Bee Venom Acupuncture for Rheumatoid Arthritis: A Systematic Review protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004602
Article Type:	Protocol
Date Submitted by the Author:	03-Dec-2013
Complete List of Authors:	Lee, Ju Ah; Korea Institute of Oriental Medicine, Son, Mi-Ju; Korea Institute of Oriental Medicine, Literature & Informatics Research Division Choi, Jiae; Korea Institute of Oriental Medicine, Yun, Kyung-Jin; Korea Institute of Oriental Medicine, Jun, Ji Hee; Korea Institute of Oriental Medicine, Lee, Myeong Soo; Korea Institute of Oriental Medicine,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Rheumatology
Keywords:	COMPLEMENTARY MEDICINE, RHEUMATOLOGY, PAIN MANAGEMENT

Bee Venom Acupuncture for Rheumatoid Arthritis:

A Systematic Review protocol

Ju Ah Lee[1], Mi Ju Son[2], Jiae Choi[1], Kyung-Jin Yun[1], Ji Hee Jun[1], Myeong Soo Lee[1*]

[1]*Medical Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea*

[2]*Medical Culture & Informatics Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea*

Short title: A protocol of systematic review of bee venom acupuncture for RA

***Correspondence to:**
Myeong Soo Lee, PhD
Medical Research Division,
Korea Institute of Oriental Medicine,
Daejeon, 305-811, South Korea
Tel: 82-(0)42-868-9266
Fax: 82-(0)42-868-9622
E-mail: drmslee@gmail.com

Lee JA: motoong@kiom.re.kr
Son MJ: mj714@kiom.re.kr
Choi J: ksjiae@kiom.re.kr
Yun KJ:mysirius@kiom.re.kr
Jun JH: zhixi04@kiom.re.kr

Key words: Bee venom acupuncture, rheumatoid arthritis, safety and efficacy, systematic review

Abstract

Introduction: This systematic review aims to analyse the trial data on the efficacy of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Methods and analysis: The following 15 databases will be searched from their inception: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, and Century Journal Project), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print.

Trial registration number: PROSPERO 2013: CRD42013005853

Article focus

- This systematic review aims to analyse the trial data on the efficacy of bee venom therapy for rheumatoid arthritis.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- A possible weakness may be the quality of the trials that we identify because the CAM research field has not been explored deeply.

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that results in the destruction of the musculoskeletal system. The disease is often progressive and results in pain, stiffness, and joint swelling. In late stages, deformity and ankylosis develop. Because of the complex, systemic nature of the disease, RA treatment is also complex and involves a variety of approaches. The major goals are to relieve pain, reduce inflammation, slow or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function.[1]

Untreated RA leads to joint destruction, functional limitation and severe disability [2 3] and has a significant impact on health-related quality of life (HRQoL). [4 5]

Description of the intervention

Bee venom (BV) therapy has been used since ancient times, including the administration honeybee stings, BV injection, and BV acupuncture (BVA).[6] Bee venom acupuncture (BVA) involves injecting purified, diluted bee venom into acupoints. [7]

How the intervention might work

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritic, and anti-cancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.[8] The analgesic effects of BVA have been reported in animal experiments [9 10] and in the clinic.[7 11] In many countries, including the United States, BV therapy has been used to treat multiple sclerosis and arthritis.[12 13] However, most of these therapeutic uses are not based on evidence.

Why is performing this review important?

Currently, BVA for RA is widely used as an effective method. However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and harm of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will help manage patients using BVA treatment.

Objectives

We will perform a systematic review to assess the safety and efficacy of BVA for treating RA.

Methods

Criteria for including studies in this review

Types of studies

All prospective randomised controlled clinical trials (RCTs) will be included if they were randomised studies of BV injection at acupoints as the sole treatment or as an adjunct to other treatments if the control group received the same treatment as the BVA group. Trials comparing BVA with any type of control intervention will be included. We will exclude trials of BV injection into parts of the body other than acupoints. Trials will also be excluded if only immunological or biological parameters were assessed. We will also exclude trials comparing 2 different types of BVA. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full.

Types of participants

Patients suffering from RA will be included.

Types of interventions

We will include those trials on BVA used alone or as combination therapy with BVA and conventional therapy versus the same conventional therapy. BVA involves injecting purified, diluted BV into acupoints. Conventional therapy would include medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors**.**

Types of outcome measures

Primary outcomes

Symptom (morning stiffness, pain, and joint swelling) evaluation

Secondary outcomes

The number of joints affected by RA

Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Rheumatoid factor (RF)

Search methods for identifying the studies

Electronic searches

We will search for trials in the following electronic databases: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and VIP.

Searching other resources

We will also perform non-electronic searches of conference proceedings, our own files of articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and

Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean Oriental Internal Medicine).

Search strategy

The strategy for searching the MEDLINE database is presented in appendix 1. Similar search strategies will be applied for the other databases.

Data collection and analysis

Study selection

The data screening and selection process will be performed independently by four authors and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements on the selection are not resolved through discussions, the arbiter (MSL) will decide.

Inclusion criteria

1. Randomised controlled trials and quasi-randomised trials.
2. No language limitation
3. No publication status restriction

Exclusion criteria

1. Animal experiments
2. Non-randomised clinical trials
3. Case report/series, news items, and letters
4. Qualitative studies

Data extraction and management

The data extraction and quality assessment will be conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form.

