Systematic review

Effectiveness of bee venom acupuncture in alleviating post-stroke shoulder pain: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Shoulder pain is a common complication of stroke. Bee venom acupuncture (BVA) is increasingly used in the treatment of post-stroke shoulder pain.

OBJECTIVE: To summarize and evaluate evidence on the effectiveness of BVA in relieving shoulder pain after stroke.

SEARCH STRATEGY: Nine databases, namely MEDLINE, EMBASE, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), the Japan Science and Technology Information Aggregator, Electronic (J-STAGE), and four Korean medical databases, namely, the National Assembly Library, the Research Information Service System, the National Discovery for Science Leaders, and OASIS, were searched from their inception through August 2014 without language restrictions.

INCLUSION CRITERIA: Randomized controlled trials (RCTs) were included if BVA was used at acupoints as the sole treatment, or as an adjunct to other treatments, for shoulder pain after stroke.

DATA EXTRACTION AND ANALYSIS: Two review authors independently selected trials for inclusion, assessed methodological quality and extracted data.

RESULTS: A total of 138 potentially relevant articles were identified, 4 of which were RCTs that met our inclusion criteria. The quality of studies included was generally low, and a preponderance of positive results was demonstrated. All four trials reported favorable effects of BVA on shoulder pain after stroke. Two RCTs assessing the effects of BVA on post-stroke shoulder pain, as opposed to saline injections, were included in the meta-analysis. Pain was significantly lower for BVA than for saline injections (standardized mean difference on 10-cm visual analog scale: 1.46 cm, 95% CI = 0.30–2.62, \( P = 0.02, n = 86 \))

CONCLUSION: This review provided evidence suggesting that BVA is effective in relieving shoulder pain after stroke. However, further studies are needed to confirm the role of BVA in alleviating post-stroke shoulder pain. Future studies should be conducted with large samples and rigorous study designs.

Keywords: bee venoms; acupuncture therapy; stroke; shoulder pain; meta-analysis; systematic review


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1 Introduction

Strokes are a major cause of mortality and disability worldwide[1]. Shoulder pain is a common complication among stroke survivors, and is linked to the contracture of the shoulder, glenohumeral subluxation, rotator cuff injury, and the spasticity of shoulder muscles. It may also interfere with the functions of upper extremities, active rehabilitation, and other daily activities[2]. The prevalence of post-stroke shoulder pain is typically 22%-23% in the general population of stroke patients, and 54%-55% among stroke survivors in rehabilitation settings[3]. Hemiplegic shoulder pain is generally treated with non-steroidal anti-inflammatory drugs, corticosteroid injections, exercise, strapping, and electrical stimulation; nevertheless, overall estimates of treatment effects for available treatments have been reported at around 30%-50% for the post-stroke population as a whole. Therefore, there is a need for complementary and alternative treatments that are efficacious in relieving post-stroke shoulder pain[4,5]. Research has demonstrated that approximately half of the stroke survivors in the U.S. use some form of complementary and alternative medicine (CAM), such as herbal, acupuncture-type, or chiropractic treatment. Patients who use CAM generally do so as a complement to conventional treatments rather than as an alternative for its presumed potential to alleviate symptoms, in addition to its lower cost and easier accessibility[6].

Bee venom acupuncture (BVA) involves injecting purified and diluted bee venom (BV) into acupoints. BVA reportedly has anti-arthritis, anti-inflammatory, analgesic, and anti-nociceptive effects, and is effective in the treatment of arthritis, pain, rheumatoid diseases, multiple sclerosis, and chronic inflammation[7]. BVA, in particular, has been used to treat a variety of painful conditions in an individualized and practical approach[8]. Several randomized controlled trials (RCTs) assessing the efficacy of acupuncture for alleviating post-stroke shoulder pain have been published[9]. However, there has been relatively little evidence in RCTs on the efficacy of BVA for treating post-stroke shoulder pain. Therefore, no systematic review of this topic is currently available. The aim of the present study was to summarize and assess the evidence on the effectiveness of BVA for relieving post-stroke shoulder pain.

