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Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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

Abstract

Objectives: This systematic review was performed to assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised clinical trials (RCTs)

Methods and analysis: We searched 14 databases up to March 2014 without a language restriction. The methodological quality of all included studies was assessed using the Cochrane Risk of Bias tool. We included all RCTs on BVA used alone or in combination with conventional therapy versus the same conventional therapy alone.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared to placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) but were not shown the improvement of morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of RA patients compared to placebo (normal saline injection) control. However, the number of trials, their quality, and the total sample size were too low to draw firm conclusions.

Trial registration: PROSPERO 2013: CRD42013005853

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 performed with a comprehensive search strategy and established the current status of the evidence with unbiased methods.
- There is only one study that investigate the effects of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).
- There is low evidence for BVA for management of RA.

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 conducted independently by two authors.
- We used of the GRADE approach to assess confidence in estimates of effect.
- We identified only one study so that we could not draw strong conclusions.

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and ankylosis develop. The complex, systemic nature of the disease makes RA treatment complex and involving a variety of approaches. The major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and 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. Different forms of the therapy include the administration of honeybee stings, injections of BV, and BV acupuncture (BVA). [6]Bee venom acupuncture (BVA) involves injecting purified and 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 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 clinical settings.[7] [11] According to animal experiments, BV exhibits anti-arthritic, anti-inflammatory and

analgesic effects attributable to the suppression of cyclooxygenase-2 and phospholipase A2 expression and a decrease in the levels of tumour necrosis factor alpha, interleukin (IL)-1, IL-6, nitric oxide and oxygen reactive species. It is also widely assumed that bioactive BV compounds including enzymes (phospholipase A2), peptides (melittin, adolapin, and apamin), and amines are associated with these actions. [7 8 12-14] However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic anti-arthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate. [15]

Why this review is important

Bee venom (BV) therapy or BV acupuncture (BVA) has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and rheumatoid arthritis (RA) in some Asian countries. [11]

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

Materials and Methods

The protocol of this SRs is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.[16]

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 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 the Century Journal Project), Wanfang and VIP. Further, we conducted 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). The strategy for searching the MEDLINE database is presented in appendix 1. Similar search strategies were applied for the other databases.

Types of studies

All prospective randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

All articles describing an RCT with patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form.

The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.[17] Our review used 'L', 'U', and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear, and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments,

incomplete outcome data, selective reporting and other sources of bias. [17]The quality of each trial was categorised into a low, unclear, or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% confidence intervals (CIs) to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were 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 contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed-effects or random-effects.

Unit of analysis issues

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

Addressing the missing data

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

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests were used to evaluate the heterogeneity of the included studies and I^2 >50 were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.[19] However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies. [19 20]

Results

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (Figure 1). The key data from the eligible RCT are summarised in Table 1.**.** This trial was conducted in Korea.[21] Four RCTs, which were conducted in China, were excluded because the BVA were not made with purified, diluted bee venom but with live bee stings, as shown in supplement 2 and 3. [22-25]

Risk of bias in the included studies

The RCT used [21] has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personal employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR, and CRP in RA patients.[21] Patients were randomised into two groups: one receiving BVA at ashi points and the other receiving normal saline injections at ashi points. After two months, the scores for morning stiffness, HAQ, pain on VAS, tender joint counts, swollen joint counts, ESR, and CRP were significantly better in the BVA group than in the placebo control group.

Adverse events

This trial did not assess adverse events related to BVA used for RA. [21]

Discussion

Only one trial testing the effects of BVA for RA is currently available.[21] There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of RA patients compared to placebo (normal saline injection) control subjects. To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,[26] but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.[21] The use of placebo is essential for differentiating nonspecific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of bee venom, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an inappropriate placebo. BVA combines biochemical effects of the bee venom and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with BVA. BVA has uncomfortable sensations such as swelling and

burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a placebo, it is important to recruit patients who have not experienced BVA.

BVA can cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment. The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[27] Although trials are conducted safely, some problems remain in using BVA in clinical practice.

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one non-randomised trial that showed favourable effects of BVA for several symptoms of RA.[28] However, this type of study, lacking in randomisation, was open to selection bias, which could lead to false-positive results.

The other type of BV therapy may be more commonly used when treating patients with RA. In considering this type of trial, we found 4 additional RCTs that compared live bee sting acupuncture combined with conventional drugs to conventional treatments alone for the treatment of RA symptoms.[22 24 25 29] Three RCTs [22 24 29] showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain, or joint swelling, while one RCT failed to do so.[25] Although these RCTs did not report serious adverse effects, live bee stings can cause fatal adverse events including anaphylaxis.[22 24 25 29]

Contributorship statement

Conceived and designed the review: MSL and JAL. Extracted the data: JHJ, and MJS. Analyzed the data: MJS, JC and JIK. Wrote the paper: JAL, MJS, JC, JIK, and MSL. Searched and selected studies: JHJ, MJS, JC. Revised the paper: JAL, MSL. Monitored data collection: MSL. The final manuscript was approved by all authors.

Competing interests

None

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Data Sharing

No additional data available

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Figure legend

Figure 1. Flow chart of trial selection process. NRS: non-randomised trial; RCT: randomised controlled trials.

Table 1. Characteristics of included randomized controlled trials of bee venom acupuncture for rheumatoid arthritis

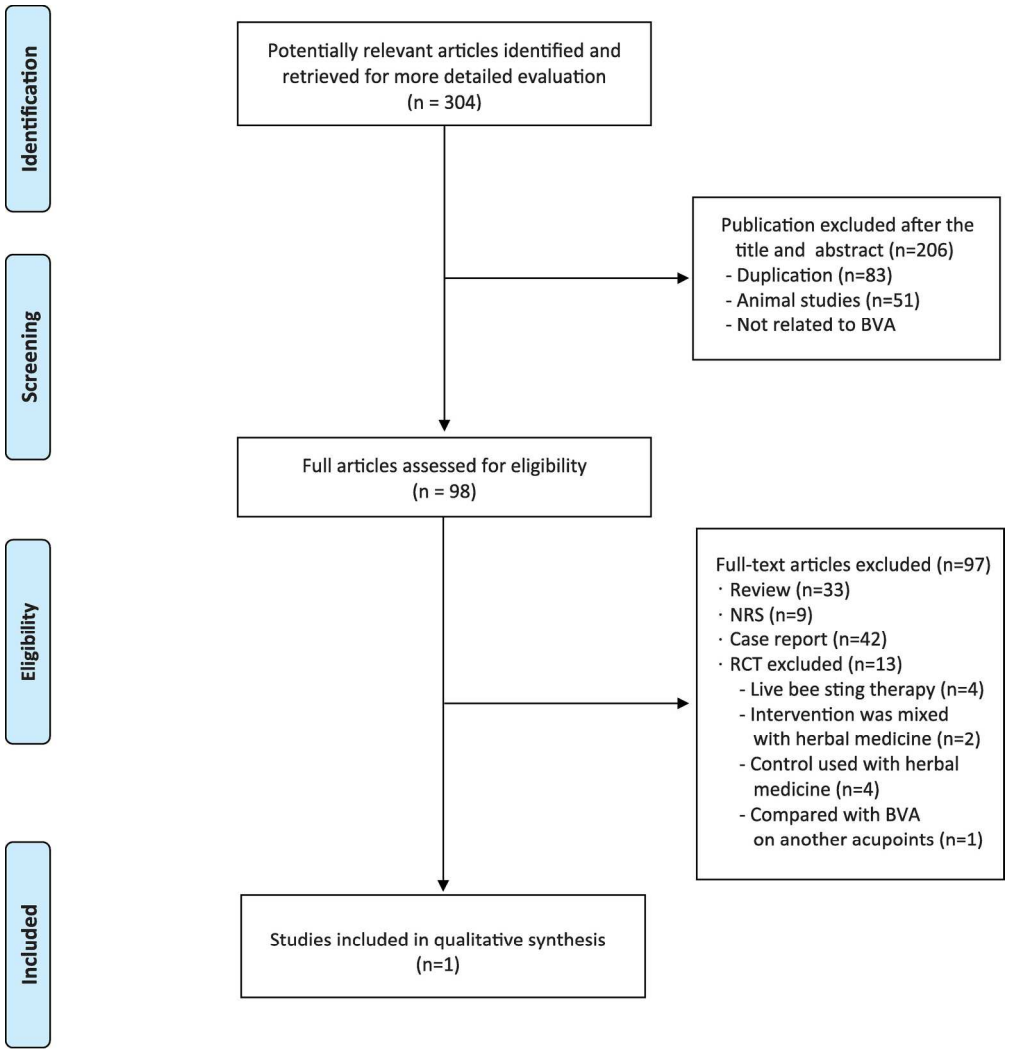
Lee 2003	
Methods	Design: prospective randomized controlled trial
Participants	Country: South Korea Number of patients included(completed / randomized): (A) 37/40 (B) 32/40 Mean age (years): (A) 49.2±9.6 (B) 47.3±8.9 Duration of disease (years): (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (Ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	*Primary outcomes:* 1) Morning stiffness, MD, -0.70[-2.00, 0.60], P<0.05 2) HAQ, MD, 0.00[-0.08, 0.08], P<0.05 3) VAS-pain, MD, -18.10[-23.71, -12.49], P<0.05 *Secondary outcomes:* 1) Tender joint count, MD, -1.30[-1.91, -0.69], P<0.0001 2) Swollen joint count, MD, -1.10[-1.72, -0.48], P=0.005 3) ESR, MD,20.10[-22.80,-17.40], P<0.00001 4) CRP, MD, -1.90[-2.86, -0.94], P=0.0001
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts:yes Intention-to-treat: No Author comment: These results suggests that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias		
Item	**Authors' judgement**	**Description**
Random sequence generation (selection bias)	Unclear risk	Described as randomized but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 11 participants were not included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; CM: Chinese medicine; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; n.r.: not reported; RA: rheumatoid arthritis VAS: visual analogue scal

Table 2. Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis					
Patient or population: patients with rheumatoid arthritis **Settings:** Korea **Intervention:** Bee venom acupuncture vs. normal saline injection as placebo					
Outcomes	**Illustrative comparative risks* (95% CI)** **Assumed risk** **Control (Normal Saline injection)**	**Corresponding risk** **Bee venom acupuncture**	**No of Participants (studies)**	**Quality of the evidence (Grade)**	**Comments**
Pain (VAS)		**16.9 WMD lower**[1] (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -10.40 (-16.47 to -4.33)
Morning stiffness		**12.1 WMD higher**[1] (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -0.30 (-1.01 to 0.41)
Swollen joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.70 to -1.70)
Tender joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.73 to -1.73)
Quality of Life (HAQ)		**0.3 WMD higher**[1] (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.20 (-0.06 to 0.46)
ESR		**19.4 WMD lower**[1] (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -2.30 (-10.17 to 5.57)
CRP		**1.7 WMD lower**[1] (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 1.40 (-8.27 to 5.47)
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **HAQ:** Health Assessment Questionnaire**: VAS:** Visual analogue scale; **WMD:** weight mean difference					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					
[1] After 2 months treatment [2] Poorly reported paper (See 'Risk of bias' table) [3] Small sample size					



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Supplement 1. Search Strategy

MEDLINE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. bechterew$ disease.tw.
9. or/1-8
10. bee venom$.tw.
11. bee sting.tw.
12. wasp venom$.tw.
13. bee venom acupuncture.tw.
14. bee venom therapy.tw.
15. bee sting therapy.tw.
16. apitoxin.tw.
17. apitherapy.tw.
18. or/10-17
19. 9 and 18

EMBASE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).tw.

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

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

#3 felty* NEAR/2 syndrome:ti,ab

#4 caplan* NEAR/2 syndrome:ti,ab

#6 sjogren* near/2 syndrome:ti,ab

#7 sicca near/2 syndrome:ti,ab

#8 still* next disease:ti,ab

#9 bechterew$ disease.tw.