Any disagreement among the authors will be resolved by discussion with all of the authors. When the reported data are insufficient or ambiguous, MSL will contact the corresponding authors by e-mail or telephone to request additional information or clarification.

Assessment of bias in the included studies

We will independently assess bias in the included studies according to the criteria from the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.[14] The quality of each trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact the authors of the assessed trials for clarification. We will resolve any differences in opinion through discussion or consultation with a third author.

Measurement of the treatment effect

For the continuous data, we will use the mean difference (MD) with 95% confidence intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.

Unit of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine the data from

each control group. Subgroup analyses of the control groups will also be performed. Each patient will be counted only once in the analysis

Dealing with the missing data

Intention-to-treat analyses that include all of the randomised patients will be performed. For patients with missing outcome data, a carry-forward of the last observed response will be used. The individual patient data will be sought from the original source or the published trial reports when the individual patient data are unavailable.

Assessment of heterogeneity

We will use the random-effect or fixed-effect model for the meta-analysis according to the data analysis. If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. According to the guidance given in *the Cochrane Handbook* for Systematic Reviews of Interventions, 50% will be the cut-off point for meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore the possible causes.[15]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[16] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies.[16 17]

Data synthesis

The differences between the intervention and control groups will be assessed. The relative risk (RR) and 95% confidence intervals will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient information, we will contact the corresponding authors to acquire and verify the data when possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random-effects or fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If there are an adequate number of studies, we will conduct subgroup analyses to interpret the heterogeneity between the studies, including the following:

1. Bee-venom therapy used alone or as combination therapy with bee-venom and conventional therapy;

2. Type of control.

Sensitivity analysis

Sensitivity analysis will be conducted according to the following criteria:

1. Methodological quality (sequence generation, allocation concealment, or blinding);

2. Sample size (small sample studies, e.g., less than 30 subjects in each group, or large sample studies, e.g., more than 30 subjects in each group);

3. Analysis-related issues (e.g., processes to handle the missing data).

Ethics and dissemination

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

Discussion

This systematic review will provide a detailed summary of the current state of evidence for the effectiveness of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

Contribution of authors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

Funding

No external funding was received. Lee JA, Choi J, Jun JH, Yun KJ and Lee MS were supported by Korea Institute of Oriental Medicine (K13281, K13400), Son MJ was supported by same institute (K13380).

Conflict of interest

None declared

References

1. Han A, Robinson V, Judd M, et al. Tai chi for treating rheumatoid arthritis. Cochrane Database Syst Rev 2004(3):CD004849
2. Odegard S, Finset A, Kvien TK, et al. Work disability in rheumatoid arthritis is predicted by physical and psychological health status: a 7-year study from the Oslo RA register. Scand J Rheumatol 2005;**34**(6):441-7
3. Yelin E. Work disability in rheumatic diseases. Curr Opin Rheumatol 2007;**19**(2):91-6
4. Kvien TK, Uhlig T. Quality of life in rheumatoid arthritis. Scand J Rheumatol 2005;**34**(5):333-41
5. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics 2004;**22**(2 Suppl 1):27-38
6. Munstedt K, Hackethal A, Schmidt K. Bee venom therapy, bee venom acupuncture of apipunture: What is the evidence behind the various health claims? Am Bee J 2005;**145**:665-68
7. Lee MS, Pittler MH, Shin BC, et al. Bee venom acupuncture for musculoskeletal pain: a review. J Pain 2008;**9**(4):289-97
8. Son DJ, Lee JW, Lee YH, et al. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. Pharmacol Ther 2007;**115**:246-70
9. Baek YH, Huh JE, Lee JD, et al. Antinociceptive effect and the mechanism of bee venom acupuncture (Apipuncture) on inflammatory pain in the rat model of collagen-induced arthritis: mediation by alpha2-adrenoceptors. Brain Research 2006;**1073-1074**:305–10
10. Chen HS, Qu F, He X, et al. The anti-nociceptive effect and the possible mechanism of acupoint stimulation caused by chemical irritants in the bee venom pain model Brain Research 2010;**1355**:61-69

11. Lee JD, Park HJ, Chae Y, et al. An overview of bee venom acupuncture in the treatment of arthritis. Evid Based Complement Alternat Med 2005;**2**:79-84

12. Hauser RA, Daguio M, Wester D, et al. Bee-Venom Therapy for Treating Multiple Sclerosis:A clinical trial. Alternative Complement Ther 2001;**7**:37-45

13. Kwon YB, Kim JH, Yoon JH, et al. The analgesic efficacy of bee venom acupuncture for knee osteoarthritis: A comparative study with needle acupuncture. Am J Chin Med 2001;**29**:187-99

14. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

15. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

16. Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**(7109):629-34

Appendix 1. Search Strategy

MEDLINE(Pubmed)