2 Methods

2.1 Search methods for identification of studies

The following electronic databases were searched from their inception through August 2014: MEDLINE, EMBASE, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), the Japan Science and Technology Information Aggregator, Electronic (J-STAGE), and four Korean medical databases (the National Assembly Library, the Research Information Service System, the National Discovery for Science Leaders, and OASIS). Our search was limited to the search strings “bee venom OR apiotherapy OR apitherapy OR apipuncture OR bee venom therapy OR bee venom acupuncture” AND “stroke OR apoplexy OR CVA OR cerebrovascular attack OR cerebrovascular accident OR cerebral infarction OR cerebral hemorrhage” in each database language. The search strategy was adjusted for each database. In addition, six Korean traditional medicine journals (Journal of Oriental Medicine, The Journal of Korean Acupuncture and Moxibustion Society, Journal of Pharmacopuncture, The Korean Journal of Meridian and Acupoint, Korean Journal of Oriental Physiology and Pathology, and The Journal of Korean Oriental Internal Medicine) were manually searched for relevant articles.

2.2 Inclusion/exclusion criteria

RCTs were included if BVA was used at acupoints, either as the sole treatment or as an adjunct to other treatments for stroke. Trials were excluded if study designs did not evaluate the effectiveness of BVA for shoulder pain after the occurrence of a stroke. No search restrictions on language or publication forms were imposed. During the first stage of selection/exclusion, titles and abstracts were analyzed, and literature that had no relevance to the present study was excluded. The second stage of selection/exclusion involved analyzing the full text of particular studies, because it was impossible to determine their relevance to the present research based solely on their abstracts.

2.3 Data extraction

Two review authors (S. M. L. and S. H. L.) independently selected trials for inclusion, assessed methodological quality, extracted data, and resolved any differences through discussion. For studies with insufficient data, we contacted the primary author to obtain and verify data where possible.

2.4 Quality assessment

The two reviewers independently assessed the methodological quality and the risk of bias of the included studies using the Cochrane classification.

2.5 Statistical analysis

The statistical analysis was performed using Review Manager (The Nordic Cochrane Centre). We extracted data on mean changes in pain from baseline, as assessed with a Visual Analog Scale (VAS) and the Fugl-Meyer Motor Assessment (FMMMA) for pain improvement, and estimated discrepancies between the intervention and control groups. Summary estimates of treatment effects were calculated using a random effects model. Statistical heterogeneity was analyzed using the I² test and was considered significant when I² > 50%. Publication bias was not a factor in the trials due to the limited number of studies.
3 Results

3.1 Description of studies
We identified a total of 138 potentially relevant articles, of which 4 met our inclusion criteria (Figure 1). Four RCTs were excluded because they were case studies, did not involve randomization, compared different types of herbal acupuncture, or compared complex treatments that could not provide information on the effects of BVA. Key data regarding the included RCTs are summarized in Table 1. All of the RCTs originated from Korea and were published in Korean between 2006 and 2011. These four RCTs assessed the effects of BVA on post-stroke shoulder pain. Two of the included RCTs compared BVA accompanied by standard therapy with saline injection accompanied by standard therapy; one compared BVA with acupuncture; and one compared BVA accompanied by standard therapy with standard therapy by itself. Stroke patients maintained standard therapy such as acupuncture, moxibustion, drugs/medication, and physiotherapy for stroke rehabilitation.

3.2 Meta-analysis of the results
The four selected RCTs employed a VAS to measure pain. All RCTs showed significant differences in pain reduction between the BVA and control therapies. We then performed a meta-analysis on the two RCTs assessing the effects of BVA vs. saline injection on post-stroke shoulder pain. We found that shoulder pain was significantly lower for BVA than for saline injection as assessed with the VAS (standardized mean difference on 10-cm VAS: 1.46 cm, 95% CI = 0.30–2.62, P = 0.02, n = 86; Figure 2). There was a difference in treatment outcomes for pain as assessed with the FMMA as well, but this difference was not statistically significant (standardized mean difference on FMMA: 1.60, 95% CI = −0.53–3.73, P = 0.14, n = 86; Figure 2).

3.3 Descriptions of BVA treatment
Treatment for post-stroke shoulder pain was applied to Jianyu (LI15) in all of the included studies. Treatment was also applied to Jianliao (TE14), Jianjing (GB21), and Naoshu (SI10) in a majority of the trials (3 out of 4). In three of the included studies, a total of 0.5 to 0.6 mL of diluted bee venom was injected; in one study, 1.5 mL was injected into acupoints according to patients’ symptomatic areas. BVA was administered 3 times weekly for a period of 2 to 4 weeks.