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

#11 bee venom* :ti,ab

#12 bee sting :ti,ab

#13 wasp venom* :ti,ab

#14 bee venom acupuncture :ti,ab

#15 bee venom therapy:ti,ab

#16 bee sting therapy:ti,ab

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

#19 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 #10 AND #19

CINAHL (EBSCOhost)

S7 S3 and S6

S6 S4 or S5

S5 TI “apitoxin” or AB “apitoxin” or TI “apitherapy” or AB “apitherapy”

S4 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”

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

S3 S1 or S2

S2 TI “bechterew* disease” or AB “bechterew* disease” or TI (arthritis N2 rheumat*) or AB (arthritis N2 rheumat*)

S1 (MH “Arthritis, Rheumatoid+”) or TI (felty* N2 syndrome) or AB (felty* N2 syndrome) or TI (caplan* N2 syndrome) or AB(caplan* N2 syndrome) or TI (rheumatoid nodule) or AB (rheumatoid nodule) or TI (sjogren* N2 syndrome) or AB (sjogren* N2 syndrome) or TI (sicca N2 syndrome) or AB (sicca N2 syndrome)

Supplement 1. Summary of randomized controlled trials of direct-Bee Sting acupuncture for rheumatoid arthritis

First author (Year) country	Mean age (years); Duration of disease (years)	Experimental intervention (Regimen)	Control intervention (Regimen)	Primary outcome		Secondary outcome		Adverse Effects
				measurement	result	measurement	result	
Liu (2008) China	(A) 47.4±10.0; 5.0±3.0 (B) 48.3±9.4; 4.9±2.6	(A) BVA (Ashi points, dialectical acupoints, 8~15bees, n.r., once every other day for 3 months, n=50), plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, twice daily for 3 months, n=50)	(1) Total improvement score (2) Joint swelling score (3) Joint pain score	(1) RR, 1.22[1.01, 1.47], P=0.04 (2) MD, -0.24[-0.42,-0.06],P=0.010 (3) MD, -0.34[-0.37, -0.31], P<0.00001	(1) Number of Joint-swelling (2) RF (3) ESR	(1) MD, -0.46[-0.62, -0.30], P<0.00001 (2) MD, -7.74[-14.10, -1.38], P=0.02 (3) MD, -4.38[-6.28, -2.48], P<0.00001	Dizziness (B:4), fever(A:1), hypersensitivity(A:4), leukopenia(B:3), loss of appetite and nausea(B:6)
Zhang (2011) China	(A) 33.8; 3.6 (B) 32.2; 3.4	(A) BVA (Ashis points near the knee, 5~15bees, n.r., two or three times a week for 3months, n=23) plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, once daily for 3 months, n=23)	(1) Total improvement score (2) VAS (3) HSS	(1) RR, 1.17[0.91, 1.50] (2) MD, -1.00[-1.20, -0.80], P<0.00001 (3) MD, 3.37[3.24, 3.50], P<0.00001	(1) ESR (2) CRP	(1) MD, -4.20[-7.35, -1.05], P=0.009 (2) MD, -2.50[-5.56, 0.56], P=0.11	Dizziness(A:1), epigastric discomfort(A:4), fever(A:2), hypersensitivity(A:1), leukopenia(B:3), rash(A:3)
Deng (2011) China	n.r.	(A) BVA (Ashi points, dialectical acupoints, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time, n.r., three times a week for 2 months, n=20) plus (B)	(B) WM (Oral:MTX:10mg, once a week for 2 months, n=20) (C) WM (Oral: Prednisone Acetate:7.5mg, once daily for 2 months, n=20) plus (B)	(1) Total improvement score (2) Morning stiffness (3) Joint pain score (4) Joint swelling score	(1) - A vs. B RR, 1.46[1.04, 2.05], P=0.03 - A vs. C RR, 1.36[1.00, 1.84], P=0.05 (2) - A vs. B MD, -0.29[-0.42, -0.17], P<0.00001 - A vs. C MD, -0.11[-0.25, 0.02], P=0.05 (3) - A vs. B MD, -0.50[-0.64, -0.36], P<0.00001 - A vs. C MD, -0.13[-0.26, 0.00], P=0.05 (4) - A vs. B MD, -0.33[-0.47, -0.19], P<0.00001 - A vs. C MD, 0.05[-0.12, 0.21], P=0.56	(1) RF (2) ESR (3) CRP	(1) - A vs. B MD, -28.00[-37.21, -18.79], P<0.00001 - A vs. C MD, -14.30[-17.60, -11.00], P<0.00001 (2) - A vs. B MD, -18.60[-27.04,-10.16], P P<0.00001 - A vs. C MD, -8.10[-15.41, -0.79], P=0.03 (3) - A vs. B MD, -10.30[-12.46,-8.14], P<0.00001 - A vs. C MD, -3.70[-5.99,-1.41], P=0.002	Epigastric discomfort (C:6),hypersensitivity (A:3), insomnia(C:3), leukopenia(B:1), nausea(A:2,B:3)

Zhou (2012) China	(A) 37.86±14.15; 15.58±5.24 (B) 36.43±10.18; 13.95±5.21 (C) 40.66±14.01; 16.58±5.32	(A) BVA (Ashi points, acupoints near the pain point, 5~10bees, n.r., three times a week for 3 months, n=40) plus NSAIDS	(B) EA (Ashi points, LI15, LI14, LI11, LI 10, SJ5, BL36, SP10, BL40, GB34, ST36, GB39, DU14, BL52, DU3, BL32, 30min, three times a week y for 3 months, n=30) plus NSAIDS (C) WM (Oral:MTX:5-10mg, once a week for 3 months; Folic acid: 10mg, once a week for 3 months, n=30) plus NSAIDS	(1) Total improvement score	(1) - A vs. B RR, 1.23[0.97, 1.56], P=0.09 - A vs. C RR, 1.04[0.87, 1.24], P=0.67	(1) ESR (2) CRP	(1) - A vs. B MD, -13.70[-15.08, -12.32], P<0.00001 - A vs. C MD, -2.72[-6.54, 1.10] P=0.16 (2) - A vs. B MD, -9.18[-11.47, -6.89], P<0.00001 - A vs. C MD, 3.93[-0.07, 7.93], P=-0.05	n.r.

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; EA: electro acupuncture; ESR: erythrocyte sedimentation rate; HSS: hss knee score; HAQ: health assessment questionnaire; MTX: methotrexate; n.r.: not reported; NSAIDS: nonsteroidal anti-inflammatory drugs; RF: rheumatoid factor; SASP: sulfasalazine; VAS: visual analogue scale; TNF-α: tumor necrosis factor-alpha; WM: Western medicine

Supplement 2. Summary of treatment direct-Bee Sting acupuncture points and other information

First author (Year)	Type of acupuncture	Total treatment (sessions)	Main acupoints	Dialectical acupoints	Treatment Rationale	Adverse events
Liu (2008)	BVA (Live bee, 8~15bees)	3 months	Ashi points	Cold dampness invasion, joint pain: CV6, RN4; Hot and humid embodiment, joint swelling pain: LI11, GV14; Phlegm and blood stasis in the resistance, Joint deformities pain:ST40,GB39;	CM theory, Clinical experience	Hypersensitivity(4), fever(1)
Zhang (2011)	BVA (Live bee, 5~15bees)	3 months	Ashis points near knee	n.r.	CM theory, Clinical experience	Fever(2), hypersensitivity(1), rash(3)
Deng (2011)	BVA (Live bee, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time)	2 months	Ashi points	Ankle:BL62, KI6, BL60, GB40; back: GV26, V12, GV3; elbow: LI11, LI4, SJ10, SJ5, LU5; knee:ST35, ST34, GB34, GB33; Shoulders:LI16, SJ14, SI10; wrist:SJ4, SJ5 LI5, SI4	CM theory, Clinical experience	Hypersensitivity (3), nausea(2)
Zhou (2012)	BVA (Live bee, 5~10bees)	3 months	Ashi points, acupoints in near in the pain point	n.r.	CM theory, Clinical experience	n.r.
Lee (2003)	BVA (Injection, Bee venom extract diluted with saline to 1:3000, from 02.ml increase to 1.0ml)	2 months	Ashi points , acupoints near the inflammation point	Metacarpophalangeal joint, Distal interphalangeal joint, Proximal interphalangeal joint, wrist: SI5, SI5, TE4, L15 PC7; elbow:LI11, TE10, SI8, HT3, S18; shoulder: LI15, TE14; knee: ST36, GB34, SP9; ankle: GB40, BL62, SP5, K16	CM theory, Clinical experience	n.r

BVA: Bee Venom Acupuncture; CM: Chinese medicine; n.r.: not reported

Supplement 1. Summary of randomized controlled trials of direct-Bee Sting acupuncture for rheumatoid arthritis

First author (Year) country	Mean age (years); Duration of disease (years)	Experimental intervention (Regimen)	Control intervention (Regimen)	Primary outcome		Secondary outcome		Adverse Effects
				measurement	result	measurement	result	
Liu (2008) China	(A) 47.4±10.0; 5.0±3.0 (B) 48.3±9.4; 4.9±2.6	(A) BVA (Ashi points, dialectical acupoints, 8~15bees, n.r., once every other day for 3 months, n=50), plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, twice daily for 3 months, n=50)	(1) Total improvement score (2) Joint swelling score (3) Joint pain score	(1) RR, 1.22[1.01, 1.47], P=0.04 (2) MD, -0.24[-0.42,-0.06],P=0.010 (3) MD, -0.34[-0.37, -0.31], P<0.00001	(1) Number of Joint-swelling (2) RF (3) ESR	(1) MD, -0.46[-0.62, -0.30], P<0.00001 (2) MD, -7.74[-14.10, -1.38], P=0.02 (3) MD, -4.38[-6.28, -2.48], P<0.00001	Dizziness (B:4), fever(A:1), hypersensitivity(A:4), leukopenia(B:3), loss of appetite and nausea(B:6)
Zhang (2011) China	(A) 33.8; 3.6 (B) 32.2; 3.4	(A) BVA (Ashis points near the knee, 5~15bees, n.r., two or three times a week for 3months, n=23) plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, once daily for 3 months, n=23)	(1) Total improvement score (2) VAS (3) HSS	(1) RR, 1.17[0.91, 1.50] (2) MD, -1.00[-1.20, -0.80], P<0.00001 (3) MD, 3.37[3.24, 3.50], P<0.00001	(1) ESR (2) CRP	(1) MD, -4.20[-7.35, -1.05], P=0.009 (2) MD, -2.50[-5.56, 0.56], P=0.11	Dizziness(A:1), epigastric discomfort(A:4), fever(A:2), hypersensitivity(A:1), leukopenia(B:3), rash(A:3)
Deng (2011) China	n.r.	(A) BVA (Ashi points, dialectical acupoints, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time, n.r., three times a week for 2 months, n=20) plus (B)	(B) WM (Oral:MTX:10mg, once a week for 2 months, n=20) (C) WM (Oral: Prednisone Acetate:7.5mg, once daily for 2 months, n=20) plus (B)	(1) Total improvement score (2) Morning stiffness (3) Joint pain score (4) Joint swelling score	(1) - A vs. B RR, 1.46[1.04, 2.05], P=0.03 - A vs. C RR, 1.36[1.00, 1.84], P=0.05 (2) - A vs. B MD, -0.29[-0.42, -0.17], P<0.00001 - A vs. C MD, -0.11[-0.25, 0.02], P=0.05 (3) - A vs. B MD, -0.50[-0.64, -0.36], P<0.00001 - A vs. C MD, -0.13[-0.26, 0.00], P=0.05 (4) - A vs. B MD, -0.33[-0.47, -0.19], P<0.00001 - A vs. C MD, 0.05[-0.12, 0.21], P=0.56	(1) RF (2) ESR (3) CRP	(1) - A vs. B MD, -28.00[-37.21, -18.79], P<0.00001 - A vs. C MD, -14.30[-17.60, -11.00], P<0.00001 (2) - A vs. B MD, -18.60[-27.04,-10.16], P P<0.00001 - A vs. C MD, -8.10[-15.41, -0.79], P=0.03 (3) - A vs. B MD, -10.30[-12.46,-8.14], P<0.00001 - A vs. C MD, -3.70[-5.99,-1.41], P=0.002	Epigastric discomfort (C:6),hypersensitivity (A:3), insomnia(C:3), leukopenia(B:1), nausea(A:2,B:3)

