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Acupuncture for Postoperative Pain following Total Knee Arthroplasty: A Systematic Review Protocol

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ABSTRACT

Background:

Total knee arthroplasty (TKA) is a common surgical method in orthopedics; however, pain management after TKA remains a significant challenge. This review provides a comprehensive evaluation of the effects of acupuncture for postoperative pain after TKA.

Methods and Analysis:

The following 10 databases will be searched until August 2015: MEDLINE, EMBASE, CENTRAL, AMED, CINAHL, three Chinese databases (the China National Knowledge Infrastructure Database, the Chongqing VIP Chinese Science and Technology Periodical Database, and Wanfang Database) and five Korean databases (the Korean Medical Database, the Korean Studies Information Service System, the National Discovery for Science Leaders, the Database Periodical Information Academic, and the Oriental Medicine Advanced Searching Integrated System). All eligible randomised controlled trials related to the use of acupuncture for postoperative pain after TKA will be included. Assessment of risk of bias will be performed with the Cochrane risk-of-bias method. Mean differences or standardised mean differences will be calculated with 95% confidence intervals (CIs) for continuous data; the risk ratio will be used with 95% CIs for dichotomous data.

Dissemination:

This systematic review will be presented in a peer-reviewed journal. The result of this review will also be disseminated at a relevant conference presentation.

Trial registration number: PROSPERO 2015: CRD42015020924

Key words

Acupuncture, analgesia, arthroplasty, postoperative, knee surgery

INTRODUCTION

Description of the condition

Total knee arthroplasty (TKA), the most common surgical technique to treat severe knee osteoarthritis and rheumatoid arthritis, is a highly successful procedure to improve knee function and pain.[1 2] However, pain after TKA remains a major complaint, and rehabilitation, which is commonly performed following the procedure, is closely associated with pain management.[3] Moreover, because the majority of patients undergoing TKA are elderly, the side effects of analgesics could be severe. Therefore, the gold standard for postoperative pain management remains unclear.[4]

Description of the intervention

Acupuncture is a complex and interactive intervention that can be used in the treatment, rehabilitation, and/or management of various diseases and conditions (*e.g.,* acute and chronic pain disorders, cerebrovascular disease, chemotherapy for cancer, and post-traumatic stress disorder). Acupuncture is the most common treatment for various musculoskeletal pains.[5] According to several recent systematic reviews (SRs), acupuncture exerts analgesic effects on pain after various types of surgeries.[6, 7]

How the intervention may work

Many studies have reported that acupuncture can be helpful for relieving pain.[5] However, the precise mechanism by which acupuncture provides postoperative analgesia remains unclear. Some studies explain the analgesic effects of acupuncture in terms of a spinal mechanism (*e.g.,* gate-control theory), hormonal effects, and peripheral events (*e.g.,* local circulation, vasodilation, and tissue healing).[8 9]

Why it is important to perform this review

TKA is commonly used for the treatment of severe advanced osteoarthritis in aged patients, and its use is continuously increasing.[1 2] When pain management and rehabilitation are performed in an appropriate manner after the operation, TKA can be considered a highly effective procedure. However,

inadequate use of analgesics for postoperative pain impairs recovery from the operation and rehabilitation.[4] Moreover, because most patients undergoing TKA are elderly, the use of analgesics, including opioids, requires careful consideration.[10] As a result, multimodal approaches for postoperative pain control have been proposed, and the postoperative analgesic effects of acupuncture have been reported in a number of studies. However, postoperative analgesic effects of acupuncture after TKA remain controversial.[11 12] Therefore, a comprehensive review of the analgesic effects of acupuncture on postoperative pain following TKA may contribute to the rehabilitation of patients undergoing TKA surgery.

OBJECTIVES

This review protocol provides a comprehensive evaluation of the analgesic effects of acupuncture on postoperative pain following TKA.

METHODS

Criteria for including studies in this review

Types of studies

Prospective randomised controlled trials (RCTs) of acupuncture therapy for postoperative pain after TKA will be included. Non-randomised studies (NRSs), including case–control trials and case studies, will be excluded. No language restriction will be applied.

Types of participants

Patients undergoing TKA will be included. We will not screen out eligible patients based on the reason for TKA.

Types of interventions

Acupuncture therapy will be defined as various needling procedures that involve stimulating certain points, such as manual acupuncture, auricular acupuncture, electroacupuncture, or dry needling on

tender points. In addition, non-penetrating stimulation on acupoints, such as acupressure, will be included. We will include traditional acupuncture, auricular acupuncture, acupressure therapies, electroacupuncture, laser acupuncture, and dry needling; therefore, we will be able to comprehensively evaluate the effects of acupuncture on postoperative pain after TKA. We will also include trials that compared acupuncture plus another typical treatment with other typical treatments alone. Control interventions will include sham/placebo acupuncture, no treatment, waiting-list membership, and conventional therapies (*e.g.,* usual care, analgesics, manual therapy).

Types of outcome measures

Primary outcomes

1. Pain: a pain-associated scale will be included (*e.g.,* visual analogue scale or numerical rating scale).

2. Functional evaluation of knee joint: the Western Ontario and McMaster University Arthritis Index (WOMAC).

Secondary outcomes

1. The range of motion (ROM) of the knee joint

2. Quality of life (QOL): a QOL-associated scale will be included (*e.g.,* Euro-QoL (EQ5D) and the 36-Item Short-Form Health Survey (SF-36)).

3. Adverse events related to acupuncture treatment.

Search methods for identification of studies

Electronic searches

According to the core, standard, ideal (COSI) model,[13] the following databases will be searched for the period from the time of their inception to August 2015 to identify relevant articles: MEDLINE/Pubmed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We will also search the following three Chinese medical databases: the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP

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Searching other resources

We will manually investigate ambiguous literature to avoid missing eligible trials.

Search strategy

The search strategies for MEDLINE/Pubmed are described in Appendix 1, and we will modify these search strategies for other databases.

Data collection and analysis

Selection of studies

Two independent review authors will screen the titles and abstracts of all searched studies, and studies will be selected through a full-text review if they meet the pre-defined eligibility criteria. When a consensus on the selection process cannot be obtained through consultations, the third author will ultimately decide. The selection process of this review will be presented in the PRISMA flow chart (Figure 1).[14]

Data extraction and management

Data will be extracted from all eligible studies by two independent reviewers. When a consensus on the data extraction cannot be obtained through consultations, the third author will decide. When the collected data are incomplete or unclear, the arbiter will contact the corresponding authors of the original articles to request additional data or an explanation of the relevant issue.

Assessment of risk of bias and reporting quality in included studies

Two independent review authors will evaluate the risk of bias of included studies using the Cochrane Collaboration's risk-of-bias (ROB) assessment method.[15] Assessment of the ROB will be performed according to the following seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data' (6) selective reporting, and (7) other sources of bias. The ROB of trials will be categorised as low, unclear, or high risk of bias. When a consensus on assessment of the ROB cannot be achieved through consultations, the third author will decide.

Measures of treatment effect

Mean differences (MDs) with 95% confidence intervals (CIs) will be used for the analysis of continuous data; standardised mean differences (SMDs) with 95% CIs will be used if different scales were used to measure a certain outcome variable. Dichotomous data will be analysed using the relative risk (RR) with 95% CIs.

Unit-of-analysis issues

If unit-of-analysis issues arise in examinations of assessment time points, we will classify time frames into four different measurement time points after TKA: (1) less than 3 h, (2) 12 h, (3) up to 24 h, and (4) more than 24 h.

Dealing with missing data

If possible, we will contact the corresponding authors of the original trials to request missing data. If it is not possible to contact the original authors or obtain missing data, the analysis will rely on the available data.

Assessment of heterogeneity

According to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity will be assessed in the following three ways: (1) a visual check of the forest plot, (2) a heterogeneity χ^2 test, and (3) Higgins I^2 statistic. In terms of the interpretation of the heterogeneity χ^2

test, a significance level of $p<0.10$ will be considered meaningful heterogeneity. In terms of the interpretation of the Higgins I^2 statistic, more than 50% will be considered meaningful heterogeneity.[16] If meaningful heterogeneity among the included studies is identified, we will perform a subgroup analysis or a meta-regression analysis to determine the reason; if the heterogeneity cannot be resolved through additional analysis, we will not pool the data.