1. arthritis, rheumatoid
2. arthritis, juvenile rheumatoid
3. nodule, rheumatoid
4. felty$ adj2 syndrome
5. caplan$ adj2 syndrome
6. sjogren$ adj2 syndrome
7. sicca adj2 syndrome
8. still$ disease.
9. bechterew$ disease.
10. or/1-9
11. bee venom
12. bee sting
13. wasp venom
14. bee venom acupuncture
15. bee venom therapy
16. apitoxin
17. apitherapy
18. or/11-17
19. 9 and 18

EMBASE

#1 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis'

#2 'rheumatoid arthritis juvenile'/exp OR 'rheumatoid arthritis juvenile'

#3 'rheumatoid nodule'/exp OR 'rheumatoid nodule'

#4 'felty syndrome'/exp OR 'felty syndrome'

#5 'caplan syndrome'/exp OR 'caplan syndrome'

#6 'sjogren s syndrome'/exp OR 'sjogren s syndrome'

#7 'sicca syndrome'/exp OR 'sicca syndrome'

#8 'still disease'/exp OR 'still disease'

#9 'bechterew disease'/exp OR 'bechterew disease'

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 'bee venom'/exp OR 'bee venom'

#12 'bee sting'/exp OR 'bee sting'

#13 'wasp venom'/exp OR 'wasp venom'

#14 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('acupuncture'/exp OR acupuncture)

#15 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('therapy'/exp OR therapy)

#16 'bee'/exp OR bee AND ('sting'/exp OR sting) AND ('therapy'/exp OR therapy)
#17 apitoxin
#18 'apitherapy'/exp OR apitherapy
#19 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #10 AND #19

The Cochrane Library (Wiley InterScience)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw
#3 felty* NEAR/2 syndrome:ti,ab,kw
#4 caplan* NEAR/2 syndrome:ti,ab,kw
#5 sjogren* near/2 syndrome:ti,ab,kw
#6 sicca near/2 syndrome:ti,ab,kw
#7 still* next disease:ti,ab,kw
#8 bechterew$ disease
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor: [Bee venoms] explode all trees
#11 bee venom* :ti,ab,kw
#12 bee sting* :ti,ab,kw
#13 wasp venom* :ti,ab,kw
#14 bee venom* acupuncture :ti,ab,kw
#15 bee venom* therapy:ti,ab,kw
#16 bee sting* therapy:ti,ab,kw
#17 apitoxin:ti,ab,kw
#18 apitherapy:ti,ab,kw
#19 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 #9 AND #19

CINAHL (EBSCOhost)

S1 (MM “Arthritis, Rheumatoid+”) OR (MM “Arthritis, Juvenile Rheumatoid”) OR (MM “Rheumatoid Nodule”)
S2 (MM “Caplan syndrome”) OR (MM “Felty’s Syndrome”) OR (MM “Still’s Disease, Adult-Onset”)
S3 TI arthritis N2 rheumat* OR AB arthritis N2 rheumat* OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI Arthritis, Juvenile Rheumatoid OR AB Arthritis, Juvenile Rheumatoid OR TI felty* N2 syndrome OR AB felty* N2 syndrome OR TI caplan* N2 syndrome OR AB caplan* N2 syndrome
S4 TI sjogren* N2 syndrome OR AB sjogren* N2 syndrome OR TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew* disease OR AB bechterew* disease

S5 S1 OR S2 OR S3 OR S4

S6 (MM"Apitherapy")

S7 TI bee venom* OR AB bee venom* OR TI bee sting* OR AB bee sting* OR TI wasp venom* OR AB wasp venom* OR TI bee venom* acupuncture OR AB bee venom* acupuncture OR TI bee venom* therapy OR AB bee venom* therapy

S8 TI apitherap* OR AB apitherap* OR TI apitoxin* OR AB apitoxin*

S9 S6 OR S7 OR S8

S10 S5 AND S9

AMED (EBSCOhost)

S1 TX Arthritis, Rheumatoid OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI arthritis N2 rheumat* OR AB arthritis N2 rheumat* OR TI felty* N2 syndrome OR AB felty* N2 syndrome OR TI caplan* N2 syndrome OR AB caplan* N2 syndrome OR TI sjogren* N2 syndrome OR AB sjogren* N2 syndrome

S2 TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew* disease OR AB bechterew* disease

S3 S1 OR S2

S4 TI bee venom OR AB bee venom OR TI bee sting OR AB bee sting OR TI wasp venom OR AB wasp venom

S5 TI apitoxin OR AB apitoxin TI apitherapy OR AB apitherapy

S6 bee venom therapy OR bee venom acupuncture

S7 S4 OR S5 OR S6

S8 S3 AND S7

BMJ Open

Bee Venom Acupuncture for Rheumatoid Arthritis: A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004602.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Mar-2014
Complete List of Authors:	Lee, Ju Ah; Korea Institute of Oriental Medicine, Son, Mi-Ju; Korea Institute of Oriental Medicine, Literature & Informatics Research Division Choi, Jiae; Korea Institute of Oriental Medicine, Yun, Kyung-Jin; Korea Institute of Oriental Medicine, Jun, Ji Hee; Korea Institute of Oriental Medicine, Lee, Myeong Soo; Korea Institute of Oriental Medicine,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Rheumatology
Keywords:	COMPLEMENTARY MEDICINE, RHEUMATOLOGY, PAIN MANAGEMENT

Bee Venom Acupuncture for Rheumatoid Arthritis:

A Systematic Review Protocol

Ju Ah Lee, Mi Ju Son, Jiae Choi, Kyung-Jin Yun, Ji Hee Jun, Myeong Soo Lee*

Korea Institute of Oriental Medicine, Daejeon, South Korea

Short title: A protocol of systematic review of bee venom acupuncture for RA

***Correspondence to:**
Myeong Soo Lee, PhD
Medical Research Division,
Korea Institute of Oriental Medicine,
Daejeon, 305-811, South Korea
Tel: 82-(0)42-868-9266
Fax: 82-(0)42-868-9622
E-mail: drmslee@gmail.com

Lee JA: motoong@kiom.re.kr
Son MJ: mj714@kiom.re.kr
Choi J: ksjiae@kiom.re.kr
Yun KJ:mysirius@kiom.re.kr
Jun JH: zhixi04@kiom.re.kr

License statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ Open and any other BMJPGL products to exploit all subsidiary rights, as set out in our license (http://group.bmj.com/products/journals/instructions-for-authors/license-forms).

Abstract

Introduction: This systematic review aims to analyse the trial data on the effects of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Methods and analysis: The following 15 databases will be searched from their inception to March 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, and Century Journal Project), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print.

Trial registration number: PROSPERO 2013: CRD42013005853

Key words: Bee venom acupuncture, rheumatoid arthritis, complementary and alternative medicine, systematic review

Article focus

- This systematic review aims to analyse the trial data on the effects of bee venom acupuncture for rheumatoid arthritis.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- A possible weakness may be the quality of the trials that we identify because the complementary and alternative medicine research field has not been explored deeply.

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that results in the destruction of the musculoskeletal system. The disease is often progressive and results in pain, stiffness, and joint swelling. In late stages, deformity and ankylosis develop. Because of the complex, systemic nature of the disease, RA treatment is also complex and involves a variety of approaches. The major goals are to relieve pain, reduce inflammation, slow or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function.[1]

Untreated RA leads to joint destruction, functional limitation and severe disability [2 3] and has a significant impact on health-related quality of life (HRQoL). [4 5]

Description of the intervention

Bee venom (BV) therapy has been used since ancient times, including the administration honeybee stings, BV injection, and BV acupuncture (BVA).[6] Bee venom acupuncture (BVA) involves injecting purified, diluted bee venom into acupoints or ashi-points on the body. [7]

How the intervention might work

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritic, and anti-cancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.[8] The analgesic effects of BVA have been reported in animal experiments [9 10] and in the clinic.[7 11] In many countries, including the United States, BV therapy has been used to treat multiple sclerosis and arthritis.[12 13] However, most of these therapeutic uses are not based on evidence.

Why is performing this review important?

Currently, BVA for RA is widely used as an effective method. However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and harm of BVA for RA. A comprehensive evaluation of the effects of BVA for RA will help manage patients using BVA treatment.

Objectives

We will perform a systematic review to assess the effects of BVA for treating RA.

Methods

Criteria for including studies in this review

Types of studies

All prospective randomised controlled clinical trials (RCTs) and quasi-RCTs will be included.

Types of participants

Patients suffering from RA will be included.

Types of interventions

We will include RCTs of BV injection at acupoints or ashi-points on the body as the sole treatment or as an adjunct to other treatments if the control group received the same treatment as the BVA group. Trials comparing BVA with any type of control intervention will be included. We will exclude trials of BV injection into parts of the body or ashi-points. Trials will also be excluded if only immunological or biological parameters were assessed. We will also exclude trials comparing 2 different types of BVA.

Types of outcome measures

Primary outcomes

Symptom (morning stiffness, pain, and joint swelling) evaluation

Secondary outcomes

The number of joints affected by RA

Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Rheumatoid factor (RF)

Search methods for identifying the studies

Electronic searches

We will search for trials in the following electronic databases from their inception to March 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and VIP.

Searching other resources

We will also perform non-electronic searches of conference proceedings, our own files of articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean Oriental Internal Medicine).

Search strategy

The strategy for searching the MEDLINE database is presented in appendix 1. Similar search strategies will be applied for the other databases.

Data collection and analysis

Study selection

The data screening and selection process will be performed independently by four authors and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements on the selection are not resolved through discussions, the arbiter (MSL) will decide. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full. The details of selection process will be shown in PRISMA flow diagram (Figure 1).

Data extraction and management

The data extraction and quality assessment will be conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form.

Any disagreement among the authors will be resolved by discussion with all of the authors. When the reported data are insufficient or ambiguous, MSL will contact the corresponding authors by e-mail or telephone to request additional information or clarification.

Assessment of bias in the included studies

We will independently assess bias in the included studies according to the criteria from the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.[14] The quality of each trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact the authors of the assessed trials for clarification. We will resolve any differences in opinion

through discussion or consultation with a third author.

Measurement of the treatment effect

For the continuous data, we will use the mean difference (MD) with 95% confidence intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.

Unit of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine the data from each control group. Subgroup analyses of the control groups will also be performed. Each patient will be counted only once in the analysis

Dealing with the missing data

We will contact the original authors for missing data whenever possible. If it is not possible to get the missing data, we will only analyse the available data.