Zhou (2012) China	(A) 37.86±14.15; 15.58±5.24 (B) 36.43±10.18; 13.95±5.21 (C) 40.66±14.01; 16.58±5.32	(A) BVA (Ashi points, acupoints near the pain point, 5~10bees, n.r., three times a week for 3 months, n=40) plus NSAIDS	(B) EA (Ashi points, LI15, LI14, LI11, LI 10, SJ5, BL36, SP10, BL40, GB34, ST36, GB39, DU14, BL52, DU3, BL32, 30min, three times a week y for 3 months, n=30) plus NSAIDS (C) WM (Oral:MTX:5-10mg, once a week for 3 months; Folic acid: 10mg, once a week for 3 months, n=30) plus NSAIDS	(1) Total improvement score	(1) - A vs. B RR, 1.23[0.97, 1.56], P=0.09 - A vs. C RR, 1.04[0.87, 1.24], P=0.67	(1) ESR (2) CRP	(1) - A vs. B MD, -13.70[-15.08, -12.32], P<0.00001 - A vs. C MD, -2.72[-6.54, 1.10] P=0.16 (2) - A vs. B MD, -9.18[-11.47, -6.89], P<0.00001 - A vs. C MD, 3.93[-0.07, 7.93], P=-0.05	n.r.

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; EA: electro acupuncture; ESR: erythrocyte sedimentation rate; HSS: hss knee score; HAQ: health assessment questionnaire; MTX: methotrexate; n.r.: not reported; NSAIDS: nonsteroidal anti-inflammatory drugs; RF: rheumatoid factor; SASP: sulfasalazine; VAS: visual analogue scale; TNF-α: tumor necrosis factor-alpha; WM: Western medicine

References

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Zhang JL, Liu XD, Ye LH, Zhang P. Clinical padomized comparison study of bee-sting therapy for knee synovitis caused by rheumatoid arthritis. Chin Arch Tradit Chin Med 2011;29(8):1904-06.

Zhou YF, Li WY. Effect of needle on hypothalamic-pituitary-adrenal axis of patient with rheumatoid arthritis. Nei Mongol J Tradit Chin Med 2012;26(5):1-3.

Supplement 3. ummary of treatment direct-Bee Sting acupuncture points and other information

First author (Year)	Type of acupuncture	Total treatment (sessions)	Main acupoints	Dialectical acupoints	Treatment Rationale	Adverse events
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Zhang (2011)	BVA (Live bee, 5~15bees)	3 months	Ashis points near knee	n.r.	CM theory, Clinical experience	Fever(2), hypersensitivity(1), rash(3)
Deng (2011)	BVA (Live bee, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time)	2 months	Ashi points	Ankle:BL62, KI6, BL60, GB40; back: GV26, V12, GV3; elbow: LI11, LI4, SJ10, SJ5, LU5; knee:ST35, ST34, GB34, GB33; Shoulders:LI16, SJ14, SI10; wrist:SJ4, SJ5 LI5, SI4	CM theory, Clinical experience	Hypersensitivity (3), nausea(2)
Zhou (2012)	BVA (Live bee, 5~10bees)	3 months	Ashi points, acupoints in near in the pain point	n.r.	CM theory, Clinical experience	n.r.
Lee (2003)	BVA (Injection, Bee venom extract diluted with saline to 1:3000, from 02.ml increase to 1.0ml)	2 months	Ashi points , acupoints near the inflammation point	Metacarpophalangeal joint, Distal interphalangeal joint, Proximal interphalangeal joint, wrist: SI5, SI5, TE4, L15 PC7; elbow:LI11, TE10, SI8, HT3, S18; shoulder: LI15, TE14; knee: ST36, GB34, SP9; ankle: GB40, BL62, SP5, K16	CM theory, Clinical experience	n.r

BVA: Bee Venom Acupuncture; CM: Chinese medicine; n.r.: not reported

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PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 1,2

PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	na

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	na
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	na
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	na
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

BMJ Open

Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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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, Medical research division Jun, Ji Hee; Korea Institute of Oriental Medicine, Kim, Jong-In; Kyung Hee University, Department of Acupuncture and Moxibustion, College of Korean Medicine Lee, Myeong Soo; Korea Institute of Oriental Medicine,
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY

Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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License statement

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 performed with a comprehensive search strategy and established 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 conducted independently by two authors.
- We used of the GRADE approach to assess confidence in estimates of effect
- We identified only one study so that we could not draw strong conclusions.

Abstract

Objective: This systematic review was performed to assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised controlled trials (RCTs).

Setting: We searched 14 databases up to March 2014 without a language restriction.

Participants: Patients with RA.

Intervention: BVA involved injecting purified, diluted BV into acupoints. We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone.

Primary outcome: Morning stiffness, pain and joint swelling

Secondary outcomes: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared to placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) but were not shown the improvement of morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of RA patients compared to placebo (normal saline injection) control. However, the number of trials, their quality, and the total sample size were too low to draw firm conclusions.

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 inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and ankylosis develop. The complex, systemic nature of the disease makes RA treatment complex and involving a variety of approaches. The major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and 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. Different forms of the therapy include the administration of honeybee stings, injections of BV, and BV acupuncture (BVA). [6]Bee venom acupuncture (BVA) involves injecting purified and 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 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 clinical settings.[7] [11] According to animal experiments, BV exhibits anti-arthritic, anti-inflammatory and analgesic effects attributable to the suppression of cyclooxygenase-2 and phospholipase A2

expression and a decrease in the levels of tumour necrosis factor alpha, interleukin (IL)-1, IL-6, nitric oxide and oxygen reactive species. It is also widely assumed that bioactive BV compounds including enzymes (phospholipase A2), peptides (melittin, adolapin, and apamin), and amines are associated with these actions. [7 8 12-14] However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic anti-arthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate. [15]

Why this review is important

Bee venom (BV) therapy or BV acupuncture (BVA) has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and rheumatoid arthritis (RA) in some Asian countries. [11]

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

Materials and Methods

The protocol of this SRs is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.[16]

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 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 the Century Journal Project), Wanfang and VIP. Further, we conducted 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). The strategy for searching the MEDLINE database is presented in Supplement 1. Similar search strategies were applied for the other databases.

Types of studies

All prospective randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

Patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form.

The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.[17] Our review used 'L', 'U', and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear, and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments,

incomplete outcome data, selective reporting and other sources of bias. [17]The quality of each trial was categorised into a low, unclear, or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% confidence intervals (CIs) to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were 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 contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed-effects or random-effects.

Unit of analysis issues

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

Addressing the missing data

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

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests were used to evaluate the heterogeneity of the included studies and I^2 >50 were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.[19] However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies. [19 20]

Results

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (Figure 1). Thirteen RCTs were among the excluded articles for the following reasons: Four RCTs, which were conducted in China, were excluded because the BVA were not made with purified, diluted bee venom but with live bee stings (Supplement 2 and 3). [21-24] Four RCTs employed herbal medicine as co-administrator,[25-28] 2 RCTs included herbal medicine as control treatment,[29 30] 1 RCT compared two different acupoints, [31] 1 RCT was not related RA,[32] and the other 1 RCT was duplicated publication.[33] The key data from the eligible RCT are summarised in Table 1. This trial was conducted in Korea.[34]

Risk of bias in the included studies

The RCT used [34] has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personal employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR, and CRP in RA patients.[34] Patients were randomised into two groups: one receiving BVA at ashi points and the other receiving normal saline injections at ashi points. After two months, the scores for morning stiffness, HAQ, pain on VAS, tender joint counts, swollen joint counts, ESR, and CRP were significantly better in the BVA group than in the placebo control group.

Adverse events

This trial did not assess adverse events related to BVA used for RA. [34]

Discussion

Only one trial testing the effects of BVA for RA is currently available.[34] There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of RA patients compared to placebo (normal saline injection) control subjects. To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,[35] but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.[34] The use of placebo is essential for differentiating nonspecific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of bee venom, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an inappropriate placebo. BVA combines biochemical effects of the bee venom and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with BVA. BVA has uncomfortable sensations such as swelling and

burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a placebo, it is important to recruit patients who have not experienced BVA.

BVA can cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment. The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[36] Although trials are conducted safely, some problems remain in using BVA in clinical practice.

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one observational study that showed favourable effects of BVA for several symptoms of RA (Supplement 4).[37] However, this type of study, lacking in control treatment, was open to selection bias, which could lead to false-positive results.

The other type of BV therapy may be more commonly used when treating patients with RA. In considering this type of trial, we found 4 additional RCTs that compared live bee sting acupuncture combined with conventional drugs to conventional treatments alone for the treatment of RA symptoms.[21 23 24 38] Three RCTs [21 23 38] showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain, or joint swelling, while one RCT failed to do so.[24] Although these RCTs did not report serious adverse effects, [22 24 25 29] live bee stings can cause fatal adverse events including anaphylaxis. [39 40] Adverse events should be examined in future studies. The injection parts may be one issue for the assessment because it is very common to inject on the painful point (Ashi point) in RA patients. Even if we expand the inclusion criteria to this points, no further

studies were found.

One could question the validity of the conclusion by pointing to the review method used (reviewing a small number of trials with many limitations). However, reasons for doing a systematic review would be to answer question not posted by individual studies, to settle controversies arising from apparently conflicting studies, or to generate new hypotheses. [41] The systematic review with a small number of trials can be done.

In conclusion, currently, very few trials have tested the effects of BVA in the management of RA. Collectively, the evidence is insufficient to suggest that BVA is an effective therapy for RA. Further studies should be of high quality, with a particular emphasis on designing adequate and appropriate control groups.

Author Contributions

Conceived and designed the review: MSL and JAL. Extracted the data: JHJ, and MJS. Analyzed the data: MJS, JC and JIK. Wrote the paper: JAL, MJS, JC, JIK, and MSL. Searched and selected studies: JHJ, MJS, JC. Revised the paper: JAL, MSL. Monitored data collection: MSL.

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Conflict of interest

None

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Figure legend

Figure 1. Flow chart of trial selection process. CCT: case series trials; RCT: randomised controlled trials.