Assessment of reporting biases

If more than 10 studies are included, we will assess the reporting biases though funnel plots. When funnel plot asymmetry is detected, we will attempt to identify possible reasons (*e.g.,* publication bias, small study effect, and true heterogeneity) through visual evaluation of the funnel plot and statistical analysis, such as Egger's test.[17]

Data synthesis

We will conduct a meta-analysis to estimate differences in primary and secondary outcomes. A meta-analysis will be performed using Review Manager Software (RevMan, version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark).[18] Depending on the level of heterogeneity among included studies, we will apply a fixed-effects model or a random-effects model. When considerable heterogeneity is observed, a random-effects model with 95% CIs will be used in the analysis of pooled effect estimates. If meaningful heterogeneity, which cannot be explained by any additional assessment such as subgroup analysis, is identified among the included studies, we will not attempt to perform a meta-analysis. If necessary, subgroup analysis will be performed with careful consideration of each subgroup.

Subgroup analysis and investigation of heterogeneity

When it is necessary to interpret the heterogeneity of included studies and the data are sufficient, we will use subgroup analysis, according to the following:

1. Type of control intervention (*e.g.,* no treatment, usual care, or sham acupuncture);

2. Type of acupuncture (*e.g.,* manual acupuncture, electroacupuncture, auricular acupuncture, acupressure, or dry needling on tender points);

3. Duration of assessment (less than 3 h, 12 h, up to 24 h, or more than 24 h).

Sensitivity analysis

We will implement a sensitivity analysis according to the following:

1. Sample size: studies will be categorised into those with small or large samples according to whether they included fewer or more than 40 participants in each group.

2. Analysis issues (*e.g.,* procedure for management of missing data).

3. Methodological qualities.

Summary of evidence

The results of the primary outcomes will be presented in summary of findings tables (SOF Tables). The evidence level of the primary outcomes will be analysed through the Grading of Recommendations Assessment Development and Evaluation (GRADE) method.

DISCUSSION

Numerous recent SRs and clinical trials have supported the effects of acupuncture for various type of postoperative pain[6 7]; however, no reviews have assessed the evidence for the analgesic effects of acupuncture for postoperative pain following TKA. Furthermore, the types of acupuncture examined by most of the RCTs that evaluated the analgesic effects of this treatment for pain after knee surgery have been too diverse to assess the overall effects.[11 12] Thus, we will comprehensively analyse the analgesic effects of acupuncture for postoperative pain after TKA; for this purpose, subgroup analysis will be conducted according to the type of acupuncture treatment, the type of control intervention, and the duration of the assessment. This review will provide current evidence for the effectiveness of acupuncture therapy for postoperative pain after TKA and will clarify the benefits experienced by

patients undergoing TKA to increase the knowledge base of practitioners of both traditional and complementary medicine.

Contributors

SC contributed to the conception of this review. The review protocol was drafted by JJ, and was revised by SC. The search strategy was established by all authors. JJ and JC will independently screen the searched studies, extract the data from the eligible studies, assess the risk of bias and conduct the meta-analysis. When a consensus between two authors cannot be achieved through consultations, SC will ultimately decide. All authors approved the publication of this review protocol.

Competing interests

None.

REFERENCES

1. Dye SF. Knee arthroplasty to maximize the envelope of function. Total Knee Arthroplasty: Springer, 2005:14-17.
2. Kurtz S. Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030. The Journal of Bone and Joint Surgery (American) 2007;**89**(4):780.
3. Danninger T. Perioperative pain control after total knee arthroplasty: An evidence based review of the role of peripheral nerve blocks. World Journal of Orthopedics 2014;**5**(3):225.
4. Sarridou DG, Chalmouki G, Braoudaki M, et al. Intravenous Parecoxib and Continuous Femoral Block for Postoperative Analgesia after Total Knee Arthroplasty. A Randomized, Double-Blind, Prospective Trial. Pain Physician 2015;**18**:267-76.
5. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;**172**(19):1444-53.

6. Sun Y, Gan TJ, Dubose JW, et al. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British Journal of Anaesthesia 2008;**101**(2):151-60.

7. Cho Y-H, Kim C-K, Heo K-H, et al. Acupuncture for Acute Postoperative Pain after Back Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Pain Practice 2015;**15**(3):279-91.

8. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects--reconsideration and a hypothesis. Acupunct Med 2002;**20**(2-3):82-99.

9. Napadow V, Ahn A, Longhurst J, et al. The status and future of acupuncture mechanism research. J Altern Complement Med 2008;**14**(7):861-69.

10. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;**11**(2 Suppl):S105-20.

11. Chen C-C, Yang C-C, Hu C-C, et al. Acupuncture for pain relief after total knee arthroplasty: a randomized controlled trial. Reg Anesth Pain Med 2015;40(1):31-36.

12. Mikashima Y, Takagi T, Tomatsu T, et al. Efficacy of acupuncture during post-acute phase of rehabilitation after total knee arthroplasty. Journal of Traditional Chinese Medicine 2012;**32**(4):545-48.

13 Bidwell S, Jensen MF. Etext on Health Technology Assessment (HTA) Information Resources: Chapter 3: Using a Search Protocol to Identify Sources of Information: The COSI Model, 2005.

14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41.

15 Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:187-241.

16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;**21**(11):1539–58.

17. Sterne JAC, Egger M, Moher D. Addressing Reporting Biases. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:297-333.

18. Deeks JJ, Higgins JPT, Altman DG. Analysing Data and Undertaking Meta-Analyses. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:243-96.

Appendix 1 The search strategies for MEDLINE/Pubmed

1. “arthroplasty, Replacement, Knee”[MeSH]
2. “knee replacement arthroplasty”[tw]
3. “total knee arthroplasty”[tw]
4. “total knee”[tw]
5. tka[tw]
6. “knee replacement”[tw]
7. “knee replacements”[tw]
8. “knee implantation”[tw]
9. “knee implant”[tw]
10. “knee implants”[tw]
11. “knee joint replacement”[tw]
12. “knee joint replacements”[tw]
13. “knee joint arthroplasty”[tw]
14. “knee joint arthroplasties’[tw]
15. “knee Replacement Arthroplasties”[tw]
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. acupuncture[MeSH]
18. “acupuncture therapy”[MeSH]
19. acupuncture[tw]
20. electroacupuncture[tw]
21. electro-acupuncture[tw]
22. acupressure[tw]
23. “dry needling”[tw]
24. auriculoacupuncture[tw]
25. auriculo-acupuncture[tw]
26. acupoint*[tw]

27. meridian*[tw]

28. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. “randomised controlled trial”[Publication Type]

30. “randomised controlled trials as topic”[MeSH]

31. “random allocation”[MeSH]

32. “double-blind method”[MeSH]

33. “single-blind method”[MeSH]

34. placebos[MeSH]

35. random*[tw]

36. rct[tw]

37. rct’s[tw]

38. rcts[tw]

39. placebo*[tw]