Assessment of heterogeneity

We will use the random-effect or fixed-effect model for the meta-analysis according to the data analysis. If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. According to the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions, 50% will be the cut-off point for

meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore the possible causes.[15]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[16] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies.[16 17]

Data synthesis

The differences between the intervention and control groups will be assessed. The relative risk (RR) and 95% confidence intervals will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient information, we will contact the corresponding authors to acquire and verify the data when possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random-effects or fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If the data are available, we will conduct subgroup analyses to assess the heterogeneity between the studies, including the following:

1. Type of BVA;

2. Type of control.

3. Duration of RA

4. Laterality of RA; bilateral RA vs. unilateral RA

Sensitivity analysis

Sensitivity analysis will be conducted according to the following criteria:

1. Sample size (small sample studies, e.g., less than 40 subjects in each group, or large sample studies, e.g., more than 40 subjects in each group);

2. Analysis-related issues (e.g., processes to handle the missing data).

Ethics and dissemination

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

Discussion

This systematic review will provide a detailed summary of the current state of evidence for the effects of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

Contribution of authors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

Funding

No external funding was received. Lee JA, Choi J, Jun JH, Yun KJ and Lee MS were supported by Korea Institute of Oriental Medicine (K14400), Son MJ was supported by same institute (K14380).

Conflict of interest

None declared

References

1. Han A, Robinson V, Jud d M, et al. Tai chi for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2004(3):CD004849
2. Odegard S, Finset A, Kvien TK, et al. Work disability in rheumatoid arthritis is predicted by physical and psychological health status: a 7-year study from the Oslo RA register. *Scand J Rheumatol* 2005;34(6):441-7
3. Yelin E. Work disability in rheumatic diseases. *Curr Opin Rheumatol* 2007;19(2):91-6
4. Kvien TK, Uhlig T. Quality of life in rheumatoid arthritis. *Scand J Rheumatol* 2005;34(5):333-41
5. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. *Pharmacoeconomics* 2004;22(2 Suppl 1):27-38
6. Munstedt K, Hackethal A, Schmidt K. Bee venom therapy, bee venom acupuncture of apipunture: What is the evidence behind the various health claims? *Am Bee J* 2005;145:665-68
7. Lee MS, Pittler MH, Shin BC, et al. Bee venom acupuncture for musculoskeletal pain: a review. *J Pain* 2008;9(4):289-97
8. Son DJ, Lee JW, Lee YH, et al. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. *Pharmacol Ther* 2007;115:246-70
9. Baek YH, Huh JE, Lee JD, et al. Antinociceptive effect and the mechanism of bee venom acupuncture (Apipuncture) on inflammatory pain in the rat model of collagen-induced arthritis: mediation by alpha2-adrenoceptors. *Brain Research* 2006;1073-1074:305–10
10. Chen HS, Qu F, He X, et al. The anti-nociceptive effect and the possible mechanism of acupoint stimulation caused by chemical irritants in the bee venom pain model *Brain Research* 2010;1355:61-69

11. Lee JD, Park HJ, Chae Y, et al. An overview of bee venom acupuncture in the treatment of arthritis. *Evid Based Complement Alternat Med* 2005;2:79-84

12. Hauser RA, Daguio M, Wester D, et al. Bee-Venom Therapy for Treating Multiple Sclerosis:A clinical trial. *Alternative Complement Ther* 2001;7:37-45

13. Kwon YB, Kim JH, Yoon JH, et al. The analgesic efficacy of bee venom acupuncture for knee osteoarthritis: A comparative study with needle acupuncture. *Am J Chin Med* 2001;29:187-99

14. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

15. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

16. Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34

Figure legends

Figure 1. Study selection flow diagram

Bee Venom Acupuncture for Rheumatoid Arthritis: A Systematic Review Protocol

Ju Ah Lee, Mi Ju Son, Jiae Choi, Kyung-Jin Yun, Ji Hee Jun, Myeong Soo Lee*

Korea Institute of Oriental Medicine, Daejeon, South Korea

Short title: A protocol of systematic review of bee venom acupuncture for RA

***Correspondence to:**
Myeong Soo Lee, PhD
Medical Research Division,
Korea Institute of Oriental Medicine,
Daejeon, 305-811, South Korea
Tel: 82-(0)42-868-9266
Fax: 82-(0)42-868-9622
E-mail: drmslee@gmail.com

Lee JA: motoong@kiom.re.kr
Son MJ: mj714@kiom.re.kr
Choi J: ksjiae@kiom.re.kr
Yun KJ:mysirius@kiom.re.kr
Jun JH: zhixi04@kiom.re.kr

License statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ Open and any other BMJPGL products to exploit all subsidiary rights, as set out in our license (http://group.bmj.com/products/journals/instructions-for-authors/license-forms).

Article focus

- This systematic review aims to analyse the trial data on the effects of bee venom acupuncture for rheumatoid arthritis.

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- A possible weakness may be the quality of the trials that we identify because the complementary and alternative medicine research field has not been explored deeply.

Abstract

Introduction: This systematic review aims to analyse the trial data on the effects of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Methods and analysis: The following 15 databases will be searched from their inception to March 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, and Century Journal Project), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print.

