

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials
AUTHORS	Lee, Ju Ah; Son, Mi-Ju; Choi, Jiae; Jun, Ji Hee; Kim, Jong-In; Lee, Myeong Soo

VERSION 1 - REVIEW

REVIEWER	Bing Zhu Institute of Acupuncture and Moxibustion, CACMS
REVIEW RETURNED	09-Aug-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Yutong Fei Beijing University of Chinese Medicine. China
REVIEW RETURNED	22-Aug-2014

GENERAL COMMENTS	<p>This review did thorough literature searching, and conducted rigorously. But there were several points I would like to discuss with the authors.</p> <p>1. In the inclusion criteria- study types. It was stated "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." But since the condition was rheumatoid arthritis, it was very common to inject on the painful point (Ashi point). So I would like to suggest keep those trials in. And as to trials only with immunological or biological parameters, why you exclude them?</p> <p>2. In the flow chart on page 24. It was listed that live bee sting therapy was excluded. Live bee sting therapy was the most traditional type of bee venom therapy. I would like to suggest to include them but analyze separately. In the last sentence of the main text, it was stated "Although these RCTs did not report serious adverse effects, live bee stings can cause fatal adverse events including anaphylaxis.^{22 24 25 29}". Reference 22, 24, 25, 29 was the four trials found and excluded by this review. I searched database and found those four articles and read through them. I didn't find any evidence that they suggest or indicate "live bee stings can cause fatal adverse events including anaphylaxis". If the last sentence could be stated in the review, please give proper reference. Thank you!</p>
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REVIEWER	Hoyeon Go Semyung Univeristy, Korea
REVIEW RETURNED	15-Sep-2014

GENERAL COMMENTS	<p>The strength of this review is follow the proper procedure for assessment of evidence of bee venom acupuncture therapy including registering to PROSPERO, publishing the protocol before full review. The main limitation is the evidence is come from one study. But it is common in the field of EBM. However, there are some revisions are needed.</p> <ol style="list-style-type: none"> 1. In the main text, the conclusion part is missing. Please add the final conclusion for this review. 2. The author noted one non-randomized controlled trial was founded. Please add the detailed information as supplement for giving information to researchers. 3. In addition to this, the information of excluded 13 RCTs may be helpful for future studies. Please consider to add these table as supplement with citation information. 4. This review included one trial and assessed the evidence from it. Please add meaning of the systematic review with small included trials.
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VERSION 1 – AUTHOR RESPONSE

Comment 1) In the inclusion criteria- study types. It was stated "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." But since the condition was rheumatoid arthritis, it was very common to inject on the painful point (Ashi point). So I would like to suggest keep those trials in. And as to trials only with immunological or biological parameters, why you exclude them?

Revision> Thank you for your valuable comments. We excluded trial of BV injections into ashi points 'only'. The protocol was already published and we cannot change it. However, we have discussed it in the discussion section (page 15, last paragraph, line 1-3 from the bottoms).

And we regarded improvement of symptom as primary outcome. Therefore, we excluded if only immunological or biological parameters were assessed.

Comment 2) In the flow chart on page 24. It was listed that live bee sting therapy was excluded. Live bee sting therapy was the most traditional type of bee venom therapy. I would like to suggest to include them but analyze seperately. In the last sentence of the main text, it was stated "Although these RCTs did not report serious adverse effects, live bee stings can cause fatal adverse events including anaphylaxis.22 24 25 29". Reference 22, 24, 25, 29 was the four trials found and excluded by this review. I searched database and found those four articles and read through them. I didn't find any evidence that they suggest or indicate "live bee stings can cause fatal adverse events including anaphylaxis". If the last sentence could be stated in the review, please give proper reference. Thank you!

Revision> This review was done follow the protocol. We discussed this modality in the results and discussion section (page 12, 1st paragraph, lines 4-6, supplement 1). In addition to this, we also showed the detail information in the supplement 1. We have also corrected the sentences and references in the discussion (page 15, last paragraph, lines 3-5).

Reviewer 2.

The strength of this review is follow the proper procedure for assessment of evidence of bee venom acupuncture therapy including registering to PROSPERO, publishing the protocol before full review. The main limitation is the evidence is come from one study. But it is common in the field of EBM. However, there are some revisions are needed.

Comment 1) In the main text, the conclusion part is missing. Please add the final conclusion for this review.

Revised> We have now added final conclusion.

Comment 2)The author noted one non-randomized controlled trial was founded. Please add the detailed information as supplement for giving information to researchers.

Revised> We have added the detailed information as supplement table.

Comment 3) In addition to this, the information of excluded 13 RCTs may be helpful for future studies. Please consider to add these table as supplement with citation information.

Revised> We have now added the citation information in the results section (page 12, 1st paragraph).

Comment 4) This review included one trial and assessed the evidence from it. Please add meaning of the systematic review with small included trials.

Revised> We have now discussed this points (page 16, 1st paragraph)

VERSION 2 – REVIEW

REVIEWER	Yutong Fei Beijing University of Chinese Medicine
REVIEW RETURNED	04-Oct-2014

GENERAL COMMENTS	<p>Thank you for your careful revision! But I still have two points to discuss with you.</p> <p>1. The authors addressed that "This systematic review aims to analyse the trial data on the effects of bee venom acupuncture for rheumatoid arthritis", but the most traditional type of bee venom acupuncture (live bee sting) was excluded because of risk of fatal adverse reaction. Only BVA involved injecting purified, diluted BV into acupoints were included. After the first review, the author provided two Korean literature from one research group as proof that live bee venom could be fatal. As long as I know, purified bee venom injection could also cause allergic reaction. Please provide reference to show that compared to live bee sting, purified, diluted BV was safer.</p> <p>2. In the review, trials used only Ashi points were excluded in the exclusion criteria. In the first review, it was suggested that such trials be included. In the revised paper, the author addressed in the discussion part "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." I think whether we should or should not include such trials should not depend on whether we could or could not find such trials.</p>
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REVIEWER	Ho-Yeon Go College of Korean Medicine, Semyung University Republic of Korea
REVIEW RETURNED	25-Sep-2014

- The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Comment 1) The authors addressed that "This systematic review aims to analyse the trial data on the effects of bee venom acupuncture for rheumatoid arthritis", but the most traditional type of bee venom acupuncture (live bee sting) was excluded because of risk of fatal adverse reaction. Only BVA involved injecting purified, diluted BV into acupoints were included. After the first review, the author provided two Korean literature from one research group as proof that live bee venom could be fatal. As long as I know, purified bee venom injection could also cause allergic reaction. Please provide reference to show that compared to live bee sting, purified, diluted BV was safer.

Revision> We have now revised the sentences with more discussion.

Comment 2) In the review, trials used only Ashi points were excluded in the exclusion criteria. In the first review, it was suggested that such trials be included. In the revised paper, the author addressed in the discussion part "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." I think whether we should or should not include such trials should not depend on whether we could or could not find such trials.

Revision> We excluded the trials using Ashi point only. However, we found our mistake to add this in both inclusion and exclusion criteria. We did not excluded it because there was no trial. We've clarified this in details and revised the discussion according to that.

Thank you for your valuable comments.