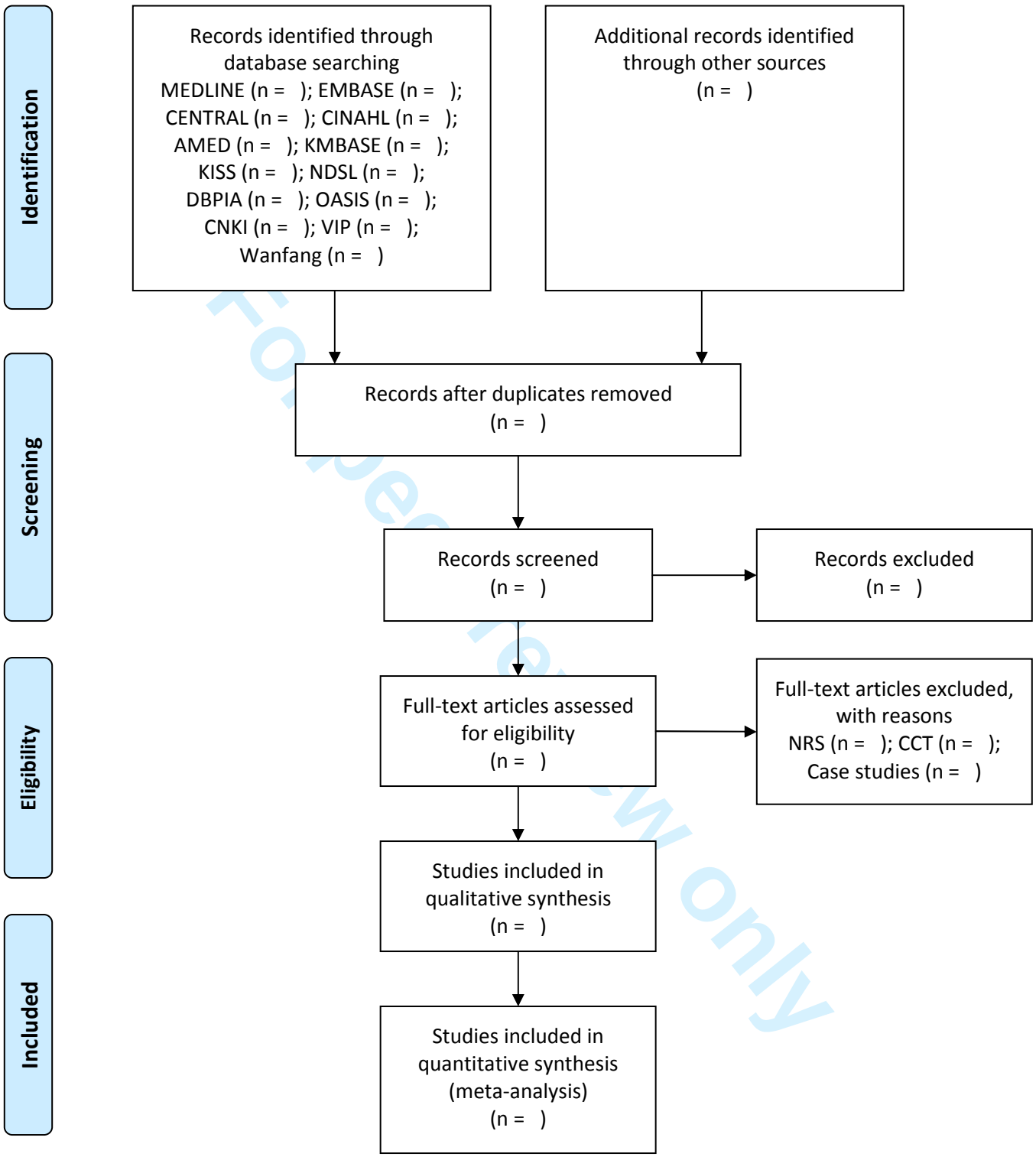
40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. 16 and 28 and 40

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/6fTMgq

Figure legends

Figure 1 PRISMA flow chart of the trial-selection process.



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ABSTRACT

Introduction:

Total knee arthroplasty (TKA) is a common surgical method in orthopedics; however, pain management after TKA remains a significant challenge. This review provides a comprehensive evaluation of the effects of acupuncture for postoperative pain after TKA.

Methods and Analysis:

The following 10 databases will be searched until August 2015: MEDLINE, EMBASE, CENTRAL, AMED, CINAHL, three Chinese databases (the China National Knowledge Infrastructure Database, the Chongqing VIP Chinese Science and Technology Periodical Database, and Wanfang Database) and five Korean databases (the Korean Medical Database, the Korean Studies Information Service System, the National Discovery for Science Leaders, the Database Periodical Information Academic, and the Oriental Medicine Advanced Searching Integrated System). All eligible randomised controlled trials related to the use of acupuncture for postoperative pain after TKA will be included. Assessment of risk of bias will be performed with the Cochrane risk-of-bias method. Mean differences or standardised mean differences will be calculated with 95% confidence intervals (CIs) for continuous data; the risk ratio will be used with 95% CIs for dichotomous data.

Dissemination:

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Trial registration number: PROSPERO 2015: CRD42015020924

Key words

Acupuncture, pain relief, arthroplasty, postoperative, knee surgery

Strengths and limitations of this study

- Selection of the studies, assessment of risk of bias, data extraction, and data pooling will be carried out by two researchers independently to perform an objective and systematic evaluation of acupuncture on postoperative pain following total knee arthroplasty.
- The results of the systematic review should be useful to practitioners for making better-informed decisions about pain control and rehabilitation after TKA.
- There may be considerable heterogeneity as a result of the various forms of acupuncture therapies.

INTRODUCTION

Description of the condition

Total knee arthroplasty (TKA), the most common surgical technique to treat severe knee osteoarthritis and rheumatoid arthritis, is a highly successful procedure to improve knee function and pain.[1 2] However, pain after TKA remains a major complaint, and rehabilitation, which is commonly performed following the procedure, is closely associated with pain management.[3 4] Moreover, because opioid analgesics are in wide use for acute postoperative pain regulation, severe adverse effects relating to their use are frequently reported.[5 6] Therefore, the gold standard for postoperative pain management remains unclear.[7]

Description of the intervention

Acupuncture is a complex and interactive intervention that can be used in the treatment, rehabilitation, and/or management of various diseases and conditions (*e.g.,* acute and chronic pain disorders, cerebrovascular disease, chemotherapy for cancer, and post-traumatic stress disorder). Acupuncture is the most common treatment for various musculoskeletal pains.[8] According to several recent systematic reviews (SRs), acupuncture exerts pain relieving effects after various types of surgeries.[9 10]

Various studies have reported that the use of acupuncture can relieve postoperative pain and reduce the dosage of opioid analgesics and their related adverse effects in the postsurgical period.[11 12]

How the intervention may work

Many studies have reported that acupuncture can be helpful for relieving pain.[8] However, the precise mechanism by which acupuncture provides postoperative analgesia remains unclear. Some studies explain the pain relieving effects of acupuncture in terms of a spinal mechanism (*e.g.,* gate-control theory), hormonal effects, and peripheral events (*e.g.,* local circulation, vasodilation, and tissue healing).[13 14] The pain-relieving effects after TKA are thought to occur via the same mechanisms. Recent studies have supported the belief that acupuncture can be a useful option for pain-regulation for patients undergoing TKA;[15 16] however, there have been few studies that demonstrate the mechanism(s).

Why it is important to perform this review

TKA is commonly used for the treatment of severe advanced osteoarthritis in aged patients, and its use is continuously increasing.[1 2] When pain management and rehabilitation are performed in an appropriate manner after the operation, TKA can be considered a highly effective procedure. However, inadequate use of analgesics for postoperative pain impairs recovery from the operation and rehabilitation.[7] Moreover, because most patients undergoing TKA are elderly, the use of analgesics, including opioids, requires careful consideration.[17] As a result, multimodal approaches for postoperative pain control have been proposed, and the postoperative pain relieving effects of acupuncture have been reported in a number of studies. In addition, acupuncture, which can be considered a type of therapeutic formula, has been systematized in comparison to other kinds of alternative therapies, such as herbal therapies, which are too heterogeneous to evaluate systematically.[18] Furthermore, the safety of acupuncture has been reported by numerous studies, whereas the risks of other alternative therapies remain unclear.[19] Thus, postoperative pain control using acupuncture therapies has more potential as a practical approach than other alternative therapies. However, the

effects of acupuncture after TKA remain controversial.[15 16 20] Moreover, few systematic reviews on the use of acupuncture for postoperative pain relief after TKA exist in the literature. Hence, a comprehensive review of the effects of acupuncture on postoperative pain following TKA may contribute to the rehabilitation of patients undergoing TKA surgery.

OBJECTIVES

This review protocol provides a comprehensive evaluation of the effects of acupuncture on postoperative pain following TKA. The primary objective is to determine the efficacy of acupuncture in the treatment of postoperative pain after TKA. The secondary objectives are to assess the effects of acupuncture on knee movement and quality of life, and to investigate the safety of acupuncture therapies.