Table 1. Characteristics of included randomized controlled trials of bee venom acupuncture for rheumatoid arthritis

Lee 2003	
Methods	Design: prospective randomized controlled trial
Participants	Country: South Korea Number of patients included(completed / randomized): (A) 37/40 (B) 32/40 Mean age (years): (A) 49.2±9.6 (B) 47.3±8.9 Duration of disease (years): (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (Ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	*Primary outcomes:* 1) Morning stiffness, MD, -0.70[-2.00, 0.60], P<0.05 2) HAQ, MD, 0.00[-0.08, 0.08], P<0.05 3) VAS-pain, MD, -18.10[-23.71, -12.49], P<0.05 *Secondary outcomes:* 1) Tender joint count, MD, -1.30[-1.91, -0.69], P<0.0001 2) Swollen joint count, MD, -1.10[-1.72, -0.48], P=0.005 3) ESR, MD,20.10[-22.80,-17.40], P<0.00001 4) CRP, MD, -1.90[-2.86, -0.94], P=0.0001
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts:yes Intention-to-treat: No Author comment: These results suggests that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias		
Item	**Authors' judgement**	**Description**
Random sequence generation (selection bias)	Unclear risk	Described as randomized but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 11 participants were not included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; CM: Chinese medicine; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; n.r.: not reported; RA: rheumatoid arthritis VAS: visual analogue scal

Table 2. Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis

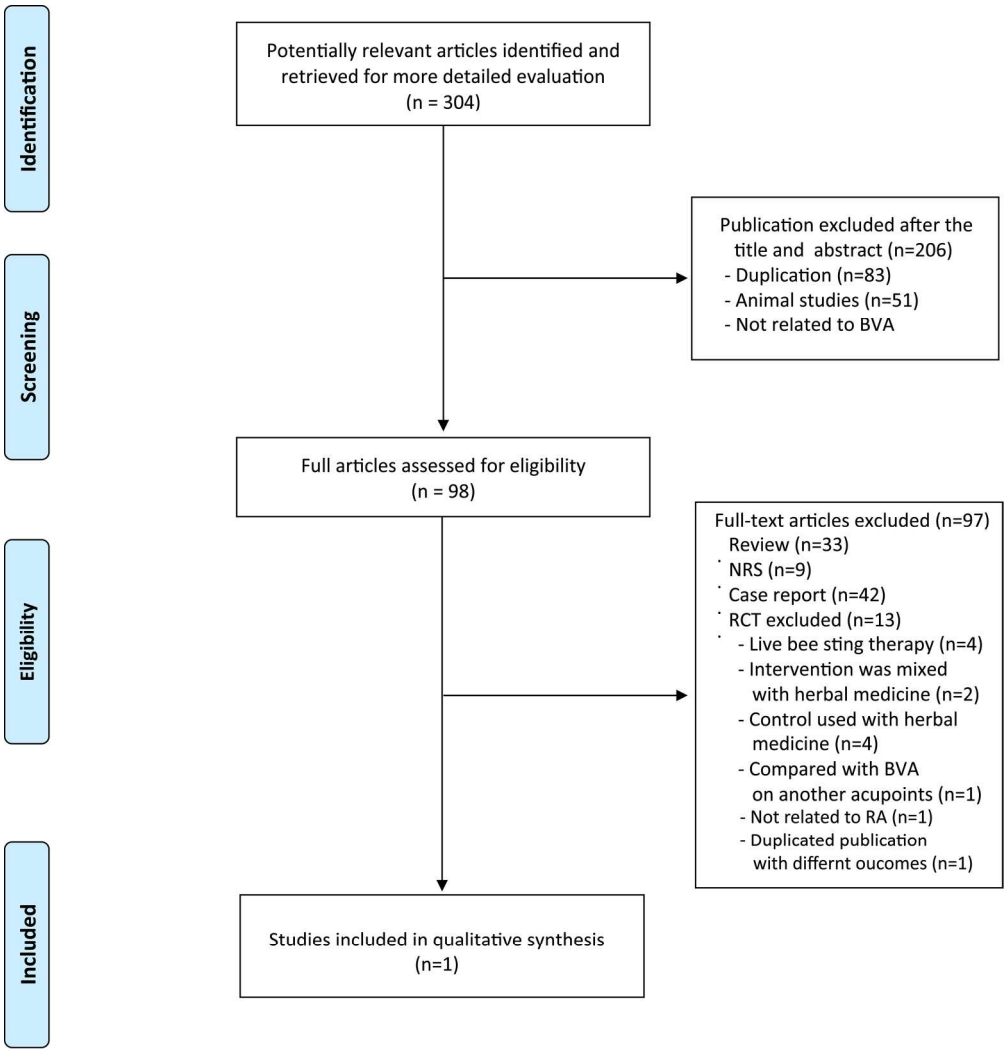
Patient or population: patients with rheumatoid arthritis
Settings: Korea
Intervention: Bee venom acupuncture vs. normal saline injection as placebo

Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (Grade)	Comments
	Assumed risk Control (Normal Saline injection)	Corresponding risk Bee venom acupuncture			
Pain (VAS)		**16.9 WMD lower**[1] (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -10.40 (-16.47 to -4.33)
Morning stiffness		**12.1 WMD higher**[1] (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -0.30 (-1.01 to 0.41)
Swollen joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.70 to -1.70)
Tender joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.73 to -1.73)
Quality of Life (HAQ)		**0.3 WMD higher**[1] (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.20 (-0.06 to 0.46)
ESR		**19.4 WMD lower**[1] (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -2.30 (-10.17 to 5.57)
CRP		**1.7 WMD lower**[1] (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 1.40 (-8.27 to 5.47)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **HAQ:** Health Assessment Questionnaire**: VAS:** Visual analogue scale; **WMD:** weight mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] After 2 months treatment
[2] Poorly reported paper (See 'Risk of bias' table)
[3] Small sample size



188x196mm (300 x 300 DPI)

Supplement 1. Search Strategy

MEDLINE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. bechterew$ disease.tw.
9. or/1-8
10. bee venom$.tw.
11. bee sting.tw.
12. wasp venom$.tw.
13. bee venom acupuncture.tw.
14. bee venom therapy.tw.
15. bee sting therapy.tw.
16. apitoxin.tw.
17. apitherapy.tw.
18. or/10-17
19. 9 and 18

EMBASE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).tw.

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

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

#3 felty* NEAR/2 syndrome:ti,ab

#4 caplan* NEAR/2 syndrome:ti,ab

#6 sjogren* near/2 syndrome:ti,ab

#7 sicca near/2 syndrome:ti,ab

#8 still* next disease:ti,ab

#9 bechterew$ disease.tw.

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

#11 bee venom* :ti,ab

#12 bee sting :ti,ab

#13 wasp venom* :ti,ab

#14 bee venom acupuncture :ti,ab

#15 bee venom therapy:ti,ab

#16 bee sting therapy:ti,ab

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

#19 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 #10 AND #19

CINAHL (EBSCOhost)

S7 S3 and S6

S6 S4 or S5

S5 TI "apitoxin" or AB "apitoxin" or TI "apitherapy" or AB "apitherapy"

S4 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"

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

S3 S1 or S2

S2 TI "bechterew* disease" or AB "bechterew* disease" or TI (arthritis N2 rheumat*) or AB (arthritis N2 rheumat*)

S1 (MH "Arthritis, Rheumatoid+") or TI (felty* N2 syndrome) or AB (felty* N2 syndrome) or TI (caplan* N2 syndrome) or AB(caplan* N2 syndrome) or TI (rheumatoid nodule) or AB (rheumatoid nodule) or TI (sjogren* N2 syndrome) or AB (sjogren* N2 syndrome) or TI (sicca N2 syndrome) or AB (sicca N2 syndrome)

Supplement 2. Summary of randomized controlled trials of direct bee sting acupuncture for rheumatoid arthritis

First author (Year) country	Mean age (years); Duration of disease (years)	Experimental intervention (Regimen)	Control intervention (Regimen)	Primary outcome		Secondary outcome		Adverse Effects
				measurement	result	measurement	result	
Liu (2008) China	(A) 47.4±10.0; 5.0±3.0 (B) 48.3±9.4; 4.9±2.6	(A) BVA (Ashi points, dialectical acupoints, 8~15bees, n.r., once every other day for 3 months, n=50), plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, twice daily for 3 months, n=50)	(1) Total improvement score (2) Joint swelling score (3) Joint pain score	(1) RR, 1.22[1.01, 1.47], P=0.04 (2) MD, -0.24[-0.42,-0.06],P=0.010 (3) MD, -0.34[-0.37, -0.31], P<0.00001	(1) Number of Joint-swelling (2) RF (3) ESR	(1) MD, -0.46[-0.62, -0.30], P<0.00001 (2) MD, -7.74[-14.10, -1.38], P=0.02 (3) MD, -4.38[-6.28, -2.48], P<0.00001	Dizziness (B:4), fever(A:1), hypersensitivity(A:4), leukopenia(B:3), loss of appetite and nausea(B:6)
Zhang (2011) China	(A) 33.8; 3.6 (B) 32.2; 3.4	(A) BVA (Ashis points near the knee, 5~15bees, n.r., two or three times a week for 3months, n=23) plus (B)	(B) WM (Oral:MTX:7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, once daily for 3 months, n=23)	(1) Total improvement score (2) VAS (3) HSS	(1) RR, 1.17[0.91, 1.50] (2) MD, -1.00[-1.20, -0.80], P<0.00001 (3) MD, 3.37[3.24, 3.50], P<0.00001	(1) ESR (2) CRP	(1) MD, -4.20[-7.35, -1.05], P=0.009 (2) MD, -2.50[-5.56, 0.56], P=0.11	Dizziness(A:1), epigastric discomfort(A:4), fever(A:2), hypersensitivity(A:1), leukopenia(B:3), rash(A:3)
Deng (2011) China	n.r.	(A) BVA (Ashi points, dialectical acupoints, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time, n.r., three times a week for 2 months, n=20) plus (B)	(B) WM (Oral:MTX:10mg, once a week for 2 months, n=20) (C) WM (Oral: Prednisone Acetate:7.5mg, once daily for 2 months, n=20) plus (B)	(1) Total improvement score (2) Morning stiffness (3) Joint pain score (4) Joint swelling score	(1) - A vs. B RR, 1.46[1.04, 2.05], P=0.03 - A vs. C RR, 1.36[1.00, 1.84], P=0.05 (2) - A vs. B MD, -0.29[-0.42, -0.17], P<0.00001 - A vs. C MD, -0.11[-0.25, 0.02], P=0.05 (3) - A vs. B MD, -0.50[-0.64, -0.36], P<0.00001 - A vs. C MD, -0.13[-0.26, 0.00], P=0.05 (4) - A vs. B MD, -0.33[-0.47, -0.19], P<0.00001 - A vs. C MD, 0.05[-0.12, 0.21], P=0.56	(1) RF (2) ESR (3) CRP	(1) - A vs. B MD, -28.00[-37.21, -18.79], P<0.00001 - A vs. C MD, -14.30[-17.60, -11.00], P<0.00001 (2) - A vs. B MD, -18.60[-27.04,-10.16], P P<0.00001 - A vs. C MD, -8.10[-15.41, -0.79], P=0.03 (3) - A vs. B MD, -10.30[-12.46,-8.14], P<0.00001 - A vs. C MD, -3.70[-5.99,-1.41], P=0.002	Epigastric discomfort (C:6),hypersensitivity (A:3), insomnia(C:3), leukopenia(B:1), nausea(A:2,B:3)

Zhou (2012) China	(A) 37.86±14.15; 15.58±5.24 (B) 36.43±10.18; 13.95±5.21 (C) 40.66±14.01; 16.58±5.32	(A) BVA (Ashi points, acupoints near the pain point, 5~10bees, n.r., three times a week for 3 months, n=40) plus NSAIDS	(B) EA (Ashi points, LI15, LI14, LI11, LI 10, SJ5, BL36, SP10, BL40, GB34, ST36, GB39, DU14, BL52, DU3, BL32, 30min, three times a week y for 3 months, n=30) plus NSAIDS (C) WM (Oral:MTX:5-10mg, once a week for 3 months; Folic acid: 10mg, once a week for 3 months, n=30) plus NSAIDS	(1) Total improvement score	(1) - A vs. B RR, 1.23[0.97, 1.56], P=0.09 - A vs. C RR, 1.04[0.87, 1.24], P=0.67	(1) ESR (2) CRP	(1) - A vs. B MD, -13.70[-15.08, -12.32], P<0.00001 - A vs. C MD, -2.72[-6.54, 1.10] P=0.16 (2) - A vs. B MD, -9.18[-11.47, -6.89], P<0.00001 - A vs. C MD, 3.93[-0.07, 7.93], P=-0.05	n.r.