Trial registration number: PROSPERO 2013: CRD42013005853

Key words: Bee venom acupuncture, rheumatoid arthritis, complementary and alternative medicine, systematic review

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that results in the destruction of the musculoskeletal system. The disease is often progressive and results in pain, stiffness, and joint swelling. In late stages, deformity and ankylosis develop. Because of the complex, systemic nature of the disease, RA treatment is also complex and involves a variety of approaches. The major goals are to relieve pain, reduce inflammation, slow or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function.[1]

Untreated RA leads to joint destruction, functional limitation and severe disability [2 3] and has a significant impact on health-related quality of life (HRQoL). [4 5]

Description of the intervention

Bee venom (BV) therapy has been used since ancient times, including the administration honeybee stings, BV injection, and BV acupuncture (BVA).[6] Bee venom acupuncture (BVA) involves injecting purified, diluted bee venom into acupoints or ashi-points on the body. [7]

How the intervention might work

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritic, and anti-cancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.[8] The analgesic effects of BVA have been reported in animal experiments [9 10] and in the clinic.[7 11] In many countries, including the United States, BV therapy has been used to treat multiple sclerosis and arthritis.[12 13] However, most of these therapeutic uses are not based on evidence.

Why is performing this review important?

Currently, BVA for RA is widely used as an effective method. However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and harm of BVA for RA. A comprehensive evaluation of the effects of BVA for RA will help manage patients using BVA treatment.

Objectives

We will perform a systematic review to assess the effects of BVA for treating RA.

Methods

Criteria for including studies in this review

Types of studies

All prospective randomised controlled clinical trials (RCTs) and quasi-RCTs will be included.

Types of participants

Patients suffering from RA will be included.

Types of interventions

We will include RCTs of BV injection at acupoints or ashi-points on the body as the sole treatment or as an adjunct to other treatments if the control group received the same treatment as the BVA group. Trials comparing BVA with any type of control intervention will be included. We will exclude trials of BV injection into parts of the body or ashi-points. Trials will also be excluded if only immunological or biological parameters were assessed. We will also exclude trials comparing 2 different types of BVA.

Types of outcome measures

Primary outcomes

Symptom (morning stiffness, pain, and joint swelling) evaluation

Secondary outcomes

The number of joints affected by RA

Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Rheumatoid factor (RF)

Search methods for identifying the studies

Electronic searches

We will search for trials in the following electronic databases from their inception to March 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and VIP.

Searching other resources

We will also perform non-electronic searches of conference proceedings, our own files of articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean Oriental Internal Medicine).

Search strategy

The strategy for searching the MEDLINE database is presented in appendix 1. Similar search strategies will be applied for the other databases.

Data collection and analysis

Study selection

The data screening and selection process will be performed independently by four authors and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements on the selection are not resolved through discussions, the arbiter (MSL) will decide. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full. The details of selection process will be shown in PRISMA flow diagram (Figure 1).

Data extraction and management

The data extraction and quality assessment will be conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form.

Any disagreement among the authors will be resolved by discussion with all of the authors. When the reported data are insufficient or ambiguous, MSL will contact the corresponding authors by e-mail or telephone to request additional information or clarification.

Assessment of bias in the included studies

We will independently assess bias in the included studies according to the criteria from the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.[14] The quality of each trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact the authors of the assessed trials for clarification. We will resolve any differences in opinion

through discussion or consultation with a third author.

Measurement of the treatment effect

For the continuous data, we will use the mean difference (MD) with 95% confidence intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.

Unit of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine the data from each control group. Subgroup analyses of the control groups will also be performed. Each patient will be counted only once in the analysis

Dealing with the missing data

We will contact the original authors for missing data whenever possible. If it is not possible to get the missing data, we will only analyse the available data.

Assessment of heterogeneity

We will use the random-effect or fixed-effect model for the meta-analysis according to the data analysis. If a meta-analysis is possible, we will use the I^2 statistic to quantify the inconsistencies among the included studies. According to the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions, 50% will be the cut-off point for

meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore the possible causes.[15]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[16] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies.[16 17]

Data synthesis

The differences between the intervention and control groups will be assessed. The relative risk (RR) and 95% confidence intervals will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient information, we will contact the corresponding authors to acquire and verify the data when possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random-effects or fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If the data are available, we will conduct subgroup analyses to assess the heterogeneity between the studies, including the following:

1. Type of BVA;

2. Type of control.

3. Duration of RA

4. Laterality of RA; bilateral RA vs. unilateral RA

Sensitivity analysis

Sensitivity analysis will be conducted according to the following criteria:

1. Sample size (small sample studies, e.g., less than 40 subjects in each group, or large sample studies, e.g., more than 40 subjects in each group);

2. Analysis-related issues (e.g., processes to handle the missing data).

Ethics and dissemination

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

Discussion

This systematic review will provide a detailed summary of the current state of evidence for the effects of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

Contribution of authors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

Funding

No external funding was received. Lee JA, Choi J, Jun JH, Yun KJ and Lee MS were supported by Korea Institute of Oriental Medicine (K14400), Son MJ was supported by same institute (K14380).