METHODS

Criteria for including studies in this review

Types of studies

Prospective randomised controlled trials (RCTs) of acupuncture therapy for postoperative pain after TKA will be included. Non-randomised studies (NRSs), including case–control trials and case studies, will be excluded. No language restriction will be applied.

Types of participants

Patients undergoing TKA will be included. We will not exclude eligible patients based on the reason for TKA.

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Acupuncture therapy will be defined as various needling procedures that stimulate acupoints, such as manual acupuncture, auricular acupuncture, or electroacupuncture. Non-penetrating stimulation on acupoints, such as acupressure or laser acupuncture, will be excluded. We will include traditional

acupuncture, auricular acupuncture and electroacupuncture; therefore, we will be able to comprehensively evaluate the effects of acupuncture on postoperative pain after TKA. We will also include trials that compared acupuncture plus another typical treatment with other typical treatments alone. Control interventions will include sham/placebo acupuncture, no treatment, waiting-list membership, and conventional therapies (*e.g.,* usual care, analgesics, manual therapy).

Types of outcome measures

Primary outcomes

1. Pain: a pain-associated scale will be included (*e.g.,* visual analogue scale or numerical rating scale).

2. Functional evaluation of knee joint: the Western Ontario and McMaster University Arthritis Index (WOMAC).

Secondary outcomes

1. The range of motion (ROM) of the knee joint

2. Quality of life (QOL): a QOL-associated scale will be included (*e.g.,* Euro-QoL (EQ5D) and the 36-Item Short-Form Health Survey (SF-36)).

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Data will be extracted from all eligible studies by two independent reviewers. When a consensus on the data extraction cannot be obtained through consultations, the third author will decide. When the collected data are incomplete or unclear, the arbiter will contact the corresponding authors of the original articles to request additional data or an explanation of the relevant issue. We will extract the characteristics of the participants (*e.g.*, average age, gender, hospitalization day, analgesics consumption, and inclusion and exclusion criteria), type of intervention, type of control intervention, sample size of each intervention group, randomization, allocation concealment and blinding method,

outcome measures, duration of follow-up, type and source of financial support, and publication status from trial reports.

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Two independent review authors will evaluate the risk of bias of included studies using the Cochrane Collaboration's risk-of-bias (ROB) assessment method.[23] Assessment of the ROB will be performed according to the following seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data' (6) selective reporting, and (7) other sources of bias. The ROB of trials will be categorised as low, unclear, or high risk of bias. When a consensus on assessment of the ROB cannot be achieved through consultations, the third author will decide.

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Mean differences (MDs) with 95% confidence intervals (CIs) will be used for the analysis of continuous data; standardised mean differences (SMDs) with 95% CIs will be used if different scales were used to measure a certain outcome variable. Dichotomous data will be analysed using the relative risk (RR) with 95% CIs.

Unit-of-analysis issues

We will only focus on patient randomized studies. If cross-over designed trials are included, we will only use data from the first session. Unit of analysis issues may arise from different follow-up times; we will group the data into three follow-up periods: (1) short-term (less than 24 h), (2) medium-term (1 - 7d), and (3) long-term (more than 1 week).

Dealing with missing data

If possible, we will contact the corresponding authors of the original trials to request missing data. If it is not possible to contact the original authors or obtain missing data, the analysis will rely on the available data.

Assessment of heterogeneity

According to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity will be assessed in the following three ways: (1) a visual check of the forest plot, (2) a heterogeneity χ^2 test, and (3) Higgins I^2 statistic. In terms of the interpretation of the heterogeneity χ^2 test, a significance level of $p<0.10$ will be considered meaningful heterogeneity. In terms of the interpretation of the Higgins I^2 statistic, more than 50% will be considered meaningful heterogeneity.[24] If meaningful heterogeneity among the included studies is identified, we will perform a subgroup analysis or a meta-regression analysis to determine the reason; if the heterogeneity cannot be resolved through additional analysis, we will not pool the data.

Assessment of reporting biases

If more than 10 studies are included, we will assess the reporting biases though funnel plots. When funnel plot asymmetry is detected, we will attempt to identify possible reasons (*e.g.,* publication bias, small study effect, and true heterogeneity) through visual evaluation of the funnel plot and statistical analysis, such as Egger's test.[25]

Data synthesis

We will conduct a meta-analysis to estimate differences in primary and secondary outcomes. A meta-analysis will be performed using Review Manager Software (RevMan, version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark).[26] Depending on the level of heterogeneity among included studies, we will apply a fixed-effects model or a random-effects model. When considerable heterogeneity is observed, a random-effects model with 95% CIs will be used in the analysis of pooled effect estimates. If meaningful heterogeneity, which cannot be explained by any additional assessment such as subgroup analysis, is identified among the included studies, we will not attempt to perform a meta-analysis. If necessary, subgroup analysis will be performed with careful consideration of each subgroup.

Subgroup analysis and investigation of heterogeneity

When it is necessary to interpret the heterogeneity of included studies and the data are sufficient, we will use subgroup analysis, according to the following:

1. Type of control intervention (*e.g.,* no treatment, usual care, or sham acupuncture);

2. Type of acupuncture (*e.g.,* manual acupuncture, electroacupuncture, auricular acupuncture or acupressure);

3. Period of follow-up (less than 24 hours, 1 – 7 days and more than 1 week).

Sensitivity analysis

We will implement a sensitivity analysis according to the following:

1. Sample size: studies will be categorised into those with small or large samples according to whether they included fewer or more than 40 participants in each group.

2. Analysis issues (*e.g.,* procedure for management of missing data).

3. Methodological qualities.

Summary of evidence

The results of the primary outcomes will be presented in summary of findings tables (SOF Tables). The evidence level of the primary outcomes will be analysed through the Grading of Recommendations Assessment Development and Evaluation (GRADE) method.

DISCUSSION

Numerous recent SRs and clinical trials have supported the effects of acupuncture for various type of postoperative pain;[9 10] however, no reviews have assessed the evidence for the effects of acupuncture for postoperative pain following TKA. Furthermore, the types of acupuncture examined by most of the RCTs that evaluated the effects of this treatment for pain after knee surgery have been too diverse to assess the overall effects.[15 16 20] Thus, we will comprehensively analyse the effects of acupuncture for postoperative pain after TKA; for this purpose, subgroup analysis will be conducted according to the type of acupuncture treatment, the type of control intervention, and follow-up period. With respect

to duration of follow-up, the condition of patients can be significantly influenced by various factors, such as psychological characteristics and pre-surgical conditions in the sub-acute or chronic postoperative period,[27] therefore we will divide our assessment into three different sessions (*e.g.*, short-, medium-, and long-term), and evaluate the results of each session separately. This review will provide current evidence for the effectiveness of acupuncture therapy for postoperative pain after TKA and will clarify the benefits experienced by patients undergoing TKA to increase the knowledge base of practitioners of both traditional and complementary medicine.

Contributors

SC contributed to the conception of this review. The review protocol was drafted by JJ, and was revised by SC. The search strategy was established by all authors. JJ and JC will independently screen the searched studies, extract the data from the eligible studies, assess the risk of bias and conduct the meta-analysis. When a consensus between two authors cannot be achieved through consultations, SC will ultimately decide. All authors approved the publication of this review protocol.

Amendments

If the review protocol is amended, we will present the date of each amendment and describe the change and rationale in this section.

Competing interests

No, there are no competing interests.

REFERENCES

1. Dye SF. Knee arthroplasty to maximize the envelope of function. Total Knee Arthroplasty: Springer, 2005:14-17.
2. Kurtz S. Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030. The Journal of Bone and Joint Surgery (American) 2007;**89**(4):780.

3. Capdevila X, Barthelet Y, Biboulet P, et al. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999;**91**(1):8-15.

4. Aveline C, Roux AL, Hetet HL, et al. Pain and recovery after total knee arthroplasty: a 12-month follow-up after a prospective randomized study evaluating Nefopam and Ketamine for early rehabilitation. Clin J Pain 2014;**30**(9):749-54.

