., greater or less than 30 participants in each group)
3. Analysis related issues (e.g., cut-off point of ordinal scale to dichotomous scale; 'almost cured, remarkably effective, and effective' as a responder versus 'almost cured and remarkably effective' as a responder).

Summary of evidence

In case there are sufficient data, the results of the main outcomes will be summarised in the 'Summary

of findings' tables using the GRADE approach to evaluate the quality of evidence.[21]

DISCUSSION

The aim of this systematic review is to evaluate the effectiveness and safety of TEA for the treatment of musculoskeletal pain. The first detailed record of the medical application of TEA was in 'Taepyeonghyeminbang (太平惠民方)' published in 982 AD.[23] However, TEA was probably not widely used because of the difficulty of the technique and the absence of proper absorbable materials. With the development of special types of absorbable medical threads, such as chromic catgut and PDO, TEA has become more widely used in Korea, China, and Taiwan.

Needle insertion during TEA treatment may induce an analgesic effect through mechanisms similar to that of manual acupuncture. The mechanisms of analgesia with acupuncture include enhanced local circulation,[24 25] segmental effects based on the gate-control theory,[24] and extrasegmental effects with descending inhibitory pain control.[26] Moreover, enhanced stimulation induced by an embedded thread might have additional pain relief mechanisms. An animal study demonstrated that TEA produced a regulative effect on nitric oxide (NO),[27] which is an important factor in the processing of persistent neuropathic pain.[28] Another animal study mentioned that the injection of PDO into mice with rheumatoid arthritis had an anti-inflammatory effect by increasing interleukin-10.[29]

This systematic review will provide current evidence on the effectiveness and safety of TEA for musculoskeletal pain. These findings will provide guidance to clinicians and patients on the use of TEA for musculoskeletal pain. Moreover, these results are also available to health care professionals in Western countries who are unfamiliar with the use of TEA. Further clinical research will be designed based on this systematic review.

Ethics and dissemination

Ethical approval is not required as this is a systematic review without using personal data or contacting patients directly. The results of this review will be disseminated in a peer-reviewed journal or conference presentation.

Abbreviations

AMED	The Allied and Complementary Medicine Database
CAM	Complementary and alternative medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
CIs	Confidence intervals
CNKI	China National Knowledge Infrastructure
DBpia	Database Periodical Information Academic
ICTRP	The World Health Organisation International Clinical Trials Registry Platform
KAMJE	Korean Association of Medical Journal Editors
KISS	Korean Studies Information Service System
KMBASE	Korean Medical Database
KNADL	Korean National Assembly Digital Library
KTKP	Korean Traditional Knowledge Portal
NDSL	National Digital Science Library
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OASIS	Oriental Medicine Advanced Searching Integrated System
PDO	Polydioxanone
PRIMSA-P	Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols
QoL	Quality of life
RCT	Randomised controlled trial
RevMan	Review Manager
ROM	Range of motion
TEA	Thread embedding acupuncture
VAS	Visual analogue scale
VIP	The Chongqing VIP Chinese Science and Technology Periodical Database

Author affiliations

[1] Dept. of Acupuncture & Moxibustion, Kyung Hee University Korean Medicine Hospital, Seoul, South Korea

[2] Dept. of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, South Korea

[3] Dept. of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea

Funding

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HI15C0070).

Competing interests

None

Contributors

YC and SL contributed to the development of the search strategy. YC and SL will search and select the studies. JDL will act as an arbiter in the selection stage. YC and SL will also read the full texts of studies, extract data, assess the risk of bias, and report quality of evidences. YC and SL contributed to the initial drafting. JK and JWK made revisions. YC, SL, JK, JWK, and JDL have read and approved the final manuscript for publication.