3.4 Risk of bias of included studies
The risk of bias was evaluated using the Cochrane classification for methodological quality (Figure 3). Two of the four included trials employed appropriate sequence generation methods, while others did not provide sufficient information with which to make an assessment. None of the studies employed allocation concealment. Only one RCT reported blinding participants, personnel, and assessors. The others did not have this information available. Trials with inadequate sequence generation, allocation concealment, and blinding tend to exaggerate treatment effects. Thus, it is necessary to improve the quality of trials by fully documenting methods of randomization, allocation concealment, and blinding employed.
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Condition (sample size: randomized/analyzed)</th>
<th>Intervention group</th>
<th>Dilution ratio</th>
<th>Amount of BV injected at each point/total amount of BV injected during each session</th>
<th>Control group</th>
<th>Main outcome measures</th>
<th>Intergroup differences (experimental versus control)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park (2011)</td>
<td>Post-stroke shoulder pain (41/40)</td>
<td>BVA (n = 21, 3 times weekly for 4 weeks), plus standard therapy (AT, drugs/medication, and physiotherapy); LI15, TE14, GB21, SI10, and according to patients’ symptomatic areas</td>
<td>n.r.</td>
<td>n.r./0.3–0.6 mL</td>
<td>Saline injection (n = 20), plus standard therapy</td>
<td>(1) 10-cm VAS</td>
<td>(1) 2.08 (1.29, 2.86)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Ko (2007)</td>
<td>Post-stroke shoulder pain (46/43)</td>
<td>BVA (n = 24, 3 times weekly for 2 weeks), plus standard therapy (AT, drugs/medication, moxibustion, and physiotherapy); LI15, TE14, GB21</td>
<td>10 000:1</td>
<td>0.2/0.6 mL</td>
<td>Saline injection (n = 22), plus standard therapy</td>
<td>(1) 10-cm VAS</td>
<td>(1) 0.89 (0.28, 1.50)</td>
<td>Pruritus: BV A, 8; control, 2. Burning sensation: BV A, 3; control, 1. Pain: BV A, 2; control, 3.</td>
</tr>
<tr>
<td>Eom (2006)</td>
<td>Post-stroke shoulder pain (30/30)</td>
<td>BVA (n = 10, 3 times weekly for 4 weeks); LI11, SI3, LI15, EX UE70, SI10</td>
<td>2 000:1</td>
<td>0.005–1/0.25–0.5 mL</td>
<td>(A) AT (n = 10)</td>
<td>(1) 100-mm VAS</td>
<td>(1) 1.09 (0.14, 2.04)</td>
<td>n.r.</td>
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<td></td>
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<td>(B) AT with BV-coating needle (n = 10)</td>
<td>(2) FMMA</td>
<td>(2) 2.70 (1.89, 3.52)</td>
<td></td>
</tr>
<tr>
<td>Lee (2006)</td>
<td>Post-stroke shoulder pain (40/40)</td>
<td>BVA (n = 20, 3 times weekly for 3 weeks), plus standard therapy (AT, drugs/medication, moxibustion, and physiotherapy); LI15, TE14, GB21, SI9, SI10, SI11, LI11, and according to patients’ symptomatic areas</td>
<td>4 000:1–10 000:1</td>
<td>n.r./0.1–1.5 mL</td>
<td>Standard therapy (n = 20)</td>
<td>10-cm VAS</td>
<td>1.06 (0.39, 1.72)</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

BVA: bee venom acupuncture; AT: acupuncture; n.r.: not reported; VAS: Visual Analog Scale; FMMA: Fugl-Meyer Motor Assessment.
Discussion

The objective of this study was to summarize and evaluate the evidence on the efficacy of BV A for relieving post-stroke shoulder pain. Our systematic review and meta-analysis suggested possible effectiveness of BV A in treating post-stroke shoulder pain. However, there were insufficient trials, and these had insufficient sample sizes, to confirm this conclusion. Future studies investigating the role of BV A in alleviating shoulder pain that employ more rigorous methodological standards are needed in order to draw firm conclusions on the matter.

Shoulder pain is a common complication following stroke, and it often interferes with activity, recovery and rehabilitation[17]. It requires coordinated multidisciplinary management to minimize interference with rehabilitation and to optimize treatment outcomes[18]. Koog et al[19] reported that aromatherapy, slow-stroke back massage, and intramuscular neuromuscular electric stimulation can be incorporated into treatment sessions for more effective control of hemiplegic shoulder pain at the end. They also noted that intramuscular botulinum neurotoxin A (BoNT/A) injections and intra-articular triamcinolone acetonide injections were not helpful at one and three months after the end of treatment. According to the present review, conflicting results were reported in research on treatments utilizing BoNT/A injections for post-stroke shoulder pain during the chronic stage[5]. Comparative studies of different kinds of injection therapies are required in order to clarify the most effective interventions for post-stroke pain according to specific etiologies, including individual states.