5. Oderda G. Challenges in the management of acute postsurgical pain. Pharmacotherapy 2012;**32**(9 Suppl):6s-11s

6. Katz J, Buis T, Cohen L. Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2008;**55**(2):88-99.

7. Elmallah RK, Cherian JJ, Pierce TP, et al. New and Common Perioperative Pain Management Techniques in Total Knee Arthroplasty. The journal of knee surgery 2015. https://www.thieme-connect.de/DOI/DOI?10.1055/s-0035-1549027 (accessed Apr 18).

8. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;**172**(19):1444-53.

9. Sun Y, Gan TJ, Dubose JW, et al. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British Journal of Anaesthesia 2008;**101**(2):151-60.

10. Cho Y-H, Kim C-K, Heo K-H, et al. Acupuncture for Acute Postoperative Pain after Back Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Pain Practice 2015;**15**(3):279-91.

11. Lu Z, Dong H, Wang Q, et al. Perioperative acupuncture modulation: more than anaesthesia. Br J Anaesth 2015;**115**(2):183-93.

12. Wang H, Xie Y, Zhang Q, et al. Transcutaneous electric acupoint stimulation reduces intra-operative remifentanil consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: a prospective, randomized, placebo-controlled trial. Br J Anaesth 2014;**112**(6):1075-82.

13. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects--reconsideration and a hypothesis. Acupunct Med 2002;**20**(2-3):82-99.

14. Napadow V, Ahn A, Longhurst J, et al. The status and future of acupuncture mechanism research. J Altern Complement Med 2008;**14**(7):861-69.

15. Chen C-C, Yang C-C, Hu C-C, et al. Acupuncture for pain relief after total knee arthroplasty: a randomized controlled trial. Reg Anesth Pain Med 2015;**40**(1):31-36.

16. Mikashima Y, Takagi T, Tomatsu T, et al. Efficacy of acupuncture during post-acute phase of rehabilitation after total knee arthroplasty. Journal of Traditional Chinese Medicine 2012;**32**(4):545-48.

17. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;**11**(2 Suppl):S105-20.

18. MacPherson H, Altman DG, Hammerschlag R, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT statement. Journal of evidence-based medicine 2010;**3**(3):140-55.

19. Lao L, Hamilton GR, Fu J, et al. Is acupuncture safe? A systematic review of case reports. Alternative therapies in health and medicine 2003;**9**(1):72-83.

20. Gejervall AL, Stener-Victorin E, Moller A, et al. Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. Human reproduction (Oxford, England) 2005;**20**(3):728-35

21 Bidwell S, Jensen MF. Etext on Health Technology Assessment (HTA) Information Resources: Chapter 3: Using a Search Protocol to Identify Sources of Information: The COSI Model, 2005.

22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41.

23 Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:187-241.

24. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;**21**(11):1539–58.

25. Sterne JAC, Egger M, Moher D. Addressing Reporting Biases. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:297-333.

26. Deeks JJ, Higgins JPT, Altman DG. Analysing Data and Undertaking Meta-Analyses. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:243-96.

27. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. Rheumatology (Oxford, England) 2013;**52**(5):916-23.

Figure legends

Figure 1 PRISMA flow chart of the trial-selection process.

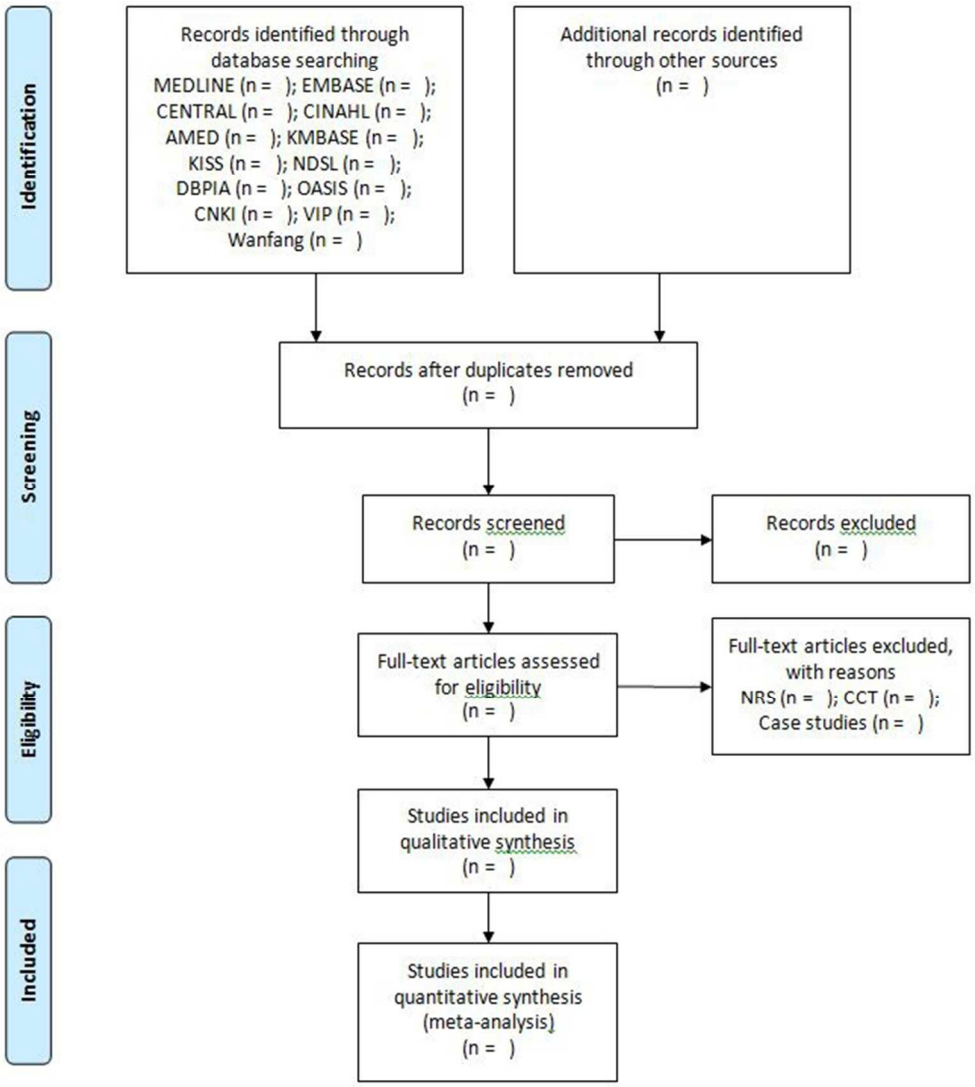

Figure 1. PRISMA flow chart of the trial-selection process. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; AMED, Allied and Complementary Medicine Database; KMBASE, Korean Medical Database; KISS, Korean Studies Information Service System; NDSL, National Discovery for Science Leaders; DBPIA, Database Periodical Information Academic; OASIS, Oriental Medicine Advanced Searching Integrated System; CNKI, China National Knowledge Infrastructure Database; VIP, Chongqing VIP Chinese Science and Technology Periodical Database; NRS, nonrandomised study; CCT, case–control trial.
175x201mm (96 x 96 DPI)

Appendix 1 The search strategies for MEDLINE/Pubmed

1. “arthroplasty, Replacement, Knee”[MeSH]

2. “knee replacement arthroplasty”[tw]

3. “total knee arthroplasty”[tw]

4. “total knee”[tw]

5. tka[tw]

6. “knee replacement”[tw]

7. “knee replacements”[tw]

8. “knee implantation”[tw]

9. “knee implant”[tw]

10. “knee implants”[tw]

11. “knee joint replacement”[tw]

12. “knee joint replacements”[tw]

13. “knee joint arthroplasty”[tw]

14. “knee joint arthroplasties’[tw]

15. “knee Replacement Arthroplasties”[tw]

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. acupuncture[MeSH]

18. “acupuncture therapy”[MeSH]

19. acupuncture[tw]

20. electroacupuncture[tw]

21. electro-acupuncture[tw]

22. acupressure[tw]

23. auriculoacupuncture[tw]

24. auriculo-acupuncture[tw]

