ABSTRACT

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

Methods and analysis: The following 14 databases will be searched from their inception to March 2014: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, six Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database and DBPIA) and three Chinese databases including CNKI (China National Knowledge Infrastructure), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

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

Trial registration number: PROSPERO 2013: CRD42013005853

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 disability2 3 and has a significant impact on health-related quality of life (HRQoL).1 5

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

How the intervention might work
BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritis and anticancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.8 The analgesic effects of BVA have been reported in animal experiments9 10 and in the clinic.7 11 In many countries, including the USA, BV therapy has been used to treat multiple sclerosis and arthritis.12 13 However, most of these therapeutic uses are not based on evidence.

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

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

METHODS

Criteria for including studies in this review
Types of studies
All prospective randomised controlled clinical trials (RCTs) and quasi-RCTs will be included.

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

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

Types of outcome measures
Primary outcomes
Symptom (morning stiffness, pain and joint swelling) evaluation.

Secondary outcomes
- The number of joints affected by RA
- Adverse effects likely to be related to RA
- Quality of life
- Erythrocyte sedimentation rate (ESR)
- C reactive protein (CRP)
- Rheumatoid factor (RF)

Search methods for identifying the studies
Electronic searches
We will search for trials in the following electronic databases from their inception to March 2014: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED and CINAHL. We will also search six Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database and DBPIA) and three Chinese databases including CNKI (China National Knowledge Infrastructure), Wanfang and VIP.

Searching other resources

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

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

Data extraction and management
The data extraction and quality assessment will be conducted by three authors (JAL, MJS and JHJ) using a pre-defined data extraction form. Any disagreement among the authors will be resolved by discussion with all of the authors. When the reported data are insufficient or ambiguous, MSL will contact the corresponding authors by e-mail or telephone to request additional information or clarification.

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

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

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

Dealing with the missing data
We will contact the original authors for missing data whenever possible. If it is not possible to get the missing data, we will only analyse the available data.
Assessment of heterogeneity
We will use the random-effect or fixed-effect model for the meta-analysis according to the data analysis. If a meta-analysis is possible, we will use the $I^2$ statistic to quantify the inconsistencies among the included studies. According to the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions, 50% will be the cut-off point for meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore the possible causes.15

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

Data synthesis
The differences between the intervention and control groups will be assessed. The RR and 95% CIs will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using Cochrane Collaboration’s Software Program, Review Manager (RevMan), V.5.2.7 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient information, we will contact the corresponding authors to acquire and verify the data when possible. $\chi^2$ and $I^2$ tests will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random-effects or fixed-effect model.

Subgroup analysis and investigation of heterogeneity
If the data are available, we will conduct subgroup analyses to assess the heterogeneity between the studies, including the following:
1. Type of BVA;
2. Type of control;
3. Duration of RA;
4. Laterality of RA, bilateral RA versus unilateral RA.

Sensitivity analysis
Sensitivity analysis will be conducted according to the following criteria:
Sample size (small sample studies eg, less than 40 participants in each group, or large sample studies eg, more than 40 participants in each group); 1. Analysis-related issues (eg, processes to handle the missing data).

**DISCUSSION**

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

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

**Competing interests** JAL, JC, K-JY, JHJ and MSL were supported by the Korea Institute of Oriental Medicine (K14400); MJS was supported by the same institute (K14380).

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**REFERENCES**