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; EA: electro acupuncture; ESR: erythrocyte sedimentation rate; HSS: hss knee score; HAQ: health assessment questionnaire; MTX: methotrexate; n.r.: not reported; NSAIDS: nonsteroidal anti-inflammatory drugs; RF: rheumatoid factor; SASP: sulfasalazine; VAS: visual analogue scale; TNF-α: tumor necrosis factor-alpha; WM: Western medicine

References

Deng M, Zhang WN. Clinical observation on 20 cases of bee needle therapy in the treatment of rheumatoid arthritis. Guiding J Tradit Chin Med Pharm 2011;17(6):71-73.

Liu XD, Zhang jl, Zheng HG, Li Z, D., Cai L, Liu FY, et al. Effect of bee-sting therapy on TNF-α and IL-1β in peripheral blood of rheumatoid arthritis patients. Chin Arch Tradit Chin Med 2008;26(5):996-97.

Zhang JL, Liu XD, Ye LH, Zhang P. Clinical padomized comparison study of bee-sting therapy for knee synovitis caused by rheumatoid arthritis. Chin Arch Tradit Chin Med 2011;29(8):1904-06.

Zhou YF, Li WY. Effect of needle on hypothalamic-pituitary-adrenal axis of patient with rheumatoid arthritis. Nei Mongol J Tradit Chin Med 2012;26(5):1-3.

Supplement 3. Summary of treatment direct bee sting acupuncture points and other information

First author (Year)	Type of acupuncture	Total treatment (sessions)	Main acupoints	Dialectical acupoints	Treatment Rationale	Adverse events
Liu (2008)	BVA (Live bee, 8~15bees)	3 months	Ashi points	Cold dampness invasion, joint pain: CV6, RN4; Hot and humid embodiment, joint swelling pain: LI11, GV14; Phlegm and blood stasis in the resistance, Joint deformities pain:ST40,GB39;	CM theory, Clinical experience	Hypersensitivity(4), fever(1)
Zhang (2011)	BVA (Live bee, 5~15bees)	3 months	Ashis points near knee	n.r.	CM theory, Clinical experience	Fever(2), hypersensitivity(1), rash(3)
Deng (2011)	BVA (Live bee, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time)	2 months	Ashi points	Ankle:BL62, KI6, BL60, GB40; back: GV26, V12, GV3; elbow: LI11, LI4, SJ10, SJ5, LU5; knee:ST35, ST34, GB34, GB33; Shoulders:LI16, SJ14, SI10; wrist:SJ4, SJ5 LI5, SI4	CM theory, Clinical experience	Hypersensitivity (3), nausea(2)
Zhou (2012)	BVA (Live bee, 5~10bees)	3 months	Ashi points, acupoints in near in the pain point	n.r.	CM theory, Clinical experience	n.r.
Lee (2003)	BVA (Injection, Bee venom extract diluted with saline to 1:3000, from 02.ml increase to 1.0ml)	2 months	Ashi points , acupoints near the inflammation point	Metacarpophalangeal joint, Distal interphalangeal joint, Proximal interphalangeal joint, wrist: SI5, SI5, TE4, L15 PC7; elbow:LI11, TE10, SI8, HT3, S18; shoulder: LI15, TE14; knee: ST36, GB34, SP9; ankle: GB40, BL62, SP5, K16	CM theory, Clinical experience	n.r

BVA: Bee Venom Acupuncture; CM: Chinese medicine; n.r.: not reported

References

Deng M, Zhang WN. Clinical observation on 20 cases of bee needle therapy in the treatment of rheumatoid arthritis. Guiding J Tradit Chin Med Pharm 2011;17(6):71-73.

Liu XD, Zhang jl, Zheng HG, Li Z, D., Cai L, Liu FY, et al. Effect of bee-sting therapy on TNF-α and IL-1β in peripheral blood of rheumatoid arthritis patients. Chin Arch Tradit Chin Med 2008;26(5):996-97.

Zhang JL, Liu XD, Ye LH, Zhang P. Clinical padomized comparison study of bee-sting therapy for knee synovitis caused by rheumatoid arthritis. Chin Arch Tradit Chin Med 2011;29(8):1904-06.

Zhou YF, Li WY. Effect of needle on hypothalamic-pituitary-adrenal axis of patient with rheumatoid arthritis. Nei Mongol J Tradit Chin Med 2012;26(5):1-3.

Supplement 4. Summary of non-randomized controlled trials of bee venom acupuncture for rheumatoid arthritis

Hwang 2001	
Methods	Design: case series
Participants	Country: South Korea Number of patients included(male / female): 15(4/11) Duration of disease (weeks): (A) < 4 (n=4), (B) 8~20 (n=2), (C) >24 (n=9) Follow-up: n.r
Intervention	BVA (Ashi points, acupoints near the inflammation point, two times a week)
Outcomes	1)VAS-pain, improvement index(score of after treatment-score of before treatment/ score of after treatment): (A) 0.80; (B) 0.68; (C) 0.51 2) Improvement of syptom(patient' assessement), Execellent(n=6); Good(n=7); Maderate(n=2)
Note	Treatment Rationale: Chines Medicine theory, Clinical experience Adverse effect: n.r. Funding: none Language: Korean Publication: full paper Withdrawal/dropouts: no

n.r: not reported

PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 1,2

PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	na

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	na
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	na
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	na
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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License statement

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 performed with a comprehensive search strategy and established 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 conducted independently by two authors.
- We used of the GRADE approach to assess confidence in estimates of effect
- We identified only one study so that we could not draw strong conclusions.

Abstract

Objective: To assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised controlled trials (RCTs).

Setting: We searched 14 databases up to March 2014 without a language restriction.

Participants: Patients with RA.

Intervention: BVA involved injecting purified, diluted BV into acupoints. We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone.

Primary outcome: Morning stiffness, pain and joint swelling

Secondary outcomes: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared to placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) but were not shown the improvement of morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of RA patients compared to placebo (normal saline injection) control. However, the number of trials, their quality, and the total sample size were too low to draw firm conclusions.

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 inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and ankylosis develop. The complex, systemic nature of the disease makes RA treatment complex and involving a variety of approaches. The major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and 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. Different forms of the therapy include the administration of honeybee stings, injections of BV, and BV acupuncture (BVA). [6]Bee venom acupuncture (BVA) involves injecting purified and 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 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 clinical settings.[7] [11] According to animal experiments, BV exhibits anti-arthritic, anti-inflammatory and analgesic effects attributable to the suppression of cyclooxygenase-2 and phospholipase A2

expression and a decrease in the levels of tumour necrosis factor alpha, interleukin (IL)-1, IL-6, nitric oxide and oxygen reactive species. It is also widely assumed that bioactive BV compounds including enzymes (phospholipase A2), peptides (melittin, adolapin, and apamin), and amines are associated with these actions. [7 8 12-14] However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic anti-arthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate. [15]

Why this review is important

Bee venom (BV) therapy or BV acupuncture (BVA) has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and rheumatoid arthritis (RA) in some Asian countries. [11]

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

Materials and Methods

The protocol of this SRs is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.[16]

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 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 the Century Journal Project), Wanfang and VIP. Further, we conducted 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). The strategy for searching the MEDLINE database is presented in Supplement 1. Similar search strategies were applied for the other databases.

Types of studies

All prospective randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

Patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form.

The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.[17] Our review used 'L', 'U', and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear, and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments,

incomplete outcome data, selective reporting and other sources of bias. [17]The quality of each trial was categorised into a low, unclear, or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% confidence intervals (CIs) to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were 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 contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed-effects or random-effects.

Unit of analysis issues

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

Addressing the missing data

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

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests were used to evaluate the heterogeneity of the included studies and I^2 >50 were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.[19] However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies. [19 20]

Results

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (Figure 1). Thirteen RCTs were among the excluded articles for the following reasons: Four RCTs, which were conducted in China, were excluded because the BVA were not made with purified, diluted bee venom but with live bee stings (Supplement 2 and 3). [21-24] Four RCTs employed herbal medicine as co-administrator,[25-28] 2 RCTs included herbal medicine as control treatment,[29 30] 1 RCT compared two different acupoints, [31] 1 RCT was not related RA,[32] and the other 1 RCT was duplicated publication.[33] The key data from the eligible RCT are summarised in Table 1. This trial was conducted in Korea.[34]

Risk of bias in the included studies

The RCT used [34] has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personal employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR, and CRP in RA patients.[34] Patients were randomised into two groups: one receiving BVA at ashi points and the other receiving normal saline injections at ashi points. After two months, the scores for morning stiffness, HAQ, pain on VAS, tender joint counts, swollen joint counts, ESR, and CRP were significantly better in the BVA group than in the placebo control group.

Adverse events

This trial did not assess adverse events related to BVA used for RA. [34]

Discussion

Only one trial testing the effects of BVA for RA is currently available.[34] There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of RA patients compared to placebo (normal saline injection) control subjects (Table 2). To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,[35] but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.[34] The use of placebo is essential for differentiating nonspecific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of bee venom, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an inappropriate placebo. BVA combines biochemical effects of the bee venom and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with BVA. BVA has uncomfortable sensations such as swelling and

burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a placebo, it is important to recruit patients who have not experienced BVA.

BVA can cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment. The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[36] Although trials are conducted safely, some problems remain in using BVA in clinical practice.

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one observational study that showed favourable effects of BVA for several symptoms of RA (Supplement 4).[37] However, this type of study, lacking in controls, was open to selection bias, which could lead to false-positive results.

The other type of BV therapy may be more commonly used when treating patients with RA. In considering this type of trial, we found 4 additional RCTs that compared live bee sting acupuncture combined with conventional drugs to conventional treatments alone for the treatment of RA symptoms.[21 23 24 38] Three RCTs [21 23 38] showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain, or joint swelling, while one RCT failed to do so.[24] Although these RCTs did not report serious adverse effects, [22 24 25 29] live bee stings can cause fatal adverse events including anaphylaxis. [39 40] Adverse events should be examined in future studies. The injection parts may be one issue for the assessment because it is very common to inject on the painful point (Ashi point) in RA patients. Even if we expand the inclusion criteria to this points, no further

studies were found.

One could question the validity of the conclusion by pointing to the review method used (reviewing a small number of trials with many limitations). However, reasons for doing a systematic review would be to answer question not posted by individual studies, to settle controversies arising from apparently conflicting studies, or to generate new hypotheses. [41] The systematic review with a small number of trials can be done.

In conclusion, currently, very few trials have tested the effects of BVA in the management of RA. Collectively, the evidence is insufficient to suggest that BVA is an effective therapy for RA. Further studies should be of high quality, with a particular emphasis on designing adequate and appropriate control groups.

Author Contributions

Conceived and designed the review: MSL and JAL. Extracted the data: JHJ, and MJS. Analyzed the data: MJS, JC and JIK. Wrote the paper: JAL, MJS, JC, JIK, and MSL. Searched and selected studies: JHJ, MJS, JC. Revised the paper: JAL, MSL. Monitored data collection: MSL.

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Conflict of interest

None

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Figure legend

Figure 1. Flow chart of trial selection process. CCT: case series trials; RCT: randomised controlled trials.