25. acupoint*[tw]

26. meridian*[tw]

27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. “randomised controlled trial”[Publication Type]

29. “randomised controlled trials as topic”[MeSH]

30. “random allocation”[MeSH]

31. “double-blind method”[MeSH]

32. “single-blind method”[MeSH]

33. placebos[MeSH]

34. random*[tw]

35. rct[tw]

36. rct’s[tw]

37. rcts[tw]

38. placebo*[tw]

39. 28 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. “pain, postoperative”[MeSH]

41. analgesia[MeSH]

42. “pain management”[MeSH]

43. “acupuncture analgesia”[MeSH]

44. postoperative[tw]

45. pain*[tw]

46. analgesi*[tw]

47. “pain relief”[tw]

48. "pain relieving"[tw]

49. 40 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. 16 and 27 and 39 and 49

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
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	#11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#3, 4
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
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, 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	#15, 16

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#7
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
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#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)	#9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#9, 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#10

BMJ Open

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Keywords:	PAIN MANAGEMENT, COMPLEMENTARY MEDICINE, Knee < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, Orthopaedic & trauma surgery < SURGERY

Acupuncture for Postoperative Pain following Total Knee Arthroplasty: A Systematic Review Protocol

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ABSTRACT

Background:

Total knee arthroplasty (TKA) is a common surgical method in orthopedics; however, pain management after TKA remains a significant challenge. This review provides a comprehensive evaluation of the effects of acupuncture for postoperative pain after TKA.

Methods and Analysis:

The following 10 databases will be searched until August 2015: MEDLINE, EMBASE, CENTRAL, AMED, CINAHL, three Chinese databases (the China National Knowledge Infrastructure Database, the Chongqing VIP Chinese Science and Technology Periodical Database, and Wanfang Database) and five Korean databases (the Korean Medical Database, the Korean Studies Information Service System, the National Discovery for Science Leaders, the Database Periodical Information Academic, and the Oriental Medicine Advanced Searching Integrated System). All eligible randomised controlled trials related to the use of acupuncture for postoperative pain after TKA will be included. Assessment of risk of bias will be performed with the Cochrane risk-of-bias method. Mean differences or standardised mean differences will be calculated with 95% confidence intervals (CIs) for continuous data; the risk ratio will be used with 95% CIs for dichotomous data.

Dissemination:

This systematic review will be presented in a peer-reviewed journal. The result of this review will also be disseminated at a relevant conference presentation.

Trial registration number: PROSPERO 2015: CRD42015020924

Key words

Acupuncture, pain relief, arthroplasty, postoperative, knee surgery

Strengths and limitations of this study

- Selection of the studies, assessment of risk of bias, data extraction, and data pooling will be carried out by two researchers independently to perform an objective and systematic evaluation of acupuncture on postoperative pain following total knee arthroplasty.
- The results of the systematic review should be useful to practitioners for making better-informed decisions about pain control and rehabilitation after TKA.
- There may be considerable heterogeneity as a result of the various forms of acupuncture therapies.

INTRODUCTION

Description of the condition

Total knee arthroplasty (TKA), the most common surgical technique to treat severe knee osteoarthritis and rheumatoid arthritis, is a highly successful procedure to improve knee function and pain.[1 2] However, pain after TKA remains a major complaint, and rehabilitation, which is commonly performed following the procedure, is closely associated with pain management.[3 4] Moreover, because opioid analgesics are in wide use for acute postoperative pain regulation, severe adverse effects relating to their use are frequently reported.[5 6] Therefore, the gold standard for postoperative pain management remains unclear.[7]

Description of the intervention

Acupuncture is a complex and interactive intervention that can be used in the treatment, rehabilitation, and/or management of various diseases and conditions (*e.g.,* acute and chronic pain disorders, cerebrovascular disease, chemotherapy for cancer, and post-traumatic stress disorder). Acupuncture is the most common treatment for various musculoskeletal pains.[8] According to several recent systematic reviews (SRs), acupuncture exerts pain relieving effects after various types of surgeries.[9 10]

Various studies have reported that the use of acupuncture can relieve postoperative pain and reduce the dosage of opioid analgesics and their related adverse effects in the postsurgical period.[11 12]

How the intervention may work

Many studies have reported that acupuncture can be helpful for relieving pain.[8] However, the precise mechanism by which acupuncture provides postoperative analgesia remains unclear. Some studies explain the pain relieving effects of acupuncture in terms of a spinal mechanism (*e.g.,* gate-control theory), hormonal effects, and peripheral events (*e.g.,* local circulation, vasodilation, and tissue healing).[13 14] The pain-relieving effects after TKA are thought to occur via the same mechanisms. Recent studies have supported the belief that acupuncture can be a useful option for pain-regulation for patients undergoing TKA;[15 16] however, there have been few studies that demonstrate the mechanism(s).

Why it is important to perform this review

TKA is commonly used for the treatment of severe advanced osteoarthritis in aged patients, and its use is continuously increasing.[1 2] When pain management and rehabilitation are performed in an appropriate manner after the operation, TKA can be considered a highly effective procedure. However, inadequate use of analgesics for postoperative pain impairs recovery from the operation and rehabilitation.[7] Moreover, because most patients undergoing TKA are elderly, the use of analgesics, including opioids, requires careful consideration.[17] As a result, multimodal approaches for postoperative pain control have been proposed, and the postoperative pain relieving effects of acupuncture have been reported in a number of studies. In addition, acupuncture, which can be considered a type of therapeutic formula, has been systematized in comparison to other kinds of alternative therapies, such as herbal therapies, which are too heterogeneous to evaluate systematically.[18] Furthermore, the safety of acupuncture has been reported by numerous studies, whereas the risks of other alternative therapies remain unclear.[19] Thus, postoperative pain control using acupuncture therapies has more potential as a practical approach than other alternative therapies. However, the

effects of acupuncture after TKA remain controversial.[15 16 20] Moreover, no systematic review on the use of acupuncture for postoperative pain relief after TKA exists in the literature. Hence, a comprehensive review of the effects of acupuncture on postoperative pain following TKA may contribute to the rehabilitation of patients undergoing TKA surgery.

OBJECTIVES

This review protocol provides a comprehensive evaluation of the effects of acupuncture on postoperative pain following TKA. The primary objective is to determine the efficacy of acupuncture in the treatment of postoperative pain after TKA. The secondary objectives are to assess the effects of acupuncture on knee movement and quality of life, and to investigate the safety of acupuncture therapies.

METHODS

Criteria for including studies in this review

Types of studies

Prospective randomised controlled trials (RCTs) of acupuncture therapy for postoperative pain after TKA will be included. Non-randomised studies (NRSs), including case–control trials and case studies, will be excluded. No language restriction will be applied.

Types of participants

Patients undergoing TKA will be included. We will not exclude eligible patients based on the reason for TKA.

Types of interventions

Acupuncture therapy will be defined as various needling procedures that stimulate acupoints, such as manual acupuncture, auricular acupuncture, or electroacupuncture. Non-penetrating stimulation on acupoints, such as acupressure or laser acupuncture, will be excluded. We will include traditional

acupuncture, auricular acupuncture and electroacupuncture; therefore, we will be able to comprehensively evaluate the effects of acupuncture on postoperative pain after TKA. We will also include trials that compared acupuncture plus another typical treatment with other typical treatments alone. Control interventions will include sham/placebo acupuncture, no treatment, waiting-list membership, and conventional therapies (*e.g.,* usual care, analgesics, manual therapy).

Types of outcome measures

Primary outcomes

1. Pain: a pain-associated scale will be included (*e.g.,* visual analogue scale or numerical rating scale).

2. Functional evaluation of knee joint: the Western Ontario and McMaster University Arthritis Index (WOMAC).

Secondary outcomes

1. The range of motion (ROM) of the knee joint

2. Quality of life (QOL): a QOL-associated scale will be included (*e.g.,* Euro-QoL (EQ5D) and the 36-Item Short-Form Health Survey (SF-36)).