REFERENCES

1. Abdulmonem A, Hanan, A, Elaf A, *et al*. The prevalence of musculoskeletal pain & its associated factors among female Saudi school teachers. *Pak J Med sci* 2014;30:1191-6.
2. Coppieters I, Ickmans K, Cagnie B, *et al*. Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. *Pain physician* 2015;18:E389-401.
3. Murthy V, Sibbritt DW, Adams J. An integrative review of complementary and alternative medicine use for back pain: a focus on prevalence, reasons for use, influential factors, self-perceived effectiveness, and communication. *Spine J* 2015;15:1870-83.
4. Ussai S, Miceli L, Pisa FE, *et al*. Impact of potential inappropriate NSAIDs use in chronic pain. *Drug Des Devel Ther* 2015;9:2073-7.
5. Cho J, Lee E, Shin WG. Evaluation of NSAID usage and appropraiteness for prevention of NSAID-related ulcer complications. *Kor J Clin Pharm* 2012;22:211-19.
6. U.S. Food & Drug Administration. FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm2015 (accessed 11 Nov 2016)
7. Ventola CL. Current Issues Regarding Complementary and Alternative Medicine (CAM) in the United States: Part 1: The Widespread Use of CAM and the Need for Better-Informed Health Care Professionals to Provide Patient Counseling. *PT* 2010;35:461-8.
8. Bauer BA, Tilburt, J. C., Sood, A., *et al*. Complementary and alternative medicine therapies for chronic pain. *Chin J Integr Med* 2016;22:403-11.
9. Rueda Garrido, J.C., Vas, J, Lopez, D.R. Acupuncture treatment of shoulder impingement syndrome: A randomized controlled trial. *Complementary Ther Med* 2016;25:92-7.
10. Lin R, Zhu, N., Liu, J., *et al*. Acupuncture-movement therapy for acute lumbar sprain: a randomized controlled clinical trial. *J Tradit Chin Med* 2016;36:19-25.
11. MacPherson H, Tilbrook, H., Richmond, S., *et al*. Alexander Technique Lessons or Acupuncture Sessions for Persons With Chronic Neck Pain: A Randomized Trial. *Ann Intern Med* 2015;163:653-62.
12. Vickers AJ, Cronin AM, Maschino AC, *et al*. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med* 2012;172:1444-53.
13. Shin HJ, Lee DJ, Kwon K, *et al*. The success of thread-embedding therapy in generating hair re-growth in mice points to its possibly having a similar effect in humans. *J Pharmacopuncture* 2015;18:20-5.
14. Darpan Bhargava, P., Anantanarayanan, Geetha Prakash, *et al*. Initial inflammatory response of skeletal muscle to commonly used suture materials: An animal model study to evaluate muscle healing after surgical repair - histopathological perspective. *Med Oral Patol Oral Cir Bucal* 2013;18:e491-6.
15. Molea G, Schonauer, F., Bifulco, G., *et al*. Comparative study on biocompatibility and absorption times of three absorbable monofilament suture materials (Polydioxanone, Poliglecaprone 25, Glycomer 631). *Br J Plast Surg* 2000;53:137-41.
16. Jaing Y, Cheng J, Ding M, *et al*. Clinical observation of lumbar disc herniation treated with material modified embedding. *J Tradit Chin Med* 2015;42:846-47.
17. Jo NY, Roh JD. Effects of embedding therapy on frozen shoulder : a prospective study. *J Korean Med* 2015;36:1-7.
18. Kim SW, Shin JC. Effects of Korean medical treatment combined with embedding acupuncture on patients with chronic lower back pain : a Retrospective Study. *The Acupuncture* 2016;33:165-71.
19. Lee JH, Yang TJ, Lee DG, *et al*. The effect of needle-embedding therapy on osteoarthritis of the knee combined with Korean medical treatment: report of five cases. *The Acupuncture* 2014;31:195-204.
20. Law D, McDonough S, Bleakley C, *et al*. Laser acupuncture for treating musculoskeletal pain: a systematic review with meta-analysis. *J Acupunct Meridian Stud* 2015;8:2-16.
21. GS HJ. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration: Available form www.cochrane-handbook.org* 2011.
22. Lee S, Park J, Kim J, *et al*. Acupuncture for postoperative pain in laparoscopic surgery: a systematic review protocol. *BMJ open* 2014;4:1-5.
23. Park YE. *Medicine Wire Injection Therapy*. Seoul: Haenglimseowon, 2003:23.
24. White A, Cummings M, Filshie J. *An introduction to western medical acupuncture.* Edinburgh, New York: Churchill Livingstone Elsevier 2008:19-40.
25. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects-reconsideration and a hypothesis. *Acupunct Med* 2002;20:82-99.

26. Silva JR, Silva ML, Prado WA. Analgesia induced by 2- or 100-Hz electroacupuncture in the rat tail-flick test depends on the activation of different descending pain inhibitory mechanisms. *J Pain* 2011;12:51-60.
27. Xie XX, Kou ST, Pu ZH, *et al*. Effects of scalp catgut embedding on SOD, NO, MDA in the rat with Parkinson's disease. *Zhongguo Zhen Jiu* 2007;27:753-6.
28. Schmidtko A. Nitric oxide-mediated pain processing in the spinal cord. *Handb Exp Pharmacol* 2015;227:103-17.
29. Sastry Gollapudi, Chang Sokso, Michael Formica, *et al*. Safety and efficacy of polydioxanone nano-fibers as anti-inflammatory agents. J *Nanomedicine Biotherapeutic Discov* 2014;4:1-6.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
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	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
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	In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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	5-7
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	7
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	Appendix 2 Qualification of searchers : YC and SL, who has received a professional education in the field of search and made search strategies several times in the past, will conduct searching.
Study records: Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-10

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
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)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
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	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8
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	8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol (continued)

Section and topic	Item No	Checklist item	Reported on page #
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9-10

Online Resource 1 Search strategies

MEDLINE (Ovid Medline)

Patient	1. exp Pain
	2. exp Pain Management
	3. exp Analgesia
	4. (pain* or analgesi* or ache* or suffering* or discomfort).mp.
	5. 1 or 2 or 3 or 4
Intervention	6. ((catgut or thread or needle or acupunctur* or acupoint*) adj3 (implantation or embed*)).mp.
	7. embedding therapy.mp.
	8. 6 or 7
	9. 5 and 8

Chinese Database (CNKI)

Intervention (meaning: TEA)	1. 埋线 OR 埋针 OR 埋藏疗法
Patient (meaning: pain)	2. 痛
Study design (meaning: randomised)	3. 随机
	4. 1 AND 2 AND 3

Korean Databases (KAMJE, KMBASE, KISS, NDSL, DBpia, KNADL, OASIS and KTKP)

Intervention (meaning: TEA)	1. 매선 OR 매침 OR 매장요법
Patient (meaning: pain)	2. 통증 OR 진통
	3. 1 AND 2

URLs of databases

MEDLINE	http://gateway.ovid.com/autologin
CENTRAL	http://www.thecochranelibrary.com/
EMBASE	https://www.embase.com
CINAHL	http://search.ebscohost.com/login.asp?profile=ehost&defaultdb=rzh
AMED	http://gateway.ovid.com/autologin
CNKI	www.cnki.net
VIP	www.cqvip.com
The Wanfang database	www.wanfangdata.com
KMBASE	http://kmbase.medric.or.kr/
KAMJE	https://kamje.or.kr/
KISS	http://kiss.kstudy.com/
KNADL	http://www.nanet.go.kr/
NDSL	http://www.ndsl.kr/index.do
OASIS	https://oasis.kiom.re.kr/
DBpia	http://www.dbpia.co.kr/
KTKP	http://www.koreantk.com
ICTRP	http://apps.who.int/trialsearch/