Table 1. Characteristics of included randomized controlled trials of bee venom acupuncture for rheumatoid arthritis

Lee 2003	
Methods	Design: prospective randomized controlled trial
Participants	Country: South Korea Number of patients included(completed / randomized): (A) 37/40 (B) 32/40 Mean age (years): (A) 49.2±9.6 (B) 47.3±8.9 Duration of disease (years): (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (Ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	*Primary outcomes:* 1) Morning stiffness, MD, -0.70[-2.00, 0.60], P<0.05 2) HAQ, MD, 0.00[-0.08, 0.08], P<0.05 3) VAS-pain, MD, -18.10[-23.71, -12.49], P<0.05 *Secondary outcomes:* 1) Tender joint count, MD, -1.30[-1.91, -0.69], P<0.0001 2) Swollen joint count, MD, -1.10[-1.72, -0.48], P=0.005 3) ESR, MD,20.10[-22.80,-17.40], P<0.00001 4) CRP, MD, -1.90[-2.86, -0.94], P=0.0001
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts:yes Intention-to-treat: No Author comment: These results suggests that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias

Item	Authors' judgement	Description
Random sequence generation (selection bias)	Unclear risk	Described as randomized but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 11 participants were not included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; CM: Chinese medicine; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; n.r.: not reported; RA: rheumatoid arthritis VAS: visual analogue scal

Table 2. Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis					
Patient or population: patients with rheumatoid arthritis **Settings:** Korea **Intervention:** Bee venom acupuncture vs. normal saline injection as placebo					
Outcomes	**Illustrative comparative risks* (95% CI)** **Assumed risk** **Control (Normal Saline injection)**	**Corresponding risk** **Bee venom acupuncture**	**No of Participants (studies)**	**Quality of the evidence (Grade)**	**Comments**
Pain (VAS)		**16.9 WMD lower**[1] (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -10.40 (-16.47 to -4.33)
Morning stiffness		**12.1 WMD higher**[1] (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -0.30 (-1.01 to 0.41)
Swollen joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.70 to -1.70)
Tender joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.73 to -1.73)
Quality of Life (HAQ)		**0.3 WMD higher**[1] (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.20 (-0.06 to 0.46)
ESR		**19.4 WMD lower**[1] (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -2.30 (-10.17 to 5.57)
CRP		**1.7 WMD lower**[1] (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 1.40 (-8.27 to 5.47)
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **HAQ:** Health Assessment Questionnaire**: VAS:** Visual analogue scale; **WMD:** weight mean difference					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					
[1] After 2 months treatment [2] Poorly reported paper (See 'Risk of bias' table) [3] Small sample size					

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Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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

Abstract

Objective: To assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised controlled trials (RCTs).

Setting: We searched 14 databases up to March 2014 without a language restriction.

Participants: Patients with RA.

Intervention: BVA involved injecting purified, diluted BV into acupoints. We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone.

Primary outcome: Morning stiffness, pain and joint swelling

Secondary outcomes: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared to placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) but were not shown the improvement of morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of RA patients compared to placebo (normal saline injection) control. However, the number of trials, their quality, and the total sample size were too low to draw firm conclusions.

Trial registration number: PROSPERO 2013: CRD42013005853

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 performed with a comprehensive search strategy and established 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 conducted independently by two authors.
- We used of the GRADE approach to assess confidence in estimates of effect
- We identified only one study so that we could not draw strong conclusions.

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and ankylosis develop. The complex, systemic nature of the disease makes RA treatment complex and involving a variety of approaches. The major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and 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. Different forms of the therapy include the administration of live bee stings, injections of BV, and BV acupuncture (BVA).[6] BVA involves injecting purified and 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 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 clinical settings.[7] [11] According to animal experiments, BV exhibits anti-arthritic, anti-inflammatory and analgesic effects attributable to the suppression of cyclooxygenase-2 and phospholipase A2 expression and a decrease in the levels of tumour necrosis factor alpha, interleukin (IL)-1, IL-

6, nitric oxide and oxygen reactive species. It is also widely assumed that bioactive BV compounds including enzymes (phospholipase A2), peptides (melittin, adolapin, and apamin), and amines are associated with these actions. [7 8 12-14] However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic anti-arthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate. [15]

Why this review is important

Bee venom (BV) therapy or BV acupuncture (BVA) has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and rheumatoid arthritis (RA) in some Asian countries. [11]

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

Materials and Methods

The protocol of this SRs is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.[16]

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 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 the Century Journal Project), Wanfang and VIP. Further, we conducted 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). The strategy for searching the MEDLINE database is presented in Supplement 1. Similar search strategies were applied for the other databases.

Types of studies

All prospective randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials

of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

Patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form. The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane

Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.[17] Our review used 'L', 'U', and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear, and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias. [17]The quality of each

trial was categorised into a low, unclear, or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% confidence intervals (CIs) to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were 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 contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed-effects or random-effects.

Unit of analysis issues

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

Addressing the missing data

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

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests were used to evaluate the heterogeneity of the included studies and I^2 >50 were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.[19] However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies. [19 20]

Results

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (Figure 1). Thirteen RCTs were among the excluded articles for the following reasons: Four RCTs, which were conducted in China, were excluded because the BVA were not made with purified, diluted bee venom but with live bee stings (Supplement 2 and 3). [21-24] Four RCTs employed herbal medicine as co-administrator,[25-28] 2 RCTs included herbal medicine as control treatment,[29 30] 1 RCT compared two different acupoints, [31] 1 RCT was not related RA,[32] and the other 1 RCT was duplicated publication.[33] The key data from the eligible RCT are summarised in Table 1. This trial was conducted in Korea.[34]

Risk of bias in the included studies

The RCT used [34] has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personal employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR, and CRP in RA patients.[34] Patients were randomised into two groups: one receiving BVA at ashi points and the other receiving normal saline injections at ashi points. After two months, the scores for morning stiffness, HAQ, pain on VAS, tender joint counts, swollen joint counts, ESR, and CRP were significantly better in the BVA group than in the placebo control group.

Adverse events

This trial did not assess adverse events related to BVA used for RA. [34]

Discussion

Only one trial testing the effects of BVA for RA is currently available.[34] There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of RA patients compared to placebo (normal saline injection) control subjects (Table 2). To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,[35] but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.[34] The use of placebo is essential for differentiating nonspecific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of bee venom, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an inappropriate placebo. BVA combines biochemical effects of the bee venom and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with BVA. BVA has uncomfortable sensations such as swelling and

burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a placebo, it is important to recruit patients who have not experienced BVA.

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one observational study that showed favourable effects of BVA for several symptoms of RA (Supplement 4).[36] However, this type of study, lacking in controls, was open to selection bias, which could lead to false-positive results.

Traditional bee venom acupuncture include live bee sting acupuncture. It may be more commonly used when treating patients with RA in China. In considering traditional BVA, we found 4 additional RCTs that compared live bee sting acupuncture combined with conventional drugs to conventional treatments alone for the treatment of RA symptoms. [21-24] Three RCTs [21-23] showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain, or joint swelling, while one RCT failed to do so.[24] These RCTs did not report serious adverse effects.

Both BVA (diluted or purified) and live bee stings can also cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment. [37-39] The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[36-40] No studies were done comparing the occurrence of adverse events between traditional live bee sting acupuncture and BVA. Although trials are conducted safely, some problems remain in using BVA in clinical practice.

The injection parts may be one issue for the assessment. Although it is very common to inject on the painful point (Ashi point) in RA patients, we excluded studies used Ashi points only because of assessing the evidence of efficacy of bee venom on acupoint. Even if we expand the inclusion criteria to this points, no further studies were found. However, many trials used acupoints with painful point. Further comparative studies are needed for finding the difference of effects of BVA on acupoints and painful points.

One could question the validity of the conclusion by pointing to the review method used (reviewing a small number of trials with many limitations). However, reasons for doing a systematic review would be to answer question not posted by individual studies, to settle controversies arising from apparently conflicting studies, or to generate new hypotheses.[41] The systematic review with a small number of trials can be done.

In conclusion, currently, very few trials have tested the effects of BVA in the management of RA. Collectively, the evidence is insufficient to suggest that BVA is an effective therapy for RA. Further studies should be of high quality, with a particular emphasis on designing adequate and appropriate control groups.

Author Contributions

Conceived and designed the review: MSL and JAL. Extracted the data: JHJ, and MJS. Analyzed the data: MJS, JC and JIK. Wrote the paper: JAL, MJS, JC, JIK, and MSL. Searched and selected studies: JHJ, MJS, JC. Revised the paper: JAL, MSL. Monitored data collection: MSL.

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Conflict of interest

None

Data Sharing Statement

No additional data available

Figure legend

Figure 1. Flow chart of trial selection process. CCT: case series trials; RCT: randomised controlled trials.

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Table 1. Characteristics of included randomised controlled trials of bee venom acupuncture for rheumatoid arthritis

Lee 2003	
Methods	Design: prospective randomised controlled trial
Participants	Country: South Korea Number of patients included(completed / randomised): (A) 37/40 (B) 32/40 Mean age (years): (A) 49.2±9.6 (B) 47.3±8.9 Duration of disease (years): (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (Ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	*Primary outcomes:* 1) Morning stiffness, MD, -0.70[-2.00, 0.60], P<0.05 2) HAQ, MD, 0.00[-0.08, 0.08], P<0.05 3) VAS-pain, MD, -18.10[-23.71, -12.49], P<0.05 *Secondary outcomes:* 1) Tender joint count, MD, -1.30[-1.91, -0.69], P<0.0001 2) Swollen joint count, MD, -1.10[-1.72, -0.48], P=0.005 3) ESR, MD,20.10[-22.80,-17.40], P<0.00001 4) CRP, MD, -1.90[-2.86, -0.94], P=0.0001
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts:yes Intention-to-treat: No Author comment: These results suggests that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias		
Item	**Authors' judgement**	**Description**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 11 participants were not included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA: Bee venom acupuncture; CRP: C - reactive protein; CM: Chinese medicine; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; n.r.: not reported; RA: rheumatoid arthritis VAS: visual analogue scale

Table 2. Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis					
Patient or population: patients with rheumatoid arthritis **Settings:** Korea **Intervention:** Bee venom acupuncture vs. normal saline injection as placebo					
Outcomes	**Illustrative comparative risks* (95% CI)**		**No of Participants (studies)**	**Quality of the evidence (Grade)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Control (Normal Saline injection)	**Bee venom acupuncture**			
Pain (VAS)		**16.9 WMD lower**[1] (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -10.40 (-16.47 to -4.33)
Morning stiffness		**12.1 WMD higher**[1] (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -0.30 (-1.01 to 0.41)
Swollen joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.70 to -1.70)
Tender joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.73 to -1.73)
Quality of Life (HAQ)		**0.3 WMD higher**[1] (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.20 (-0.06 to 0.46)
ESR		**19.4 WMD lower**[1] (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -2.30 (-10.17 to 5.57)
CRP		**1.7 WMD lower**[1] (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 1.40 (-8.27 to 5.47)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **HAQ:** Health Assessment Questionnaire**: VAS:** Visual analogue scale; **WMD:** weight mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] After 2 months treatment
[2] Poorly reported paper (See 'Risk of bias' table)
[3] Small sample size

Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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License statement

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 performed with a comprehensive search strategy and established 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 conducted independently by two authors.
- We used of the GRADE approach to assess confidence in estimates of effect
- We identified only one study so that we could not draw strong conclusions.

Abstract

Objective: To assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised controlled trials (RCTs).

Setting: We searched 14 databases up to March 2014 without a language restriction.

Participants: Patients with RA.

Intervention: BVA involved injecting purified, diluted BV into acupoints. We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone.

Primary outcome: Morning stiffness, pain and joint swelling

Secondary outcomes: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared to placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) but were not shown the improvement of morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of RA patients compared to placebo (normal saline injection) control. However, the number of trials, their quality, and the total sample size were too low to draw firm conclusions.

Trial registration number: PROSPERO 2013: CRD42013005853

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

Introduction

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and ankylosis develop. The complex, systemic nature of the disease makes RA treatment complex and involving a variety of approaches. The major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and 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. Different forms of the therapy include the administration of ~~honeybee~~live bee stings, injections of BV, and BV acupuncture (BVA~~).)~~.[6] ~~Bee venom acupuncture (~~ BVA~~)~~ involves injecting purified and diluted bee venom into acupoints. [7]

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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 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 clinical settings.[7] [11] According to animal experiments, BV exhibits anti-arthritic, anti-inflammatory and analgesic effects attributable to the suppression of cyclooxygenase-2 and phospholipase A2

expression and a decrease in the levels of tumour necrosis factor alpha, interleukin (IL)-1, IL-6, nitric oxide and oxygen reactive species. It is also widely assumed that bioactive BV compounds including enzymes (phospholipase A2), peptides (melittin, adolapin, and apamin), and amines are associated with these actions. [7 8 12-14] However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic anti-arthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate. [15]

Why this review is important

Bee venom (BV) therapy or BV acupuncture (BVA) has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and rheumatoid arthritis (RA) in some Asian countries. [11]

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

Materials and Methods

The protocol of this SRs is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.[16]

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 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 the Century Journal Project), Wanfang and VIP. Further, we conducted 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). The strategy for searching the MEDLINE database is presented in Supplement 1. Similar search strategies were applied for the other databases.