3. Adverse events related to acupuncture treatment.

Search methods for identification of studies

Electronic searches

According to the core, standard, ideal (COSI) model,[21] the following databases will be searched for the period from the time of their inception to August 2015 to identify relevant articles: MEDLINE/Pubmed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We will also search the following three Chinese medical databases: the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and Wanfang Database. In addition, we will search the following five Korean medical databases: the Korean Medical Database (KMBASE),

the Korean Studies Information Service System (KISS), the National Discovery for Science Leaders (NDSL), the Database Periodical Information Academic (DBPIA), and the Oriental Medicine Advanced Searching Integrated System (OASIS).

Searching other resources

We will manually investigate ambiguous literature to avoid missing eligible trials. We will search reference lists of all eligible studies. In addition, the clinical trial registers (e.g., Clinical trials.gov, Current Controlled Trials, Chinese Clinical Trial Register and Australian and New Zealand Clinical Registry) also will be searched for ongoing or unpublished trials.

Search strategy

The search strategies for MEDLINE/Pubmed are described in Appendix 1, and we will modify these search strategies for other databases.

Data collection and analysis

Selection of studies

Two independent review authors will screen the titles and abstracts of all searched studies, and studies will be selected through a full-text review if they meet the pre-defined eligibility criteria. When a consensus on the selection process cannot be obtained through consultations, the third author will ultimately decide. The selection process of this review will be presented in the PRISMA flow chart (Figure 1).[22]

Data extraction and management

Data will be extracted from all eligible studies by two independent reviewers. When a consensus on the data extraction cannot be obtained through consultations, the third author will decide. When the collected data are incomplete or unclear, the arbiter will contact the corresponding authors of the original articles to request additional data or an explanation of the relevant issue. We will extract the characteristics of the participants (*e.g.*, average age, gender, hospitalization day, analgesics

consumption, and inclusion and exclusion criteria), type of intervention, type of control intervention, sample size of each intervention group, randomization, allocation concealment and blinding method, outcome measures, duration of follow-up, type and source of financial support, and publication status from trial reports.

Assessment of risk of bias and reporting quality in included studies

Two independent review authors will evaluate the risk of bias of included studies using the Cochrane Collaboration's risk-of-bias (ROB) assessment method.[23] Assessment of the ROB will be performed according to the following seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data' (6) selective reporting, and (7) other sources of bias. The ROB of trials will be categorised as low, unclear, or high risk of bias. When a consensus on assessment of the ROB cannot be achieved through consultations, the third author will decide.

Measures of treatment effect

Mean differences (MDs) with 95% confidence intervals (CIs) will be used for the analysis of continuous data; standardised mean differences (SMDs) with 95% CIs will be used if different scales were used to measure a certain outcome variable. Dichotomous data will be analysed using the relative risk (RR) with 95% CIs.

Unit-of-analysis issues

We will only focus on patient randomized studies. If cross-over designed trials are included, we will only use data from the first session. Unit of analysis issues may arise from different follow-up times; we will group the data into three follow-up periods: (1) short-term (less than 24 h), (2) medium-term (1 - 7d), and (3) long-term (more than 1 week).

Dealing with missing data

If possible, we will contact the corresponding authors of the original trials to request missing data. If it is not possible to contact the original authors or obtain missing data, the analysis will rely on the available data.

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According to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity will be assessed in the following three ways: (1) a visual check of the forest plot, (2) a heterogeneity χ^2 test, and (3) Higgins I^2 statistic. In terms of the interpretation of the heterogeneity χ^2 test, a significance level of $p<0.10$ will be considered meaningful heterogeneity. In terms of the interpretation of the Higgins I^2 statistic, more than 50% will be considered meaningful heterogeneity.[24] If meaningful heterogeneity among the included studies is identified, we will perform a subgroup analysis or a meta-regression analysis to determine the reason; if the heterogeneity cannot be resolved through additional analysis, we will not pool the data.

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We will conduct a meta-analysis to estimate differences in primary and secondary outcomes. A meta-analysis will be performed using Review Manager Software (RevMan, version 5.3.5 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark).[26] Depending on the level of heterogeneity among included studies, we will apply a fixed-effects model or a random-effects model. When considerable heterogeneity is observed, a random-effects model with 95% CIs will be used in the analysis of pooled effect estimates. If meaningful heterogeneity, which cannot be explained by any additional assessment such as subgroup analysis, is identified among the included studies, we will not attempt to

perform a meta-analysis. If necessary, subgroup analysis will be performed with careful consideration of each subgroup.

Subgroup analysis and investigation of heterogeneity

When it is necessary to interpret the heterogeneity of included studies and the data are sufficient, we will use subgroup analysis, according to the following:

1. Type of control intervention (*e.g.,* no treatment, usual care, or sham acupuncture);

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The results of the primary outcomes will be presented in summary of findings tables (SOF Tables). The evidence level of the primary outcomes will be analysed through the Grading of Recommendations Assessment Development and Evaluation (GRADE) method.

DISCUSSION

Numerous recent SRs and clinical trials have supported the effects of acupuncture for various type of postoperative pain;[9 10] however, no reviews have assessed the evidence for the effects of acupuncture for postoperative pain following TKA. Furthermore, the types of acupuncture examined by most of the RCTs that evaluated the effects of this treatment for pain after knee surgery have been too diverse to assess the overall effects.[15 16 20] Thus, we will comprehensively analyse the effects of acupuncture

for postoperative pain after TKA; for this purpose, subgroup analysis will be conducted according to the type of acupuncture treatment, the type of control intervention, and follow-up period. With respect to duration of follow-up, the condition of patients can be significantly influenced by various factors, such as psychological characteristics and pre-surgical conditions in the sub-acute or chronic postoperative period,[27] therefore we will divide our assessment into three different sessions (*e.g.*, short-, medium-, and long-term), and evaluate the results of each session separately. This review will provide current evidence for the effectiveness of acupuncture therapy for postoperative pain after TKA and will clarify the benefits experienced by patients undergoing TKA to increase the knowledge base of practitioners of both traditional and complementary medicine.

Contributors

SC contributed to the conception of this review. The review protocol was drafted by JJ, and was revised by SC. The search strategy was established by all authors. JJ and JC will independently screen the searched studies, extract the data from the eligible studies, assess the risk of bias and conduct the meta-analysis. When a consensus between two authors cannot be achieved through consultations, SC will ultimately decide. All authors approved the publication of this review protocol.

Amendments

If the review protocol is amended, we will present the date of each amendment and describe the change and rationale in this section.

Competing interests

No, there are no competing interests.

REFERENCES

1. Dye SF. Knee arthroplasty to maximize the envelope of function. Total Knee Arthroplasty: Springer, 2005:14-17.

2. Kurtz S. Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030. The Journal of Bone and Joint Surgery (American) 2007;**89**(4):780.

3. Capdevila X, Barthelet Y, Biboulet P, et al. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999;**91**(1):8-15.

4. Aveline C, Roux AL, Hetet HL, et al. Pain and recovery after total knee arthroplasty: a 12-month follow-up after a prospective randomized study evaluating Nefopam and Ketamine for early rehabilitation. Clin J Pain 2014;**30**(9):749-54.

5. Oderda G. Challenges in the management of acute postsurgical pain. Pharmacotherapy 2012;**32**(9 Suppl):6s-11s

6. Katz J, Buis T, Cohen L. Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2008;**55**(2):88-99.

7. Elmallah RK, Cherian JJ, Pierce TP, et al. New and Common Perioperative Pain Management Techniques in Total Knee Arthroplasty. The journal of knee surgery 2015. https://www.thieme-connect.de/DOI/DOI?10.1055/s-0035-1549027 (accessed Apr 18).

8. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;**172**(19):1444-53.

9. Sun Y, Gan TJ, Dubose JW, et al. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British Journal of Anaesthesia 2008;**101**(2):151-60.

10. Cho Y-H, Kim C-K, Heo K-H, et al. Acupuncture for Acute Postoperative Pain after Back Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Pain Practice 2015;**15**(3):279-91.

11. Lu Z, Dong H, Wang Q, et al. Perioperative acupuncture modulation: more than anaesthesia. Br J Anaesth 2015;**115**(2):183-93.