BV A reduces inflammatory and other pain behaviors via counter irritation. Research has shown that bee venom-induced antinociception is mediated by descending adrenergic and serotonergic pathways and spinal α2-adrenoceptors. The effects of BV components could be mediated, at least in part, by the activation of the hypothalamic-pituitary-adrenal axis and the release of corticosteroids with anti-inflammatory effects. Melittin has been shown to have anti-inflammatory or antinociceptive effects in several models.
and studies of BV effects. Other components have been shown to have anti-inflammatory properties, including apamin, mast cell degranulating peptide, and adolapin.  

Lee et al. indicated that BV A has significant anti-inflammatory and analgesic effects, which can be explained by the pharmacological effects of the bioactive compounds and mechanical functions involved in direct acupuncture stimulation. They also noted that BV A can have severe adverse effects, such as anaphylaxis; these are, however, infrequent, provided that BV A is practiced according to established safety rules (i.e., in appropriate acupoints, and with appropriate amounts and concentrations of BV).

Pretests for the identification of BV hypersensitivity and allergy were conducted for participant safety in all studies included in our systematic review. However, the occurrence of adverse side effects, such as skin redness, itching, and pain in local areas, was documented in only one study (conducted by Ko et al.). No significant differences between the BV A and saline groups were found with regard to these side effects, which are considered mild. None of the studies included in our review mentioned anaphylaxis, which is considered a critical or life-threatening side effect. Trials should include a full description of adverse effects due to BV A allergic reactions before the widespread use of this treatment. To ensure participant safety, such trials should also include information on the frequency and relative risks of adverse effects.

This systematic review had several limitations. First, we made considerable effort to retrieve all relevant studies, but cannot be certain that our searches were all-inclusive owing to the existence of gray literature. Second, all of the included RCTs were conducted in a single country, Korea, where BV A has been extensively researched and practiced. Third, the paucity and suboptimal methodological quality of the primary data prevents any substantive conclusions from being reached.

Future RCTs assessing the effectiveness of BV A for relief of post-stroke shoulder pain must overcome selection, performance, and detection biases. A large-scale study employing multi-center trials is recommended. There is a necessity for long-term follow-up studies to determine the efficacy and safety of BV A, and the persistence of its effects. Although evidence of BV A’s effectiveness for reducing pain is growing, intensive demographic epidemiological surveys of its use in post-stroke survivors are required in order to ascertain important determinants of its use for these conditions. Future studies with large samples and rigorous study designs are needed to confirm the role of BV A in various diseases including post-stroke shoulder pain. Further, adhering to the Consolidated Standards for Reporting Trials (CONSORT) statement in the reporting of RCTs and the Standards for Reporting Interventions in Controlled Trials of Acupuncture ( STRICTA) would be essential to improving the reporting quality of research on BV A. Through rigorous designs, reasonable appraisals, and critical analyses, more robust conclusions on the treatment’s efficacy for alleviating post-stroke shoulder pain can be attained. In conclusion, this review provides tentative evidence for the effectiveness of BV A in relieving post-stroke shoulder pain. Further studies are required to reach firm conclusions on the matter, and must be conducted with large samples and employ rigorous study designs.

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6 Competing interests

The authors declare there are no competing interests.

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**Submission Guide**

*Journal of Integrative Medicine* (JIM) is an international, peer-reviewed, PubMed-indexed journal, publishing papers on all aspects of integrative medicine, such as acupuncture and traditional Chinese medicine, Ayurvedic medicine, herbal medicine, homeopathy, nutrition, chiropractic, mind-body medicine, Tai Chi, Qigong, meditation, and any other modalities of complementary and alternative medicine (CAM). Article types include reviews, systematic reviews and meta-analyses, randomized controlled and pragmatic trials, translational and patient-centered effectiveness outcome studies, case series and reports, clinical trial protocols, preclinical and basic science studies, papers on methodology and CAM history or education, editorials, global views, commentaries, short communications, book reviews, conference proceedings, and letters to the editor.

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