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Types of studies

All prospective randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

Patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form.

The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane Handbook version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.[17] Our review used 'L', 'U', and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear, and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

Data collection and synthesis

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a predefined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by e-mail or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, version 5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments,

incomplete outcome data, selective reporting and other sources of bias. [17]The quality of each trial was categorised into a low, unclear, or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% confidence intervals (CIs) to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were 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 contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed-effects or random-effects.

Unit of analysis issues

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

Addressing the missing data

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

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. Chi-squared and I-squared tests were used to evaluate the heterogeneity of the included studies and I^2 >50 were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes. [18]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.[19] However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies. [19 20]

Results

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (Figure 1). Thirteen RCTs were among the excluded articles for the following reasons: Four RCTs, which were conducted in China, were excluded because the BVA were not made with purified, diluted bee venom but with live bee stings (Supplement 2 and 3).[21-24] Four RCTs employed herbal medicine as co-administrator,[25-28] 2 RCTs included herbal medicine as control treatment,[29 30] 1 RCT compared two different acupoints,[31] 1 RCT was not related RA,[32] and the other 1 RCT was duplicated publication.[33] The key data from the eligible RCT are summarised in Table 1. This trial was conducted in Korea.[34]

Risk of bias in the included studies

The RCT used [34] has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personal employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR, and CRP in RA patients.[34] Patients were randomised into two groups: one receiving BVA at ashi points and the other receiving normal saline injections at ashi points. After two months, the scores for morning stiffness, HAQ, pain on VAS, tender joint counts, swollen joint counts, ESR, and CRP were significantly better in the BVA group than in the placebo control group.

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Adverse events

This trial did not assess adverse events related to BVA used for RA. [34]

Discussion

Only one trial testing the effects of BVA for RA is currently available.[34] There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of RA patients compared to placebo (normal saline injection) control subjects (Table 2). To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

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This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,[35] but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.[34] The use of placebo is essential for differentiating nonspecific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of bee venom, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an inappropriate placebo. BVA combines biochemical effects of the bee venom and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with BVA. BVA has uncomfortable sensations such as swelling and

burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a placebo, it is important to recruit patients who have not experienced BVA.

~~BVA can cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment. The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[36] Although trials are conducted safely, some problems remain in using BVA in clinical practice.~~

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one observational study that showed favourable effects of BVA for several symptoms of RA (Supplement 4).~~[37]~~[36] However, this type of study, lacking in controls, was open to selection bias, which could lead to false-positive results.

~~The other type of BV therapy~~Traditional bee venom acupuncture include live bee sting acupuncture. It may be more commonly used when treating patients with RA in China. In considering ~~this type of trial~~traditional BVA, we found 4 additional RCTs that compared live bee sting acupuncture combined with conventional drugs to conventional treatments alone for the treatment of RA symptoms.~~[21 23 24 38]~~ [21-24] Three RCTs ~~[21 23 38]~~[21-23] showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain, or joint swelling, while one RCT failed to do so.[24] ~~Although these~~ These RCTs did not report serious adverse effects.~~[22 24 25 29]~~

Both BVA (diluted or purified) and live bee stings can ~~cause fatal~~ also cause diverse clinical

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responses depending on the amount of venom used and the frequency and duration of the treatment. [37-39] The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.[36-40] No studies were done comparing the occurrence of adverse events ~~including anaphylaxis.[39-40] Adverse events should be examined in future studies.~~ between traditional live bee sting acupuncture and BVA. Although trials are conducted safely, some problems remain in using BVA in clinical practice.

The injection parts may be one issue for the assessment ~~because~~. Although it is very common to inject on the painful point (Ashi point) in RA patients, we excluded studies used Ashi points only because of assessing the evidence of efficacy of bee venom on acupoint. Even if we expand the inclusion criteria to this points, no further studies were found. However, many trials used acupoints with painful point. Further comparative studies are needed for finding the difference of effects of BVA on acupoints and painful points.

One could question the validity of the conclusion by pointing to the review method used (reviewing a small number of trials with many limitations). However, reasons for doing a systematic review would be to answer question not posted by individual studies, to settle controversies arising from apparently conflicting studies, or to generate new hypotheses. [41] The systematic review with a small number of trials can be done.

In conclusion, currently, very few trials have tested the effects of BVA in the management of RA. Collectively, the evidence is insufficient to suggest that BVA is an effective therapy for RA. Further studies should be of high quality, with a particular emphasis on designing adequate and appropriate control groups.

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Author Contributions

Conceived and designed the review: MSL and JAL. Extracted the data: JHJ, and MJS. Analyzed the data: MJS, JC and JIK. Wrote the paper: JAL, MJS, JC, JIK, and MSL. Searched and selected studies: JHJ, MJS, JC. Revised the paper: JAL, MSL. Monitored data collection: MSL.

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Conflict of interest

None

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Figure legend

Figure 1. Flow chart of trial selection process. CCT: case series trials; RCT: randomised controlled trials.

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Table 1. Characteristics of included randomized controlled trials of bee venom acupuncture for rheumatoid arthritis

Lee 2003	
Methods	Design: prospective randomized controlled trial
Participants	Country: South Korea Number of patients included(completed / randomized): (A) 37/40 (B) 32/40 Mean age (years): (A) 49.2±9.6 (B) 47.3±8.9 Duration of disease (years): (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (Ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	*Primary outcomes:* 1) Morning stiffness, MD, -0.70[-2.00, 0.60], P<0.05 2) HAQ, MD, 0.00[-0.08, 0.08], P<0.05 3) VAS-pain, MD, -18.10[-23.71, -12.49], P<0.05 *Secondary outcomes:* 1) Tender joint count, MD, -1.30[-1.91, -0.69], P<0.0001 2) Swollen joint count, MD, -1.10[-1.72, -0.48], P=0.005 3) ESR, MD,20.10[-22.80,-17.40], P<0.00001 4) CRP, MD, -1.90[-2.86, -0.94], P=0.0001
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts:yes Intention-to-treat: No Author comment: These results suggests that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias		
Item	**Authors' judgement**	**Description**
Random sequence generation (selection bias)	Unclear risk	Described as randomized but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 11 participants were not included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA: Bee Venom Acupuncture; CRP: C - reactive protein; CM: Chinese medicine; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; n.r.: not reported; RA: rheumatoid arthritis VAS: visual analogue scal

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Table 2. Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis					
Patient or population: patients with rheumatoid arthritis **Settings:** Korea **Intervention:** Bee venom acupuncture vs. normal saline injection as placebo					
Outcomes	**Illustrative comparative risks* (95% CI)**		**No of Participants (studies)**	**Quality of the evidence (Grade)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Control (Normal Saline injection)	**Bee venom acupuncture**			
Pain (VAS)		**16.9 WMD lower**[1] (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -10.40 (-16.47 to -4.33)
Morning stiffness		**12.1 WMD higher**[1] (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -0.30 (-1.01 to 0.41)
Swollen joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.70 to -1.70)
Tender joint count		**0.9 WMD lower**[1] (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.50 (-0.73 to -1.73)
Quality of Life (HAQ)		**0.3 WMD higher**[1] (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 0.20 (-0.06 to 0.46)
ESR		**19.4 WMD lower**[1] (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** -2.30 (-10.17 to 5.57)
CRP		**1.7 WMD lower**[1] (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊖⊖ **low**[2,3]	**After 1 month** 1.40 (-8.27 to 5.47)
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **HAQ:** Health Assessment Questionnaire**: VAS:** Visual analogue scale; **WMD:** weight mean difference					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					
[1] After 2 months treatment [2] Poorly reported paper (See 'Risk of bias' table) [3] Small sample size					

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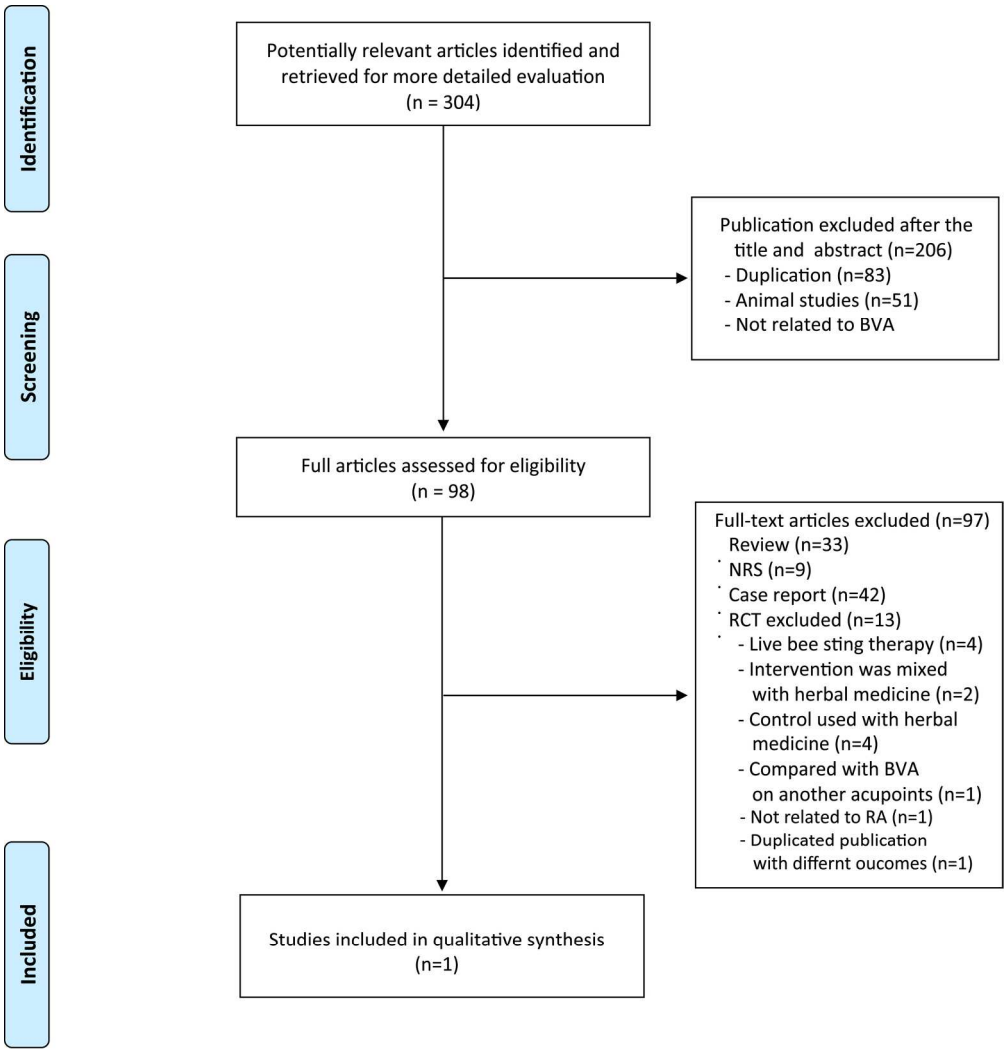

188x196mm (300 x 300 DPI)

Supplement 1. Search Strategy

MEDLINE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. (sjogren$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still$ disease.tw.
8. bechterew$ disease.tw.
9. or/1-8
10. bee venom$.tw.
11. bee sting.tw.
12. wasp venom$.tw.
13. bee venom acupuncture.tw.
14. bee venom therapy.tw.
15. bee sting therapy.tw.
16. apitoxin.tw.
17. apitherapy.tw.
18. or/10-17
19. 9 and 18

EMBASE

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).tw.