12. Wang H, Xie Y, Zhang Q, et al. Transcutaneous electric acupoint stimulation reduces intra-operative remifentanil consumption and alleviates postoperative side-effects in patients undergoing

sinusotomy: a prospective, randomized, placebo-controlled trial. Br J Anaesth 2014;**112**(6):1075-82.

13. Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects--reconsideration and a hypothesis. Acupunct Med 2002;**20**(2-3):82-99.

14. Napadow V, Ahn A, Longhurst J, et al. The status and future of acupuncture mechanism research. J Altern Complement Med 2008;**14**(7):861-69.

15. Chen C-C, Yang C-C, Hu C-C, et al. Acupuncture for pain relief after total knee arthroplasty: a randomized controlled trial. Reg Anesth Pain Med 2015;**40**(1):31-36.

16. Mikashima Y, Takagi T, Tomatsu T, et al. Efficacy of acupuncture during post-acute phase of rehabilitation after total knee arthroplasty. Journal of Traditional Chinese Medicine 2012;**32**(4):545-48.

17. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;**11**(2 Suppl):S105-20.

18. MacPherson H, Altman DG, Hammerschlag R, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT statement. Journal of evidence-based medicine 2010;**3**(3):140-55.

19. Lao L, Hamilton GR, Fu J, et al. Is acupuncture safe? A systematic review of case reports. Alternative therapies in health and medicine 2003;**9**(1):72-83.

20. Gejervall AL, Stener-Victorin E, Moller A, et al. Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. Human reproduction (Oxford, England) 2005;**20**(3):728-35

21 Bidwell S, Jensen MF. Etext on Health Technology Assessment (HTA) Information Resources: Chapter 3: Using a Search Protocol to Identify Sources of Information: The COSI Model, 2005.

22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41.

23 Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:187-241.

24. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;**21**(11):1539–58.

25. Sterne JAC, Egger M, Moher D. Addressing Reporting Biases. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:297-333.

26. Deeks JJ, Higgins JPT, Altman DG. Analysing Data and Undertaking Meta-Analyses. In: Fellow JPTHSSV, Director SGF, eds. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd, 2008:243-96.

27. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. Rheumatology (Oxford, England) 2013;**52**(5):916-23.

Figure legends

Figure 1 PRISMA flow chart of the trial-selection process.

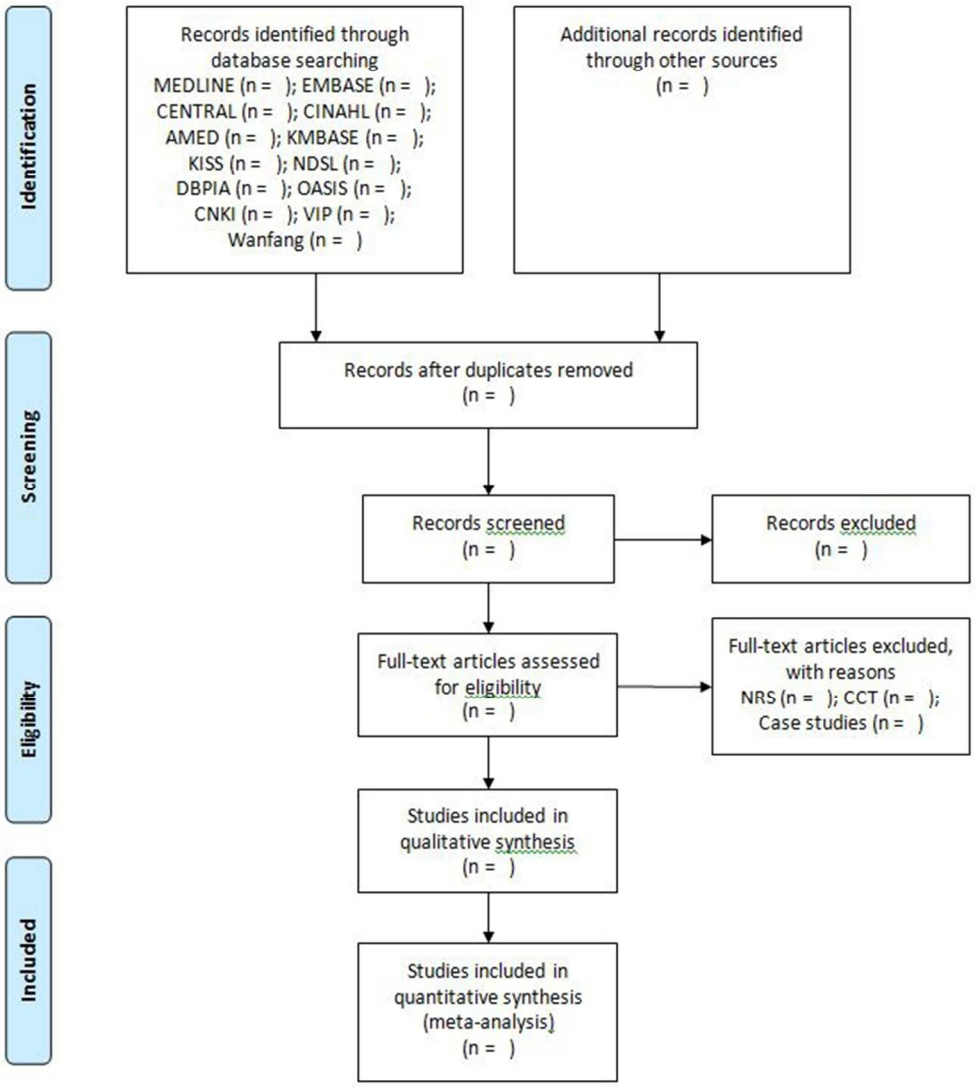

Figure 1. PRISMA flow chart of the trial-selection process. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; AMED, Allied and Complementary Medicine Database; KMBASE, Korean Medical Database; KISS, Korean Studies Information Service System; NDSL, National Discovery for Science Leaders; DBPIA, Database Periodical Information Academic; OASIS, Oriental Medicine Advanced Searching Integrated System; CNKI, China National Knowledge Infrastructure Database; VIP, Chongqing VIP Chinese Science and Technology Periodical Database; NRS, nonrandomised study; CCT, case–control trial.
175x201mm (96 x 96 DPI)

Appendix 1 The search strategies for MEDLINE/Pubmed

1. “arthroplasty, Replacement, Knee”[MeSH]
2. “knee replacement arthroplasty”[tw]
3. “total knee arthroplasty”[tw]
4. “total knee”[tw]
5. tka[tw]
6. “knee replacement”[tw]
7. “knee replacements”[tw]
8. “knee implantation”[tw]
9. “knee implant”[tw]
10. “knee implants”[tw]
11. “knee joint replacement”[tw]
12. “knee joint replacements”[tw]
13. “knee joint arthroplasty”[tw]
14. “knee joint arthroplasties’[tw]
15. “knee Replacement Arthroplasties”[tw]
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. acupuncture[MeSH]
18. “acupuncture therapy”[MeSH]
19. acupuncture[tw]
20. electroacupuncture[tw]
21. electro-acupuncture[tw]
22. auriculoacupuncture[tw]
23. auriculo-acupuncture[tw]
24. acupoint*[tw]

25. meridian*[tw]

26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. “randomised controlled trial”[Publication Type]

28. “randomised controlled trials as topic”[MeSH]

29. “random allocation”[MeSH]

30. “double-blind method”[MeSH]

31. “single-blind method”[MeSH]

32. placebos[MeSH]

33. random*[tw]

34. rct[tw]

35. rct’s[tw]

36. rcts[tw]

37. placebo*[tw]

38. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39. “pain, postoperative”[MeSH]

40. analgesia[MeSH]

41. “pain management”[MeSH]

42. “acupuncture analgesia”[MeSH]

43. postoperative[tw]

44. pain*[tw]

45. analgesi*[tw]

46. “pain relief”[tw]

47. "pain relieving"[tw]

48. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

49. 16 and 26 and 38 and 48

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	#1
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	#11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#3, 4
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
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, 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	#15, 16

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#7
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
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#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)	#9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#9, 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#10