Conflict of interest

None declared

References

1. Han A, Robinson V, Judd M, et al. Tai chi for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2004(3):CD004849
2. Odegard S, Finset A, Kvien TK, et al. Work disability in rheumatoid arthritis is predicted by physical and psychological health status: a 7-year study from the Oslo RA register. *Scand J Rheumatol* 2005;34(6):441-7
3. Yelin E. Work disability in rheumatic diseases. *Curr Opin Rheumatol* 2007;19(2):91-6
4. Kvien TK, Uhlig T. Quality of life in rheumatoid arthritis. *Scand J Rheumatol* 2005;34(5):333-41
5. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. *Pharmacoeconomics* 2004;22(2 Suppl 1):27-38
6. Munstedt K, Hackethal A, Schmidt K. Bee venom therapy, bee venom acupuncture of apipunture: What is the evidence behind the various health claims? *Am Bee J* 2005;145:665-68
7. Lee MS, Pittler MH, Shin BC, et al. Bee venom acupuncture for musculoskeletal pain: a review. *J Pain* 2008;9(4):289-97
8. Son DJ, Lee JW, Lee YH, et al. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. *Pharmacol Ther* 2007;115:246-70
9. Baek YH, Huh JE, Lee JD, et al. Antinociceptive effect and the mechanism of bee venom acupuncture (Apipuncture) on inflammatory pain in the rat model of collagen-induced arthritis: mediation by alpha2-adrenoceptors. *Brain Research* 2006;1073-1074:305–10
10. Chen HS, Qu F, He X, et al. The anti-nociceptive effect and the possible mechanism of acupoint stimulation caused by chemical irritants in the bee venom pain model *Brain Research* 2010;1355:61-69

11. Lee JD, Park HJ, Chae Y, et al. An overview of bee venom acupuncture in the treatment of arthritis. *Evid Based Complement Alternat Med* 2005;2:79-84

12. Hauser RA, Daguio M, Wester D, et al. Bee-Venom Therapy for Treating Multiple Sclerosis:A clinical trial. *Alternative Complement Ther* 2001;7:37-45

13. Kwon YB, Kim JH, Yoon JH, et al. The analgesic efficacy of bee venom acupuncture for knee osteoarthritis: A comparative study with needle acupuncture. *Am J Chin Med* 2001;29:187-99

14. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

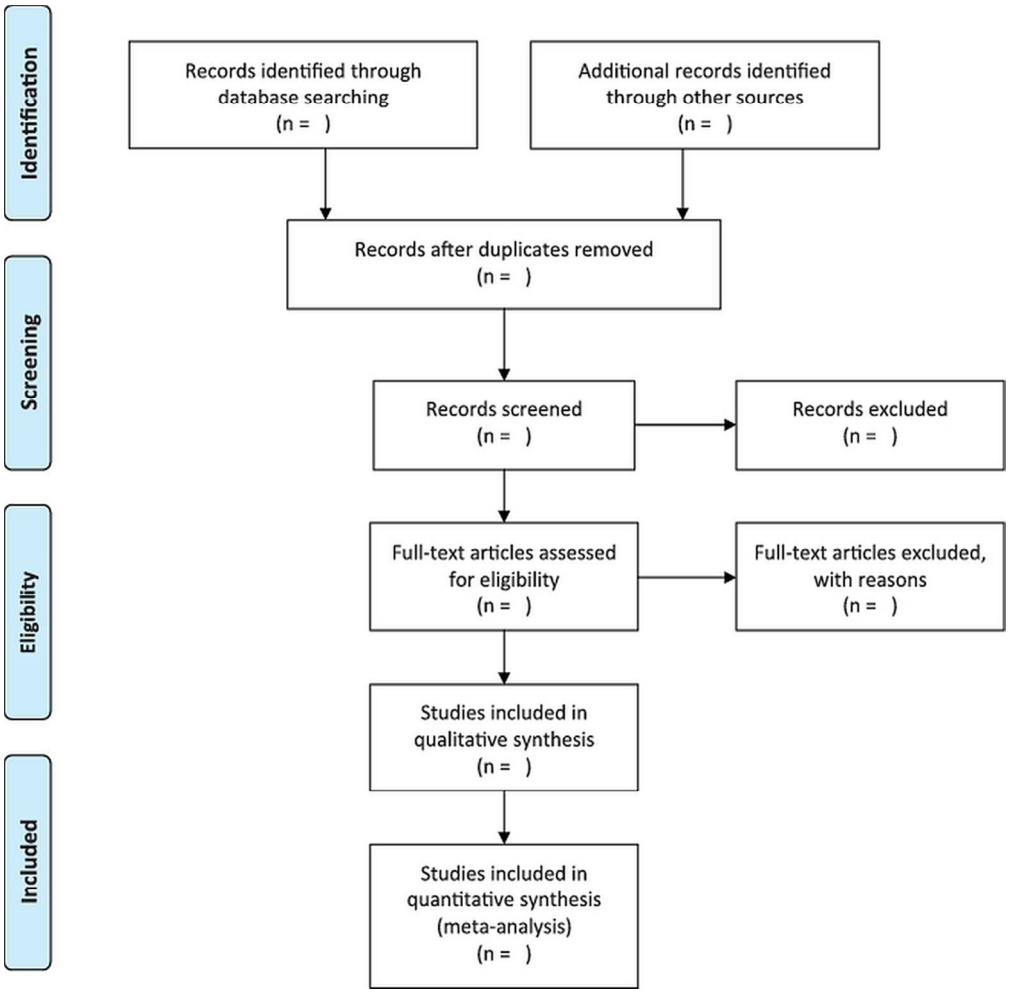
15. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

16. Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011) The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34

Figure legends

Figure 1. Study selection flow diagram



90x88mm (300 x 300 DPI)

Appendix 1. Search Strategy

MEDLINE(Pubmed)

1. arthritis, rheumatoid
2. arthritis, juvenile rheumatoid
3. nodule, rheumatoid
4. felty$ adj2 syndrome
5. caplan$ adj2 syndrome
6. sjogren$ adj2 syndrome
7. sicca adj2 syndrome
8. still$ disease.
9. bechterew$ disease.
10. or/1-9
11. bee venom
12. bee sting
13. wasp venom
14. bee venom acupuncture
15. bee venom therapy
16. apitoxin
17. apitherapy
18. or/11-17
19. 9 and 18

EMBASE

#1 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis'

#2 'rheumatoid arthritis juvenile'/exp OR 'rheumatoid arthritis juvenile'

#3 'rheumatoid nodule'/exp OR 'rheumatoid nodule'

#4 'felty syndrome'/exp OR 'felty syndrome'

#5 'caplan syndrome'/exp OR 'caplan syndrome'

#6 'sjogren s syndrome'/exp OR 'sjogren s syndrome'

#7 'sicca syndrome'/exp OR 'sicca syndrome'

#8 'still disease'/exp OR 'still disease'

#9 'bechterew disease'/exp OR 'bechterew disease'

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 'bee venom'/exp OR 'bee venom'

#12 'bee sting'/exp OR 'bee sting'

#13 'wasp venom'/exp OR 'wasp venom'

#14 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('acupuncture'/exp OR acupuncture)

#15 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('therapy'/exp OR therapy)

#16 'bee'/exp OR bee AND ('sting'/exp OR sting) AND ('therapy'/exp OR therapy)
#17 apitoxin
#18 'apitherapy'/exp OR apitherapy
#19 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #10 AND #19

The Cochrane Library (Wiley InterScience)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw
#3 felty* NEAR/2 syndrome:ti,ab,kw
#4 caplan* NEAR/2 syndrome:ti,ab,kw
#5 sjogren* near/2 syndrome:ti,ab,kw
#6 sicca near/2 syndrome:ti,ab,kw
#7 still* next disease:ti,ab,kw
#8 bechterew$ disease
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor: [Bee venoms] explode all trees
#11 bee venom* :ti,ab,kw
#12 bee sting* :ti,ab,kw
#13 wasp venom* :ti,ab,kw
#14 bee venom* acupuncture :ti,ab,kw
#15 bee venom* therapy:ti,ab,kw
#16 bee sting* therapy:ti,ab,kw
#17 apitoxin:ti,ab,kw
#18 apitherapy:ti,ab,kw
#19 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 #9 AND #19

CINAHL (EBSCOhost)

S1 (MM “Arthritis, Rheumatoid+”) OR (MM “Arthritis, Juvenile Rheumatoid”) OR (MM “Rheumatoid Nodule”)
S2 (MM “Caplan syndrome”) OR (MM “Felty’s Syndrome”) OR (MM “Still’s Disease, Adult-Onset”)
S3 TI arthritis N2 rheumat* OR AB arthritis N2 rheumat* OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI Arthritis, Juvenile Rheumatoid OR AB Arthritis, Juvenile Rheumatoid OR TI felty* N2 syndrome OR AB felty* N2 syndrome OR TI caplan* N2 syndrome OR AB caplan* N2 syndrome
S4 TI sjogren* N2 syndrome OR AB sjogren* N2 syndrome OR TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew* disease OR AB bechterew* disease

S5 S1 OR S2 OR S3 OR S4

S6 (MM"Apitherapy")

S7 TI bee venom* OR AB bee venom* OR TI bee sting* OR AB bee sting* OR TI wasp venom* OR AB wasp venom* OR TI bee venom* acupuncture OR AB bee venom* acupuncture OR TI bee venom* therapy OR AB bee venom* therapy

S8 TI apitherap* OR AB apitherap* OR TI apitoxin* OR AB apitoxin*

S9 S6 OR S7 OR S8

S10 S5 AND S9

AMED (EBSCOhost)

S1 TX Arthritis, Rheumatoid OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI arthritis N2 rheumat* OR AB arthritis N2 rheumat* OR TI felty* N2 syndrome OR AB felty* N2 syndrome OR TI caplan* N2 syndrome OR AB caplan* N2 syndrome OR TI sjogren* N2 syndrome OR AB sjogren* N2 syndrome

S2 TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew* disease OR AB bechterew* disease

S3 S1 OR S2

S4 TI bee venom OR AB bee venom OR TI bee sting OR AB bee sting OR TI wasp venom OR AB wasp venom

S5 TI apitoxin OR AB apitoxin TI apitherapy OR AB apitherapy

S6 bee venom therapy OR bee venom acupuncture

S7 S4 OR S5 OR S6

S8 S3 AND S7