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

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

#3 felty* NEAR/2 syndrome:ti,ab

#4 caplan* NEAR/2 syndrome:ti,ab

#6 sjogren* near/2 syndrome:ti,ab

#7 sicca near/2 syndrome:ti,ab

#8 still* next disease:ti,ab

#9 bechterew$ disease.tw.

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

#11 bee venom* :ti,ab

#12 bee sting :ti,ab

#13 wasp venom* :ti,ab

#14 bee venom acupuncture :ti,ab

#15 bee venom therapy:ti,ab

#16 bee sting therapy:ti,ab

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

#19 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 #10 AND #19

CINAHL (EBSCOhost)

S7 S3 and S6

S6 S4 or S5

S5 TI “apitoxin” or AB “apitoxin” or TI “apitherapy” or AB “apitherapy”

S4 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”

#17 apitoxin:ti,ab

#18 apitherapy:ti,ab

S3 S1 or S2

S2 TI “bechterew* disease” or AB “bechterew* disease” or TI (arthritis N2 rheumat*) or AB (arthritis N2 rheumat*)

S1 (MH “Arthritis, Rheumatoid+”) or TI (felty* N2 syndrome) or AB (felty* N2 syndrome) or TI (caplan* N2 syndrome) or AB(caplan* N2 syndrome) or TI (rheumatoid nodule) or AB (rheumatoid nodule) or TI (sjogren* N2 syndrome) or AB (sjogren* N2 syndrome) or TI (sicca N2 syndrome) or AB (sicca N2 syndrome)

Supplement 2. Summary of randomised controlled trials of bee sting therapy on acupoints for rheumatoid arthritis

First author (Year)	Mean age (yr); Duration of disease (yrs)	Experimental intervention (Regimen)	Control intervention (Regimen)	Primary outcome		Secondary outcome	
				measurement	result	measurement	result
Liu (2008)	(A) 47.4; 5.0 (B) 48.3; 4.9	(A) Bee sting therapy (Ashi points, dialectical acupoints, 8-15bees, n.r., once every other day for 3 months, n=50), plus (B)	(B) WM (Oral: MTX: 7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, twice daily for 3 months, n=50)	(1) Total improvement score (2) Joint swelling score (3) Joint pain score	(1) RR, 1.22[1.01, 1.47], P=0.04 (2) MD, -0.24[-0.42,-0.06],P=0.010 (3) MD, -0.34[-0.37, -0.31], P<0.00001	(1) Number of Joint-swelling (2) RF (3) ESR	(1) MD, -0.46[-0.62, -0.30], P<0.00001 (2) MD, -7.74[-14.10, -1.38], P=0.02 (3) MD, -4.38[-6.28, -2.48], P<0.00001
Zhang (2011) China	(A) 33.8; 3.6 (B) 32.2; 3.4	(A) Bee sting therapy (Ashis points near the knee, 5-15bees, n.r., two or three times a week for 3months, n=23), plus (B)	(B) WM (Oral: MTX: 7.5mg, once a week for 3 months; SASP:0.5g, third daily for 3 months; Meloxicam:7.5mg, once daily for 3 months, n=23)	(1) Total improvement score (2) VAS (3) HSS	(1) RR, 1.17[0.91, 1.50] (2) MD, -1.00[-1.20, -0.80], P<0.00001 (3) MD, 3.37[3.24, 3.50], P<0.00001	(1) ESR (2) CRP	(1) MD, -4.20[-7.35, -1.05], P=0.009 (2) MD, -2.50[-5.56, 0.56], P=0.11
Deng (2011) China	n.r.	(A) Bee sting therapy (Ashi points, dialectical acupoints, before 15-25d: 2~3bees; after 15-25d: 1~3bees increase every time, n.r., three times a week for 2 months, n=20), plus (B)	(B) WM (Oral: MTX: 10mg, once a week for 2 months, n=20) (C) WM (Oral: Prednisone Acetate:7.5mg, once daily for 2 months, n=20) plus (B)	(1) Total improvement score (2) Morning stiffness (3) Joint pain score (4) Joint swelling score	(1) A vs. B: RR, 1.46[1.04, 2.05], P=0.03; A vs. C: RR, 1.36[1.00, 1.84], P=0.05 (2) A vs. B: MD, -0.29 [-0.42, -0.17], P<0.00001; A vs. C: MD, -0.11[-0.25, 0.02], P=0.05 (3) A vs. B: MD, -0.50 [-0.64, -0.36], P<0.00001; A vs. C: MD, -0.13[-0.26, 0.00], P=0.05 (4) A vs. B: MD, -0.33[-0.47, -0.19], P<0.00001; A vs. C: MD, 0.05[-0.12, 0.21], P=0.56	(1) RF (2) ESR (3) CRP	(1) A vs. B: MD, -28.00[-37.21, -18.79], P<0.00001; A vs. C: MD, -14.30[-17.60, -11.00], P<0.00001 (2) A vs. B: MD, -18.60 [-27.04,-10.16], P P<0.00001; A vs. C: MD, -8.10[-15.41, -0.79], P=0.03 (3) A vs. B: MD, -10.30 [-12.46,-8.14], P<0.00001; A vs. C: MD, -3.70[-5.99,-1.41], P=0.002
Zhou (2012) China	(A) 37.9; 15.6 (B) 36.4; 14.0 (C) 40.7; 16.6	(A) Bee sting therapy (Ashi points, acupoints near the pain point, 5~10bees, n.r., three times a week for 3 months, n=40) plus NSAIDS	(B) EA (30min, three times a week y for 3 months, n=30) plus NSAIDS (C) WM (Oral:MTX:5-10mg, once a week for 3 months; Folic acid: 10mg, once a week for 3 months, n=30) plus NSAIDS	Total improvement score	A vs. B: RR, 1.23[0.97, 1.56], P=0.09; A vs. C: RR, 1.04 [0.87, 1.24], P=0.67	(1) ESR (2) CRP	(1) A vs. B: MD, -13.70[-15.08, -12.32], P<0.00001; A vs. C: MD, -2.72[-6.54, 1.10] P=0.16 (2) A vs. B: MD, -9.18[-11.47, -6.89], P<0.00001; A vs. C: MD, 3.93[-0.07, 7.93], P= 0.05

CRP: C - reactive protein; EA: electro acupuncture; ESR: erythrocyte sedimentation rate; HSS: hss knee score; HAQ: health assessment questionnaire; MTX: methotrexate; n.r.: not reported; NSAIDS: nonsteroidal anti-inflammatory drugs; RF: rheumatoid factor; SASP: sulfasalazine; VAS: visual analogue scale; TNF-α: tumor necrosis factor-alpha; WM: Western medicine

References

Deng M, Zhang WN. Clinical observation on 20 cases of bee needle therapy in the treatment of rheumatoid arthritis. Guiding J Tradit Chin Med Pharm 2011;17(6):71-73.
Liu XD, Zhang jl, Zheng HG, Li Z, D., Cai L, Liu FY, et al. Effect of bee-sting therapy on TNF-α and IL-1β in peripheral blood of rheumatoid arthritis patients. Chin Arch Tradit Chin Med 2008;26(5):996-97.
Zhang JL, Liu XD, Ye LH, Zhang P. Clinical randomized comparison study of bee-sting therapy for knee synovitis caused by rheumatoid arthritis. Chin Arch Tradit Chin Med 2011;29(8):1904-06.
Zhou YF, Li WY. Effect of needle on hypothalamic-pituitary-adrenal axis of patient with rheumatoid arthritis. Nei Mongol J Tradit Chin Med 2012;26(5):1-3.

Supplement 3. Summary of treatment bee sting therapy on acupoints for rheumatoid arthritis

First author (Year)	Type of acupuncture	Total treatment (sessions)	Main acupoints	Dialectical acupoints	Treatment Rationale	Adverse events
Liu (2008)	Bee sting therapy (Live bee, 8-15bees)	3 months	Ashi points	Cold dampness invasion, joint pain: CV6, RN4; Hot and humid embodiment, joint swelling pain: LI11, GV14; Phlegm and blood stasis in the resistance, Joint deformities pain:ST40,GB39	CM theory, Clinical experience	Dizziness (B:4), fever(A:1), hypersensitivity(A:4), leukopenia(B:3), loss of appetite and nausea(B:6)
Zhang (2011)	Bee sting therapy (Live bee, 5-15bees)	3 months	Ashis points near knee	n.r.	CM theory, Clinical experience	Dizziness(A:1), epigastric discomfort(A:4), fever(A:2), hypersensitivity(A:1), leukopenia(B:3), rash(A:3)
Deng (2011)	Bee sting therapy (Live bee, before 15-25days: 2-3bees; after 15-25days: 1-3bees increase every time)	2 months	Ashi points	Ankle:BL62, KI6, BL60, GB40; back: GV26, V12, GV3; elbow: LI11, LI4, SJ10, SJ5, LU5; knee:ST35, ST34, GB34, GB33; Shoulders:LI16, SJ14, SI10; wrist:SJ4, SJ5 LI5, SI4	CM theory, Clinical experience	Epigastric discomfort (C:6),hypersensitivity (A:3), insomnia(C:3), leukopenia(B:1), nausea(A:2,B:3)
Zhou (2012)	Bee sting therapy (Live bee, 5-10bees)	3 months	Ashi points, acupoints in near in the pain point	n.r.	CM theory, Clinical experience	n.r.

CM: Chinese medicine; n.r.: not reported

References

Deng M, Zhang WN. Clinical observation on 20 cases of bee needle therapy in the treatment of rheumatoid arthritis. Guiding J Tradit Chin Med Pharm 2011;17(6):71-73.

Liu XD, Zhang jl, Zheng HG, Li Z, D., Cai L, Liu FY, et al. Effect of bee-sting therapy on TNF-α and IL-1β in peripheral blood of rheumatoid arthritis patients. Chin Arch Tradit Chin Med 2008;26(5):996-97.

Zhang JL, Liu XD, Ye LH, Zhang P. Clinical randomized comparison study of bee-sting therapy for knee synovitis caused by rheumatoid arthritis. Chin Arch Tradit Chin Med 2011;29(8):1904-06.

Zhou YF, Li WY. Effect of needle on hypothalamic-pituitary-adrenal axis of patient with rheumatoid arthritis. Nei Mongol J Tradit Chin Med 2012;26(5):1-3.

Supplement 4. Summary of non-randomized controlled trials of Bee Venom acupuncture for rheumatoid arthritis

Hwang 2001	
Methods	Design: case series trial
Participants	Country: South Korea Number of patients included(male / female): 15(4/11) Duration of disease (weeks): (A) < 4 (n=4), (B) 8-20 (n=2), (C) >24 (n=9) Follow-up: n.r
Intervention	BVA (Ashi points, acupoints near the inflammation point, two times a week)
Outcomes	1) Pain (VAS), improvement index (score of after treatment-score of before treatment/ score of after treatment). (A) 0.80; (B)0.68; (C) 0.51 2) Improvement of symptom (patient' assessment), Excellent (n=6); Good (n=7); Moderate (n=2)
Note	Treatment Rationale: CM theory, Clinical experience Adverse effect: n.r. Funding: none Language: Korean Publication: full paper Withdrawal/dropouts: no

n.r: not reported; VAS: visual analogue scale

Reference

Hwang YJ, Lee BC. Clinical study of anaphylaxis on bee-venom acupuncture. J Korean Acupunct Mox Soc 2000;17(4):149-59.

PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 1,2

PRISMA 2009 Checklist: Bee venom acupuncture for rheumatoid arthritis: A systematic review of randomised clinical trials

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	na

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	na
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	na
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	na
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17