

# Bee Venom Acupuncture for Shoulder Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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## Key Words

bee venom, meta-analysis, pharmacopuncture, shoulder pain, systematic review

## Abstract

**Objectives:** Our review aimed to summarize and evaluate evidence on the effectiveness of bee venom acupuncture (BVA) in the treatment of shoulder pain.

**Methods:** Randomized controlled trials (RCTs) evaluating the effectiveness of BVA on shoulder pain were searched up to October 2019 in 11 electronic databases (Medline, Embase, CENTRAL, CiNii, CNKI, VIP, Wanfang, Kmbase, NDSL, RISS, OASIS). The methodological quality of the included RCTs were evaluated using Cochrane Risk of Bias tool and a meta-analysis was performed.

**Results:** Seven studies were included in the review, and four studies were included in the meta-analysis. Comparing BVA plus conventional therapy (CT) with saline injection plus CT, it showed an effect in favor of BVA plus CT in visual analog scale (VAS) and pain rating scale (PRS) ( $p = 0.02$ ,  $p = 0.009$ , respectively). Comparing BVA plus physiotherapy (PT) with saline injection plus PT, it showed that there was no significant difference in VAS and verbal rating scale (VRS) between the two groups.

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**Conclusion:** This systematic review and meta-analysis suggest that BVA could be beneficial as an adjuvant treatment for shoulder pain.

## 1. Introduction

Bee venom (BV) therapy has been used since ancient times. Bee venom acupuncture (BVA) is a treatment that involves injecting purified and diluted BV into acupoints [1]. In some Asian countries, including Korea and China, BVA is used to treat inflammatory diseases and cancers and reduce pain [2, 3]. In particular, BVA has been used to treat a variety of painful conditions in a practical approach. BV contains many enzymes, peptides, and amines. Among these components, adolapin has anti-inflammatory and analgetic properties, and melittin also regulates the inflammatory response by inhibiting the DNA-binding activity of NF- $\kappa$ B [4, 5].

Shoulder pain is the most common symptom of musculoskeletal disorders, accounting for approximately 16% of all complaints [6]. A considerable number of patients (41%) with new-onset shoulder pain show persistent or recurrent symptoms 12 months after presenting to their general practitioner [7]. Regardless of the cause of the shoulder pain, there is no universally effective treatment. In addition, most treatments are accompanied by varying degrees of side effects. Thus, finding an effective and safe complementary and alternative therapy is necessary.

There has been a systematic review and meta-analysis of randomized control trials (RCTs) to assess

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the efficacy of BVA in reducing shoulder pain. Lim et al. [8] reviewed and meta-analyzed the effectiveness of BVA in alleviating post-stroke shoulder pain, but this review was limited to the shoulder pain after the occurrence of a stroke. Also, Lee et al. [9] reviewed the efficacy of BVA for various musculoskeletal pain, and suggested the evidence for the effectiveness of BVA in musculoskeletal pain management. However, this review needs to be updated.

Although there have been several clinical studies and few reviews of the effectiveness of BVA, there has been relatively little evidence evaluating BVA efficacy in the treatment of shoulder pain caused by various causes. We aimed to summarize on the effectiveness of BVA to treat shoulder pain.

## 2. Materials and Methods

### 2.1. Data sources

The search for relevant literature was conducted in the following 11 electronic databases from their inception to October 2019: Medline (PubMed), Excerpta Medica database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL), Scholarly and Academic Information Navigator (CiNii), Chinese medical databases (China National Knowledge Infrastructure, Wanfang, and Journal integration platform), and Korean medical databases (Kmbase, National Discovery for Science Leaders, Research Information Sharing Service, and Oriental Medicine Advanced Searching Integrated System). The references in all located articles were manually searched for further relevant articles. We also searched the grey literature of theses, dissertations, letters, government documents, research reports, conference proceedings, and abstracts to avoid publication bias.

### 2.2. Search strategy

The keywords searched were: ["bee venoms" OR apitoxin OR apitherapy OR apipuncture OR "bee venom therapy" OR "bee venom acupuncture" OR "bee sting" OR "wasp venom"] AND ["shoulder pain" OR bursitis OR "shoulder impingement syndrome" OR "rotator cuff" OR "adhesive capsulitis" OR tendinitis OR tendonitis OR "frozen shoulder" OR shoulder\*]. Searches were conducted in Korean, English, and Chinese. We adjusted search strategies for each of the databases. No restrictions were imposed on language, publication type or date. The detailed search strategies were described in the Appendix 1.

### 2.3. Eligibility criteria

(1) Types of studies: The studies were restricted to RCTs that compared the efficacy of bee venom treatment with a control group, either placebo treatment or no treatment, in decreasing shoulder pain. Other study designs such as *in vivo*, *in vitro*, case reports, case series, conference papers, editorials, abstracts, retrospective studies, and cross-over designs were excluded. In addition, non-randomized and quasi-randomized trials were excluded. (2) Types of par-

ticipants: Participants were patients with shoulder pain caused by musculoskeletal disorders. No restrictions were placed on age, sex, ethnicity, degree of pain, or disease duration. (3) Types of interventions: Bee venom therapy for shoulder pain caused by musculoskeletal disorders was considered an intervention. Interventions combined with other treatments were also included. There were no restrictions on frequency, bee venom dosage, and treatment duration. Bee venom was injected into the acupoints of the patients using a syringe. Live bee stings were excluded. The comparisons in this meta-analysis included placebo treatment, such as normal saline injection, acupuncture, or conventional therapy (CT). (4) Outcome measures: The primary outcome measure was the improvement in shoulder pain as a result of bee venom therapy in RCTs. In this review, the scales that assessed shoulder pain were the visual analog scale (VAS), pain rating scale (PRS) [10], verbal rating scale (VRS) [11]. Secondary outcome measures included the shoulder pain and disability index (SPADI) [12], and adverse events.

### 2.4. Study selection and data extraction

The study selection was conducted independently by two reviewers, (JHL and LS). Duplicate studies were excluded by comparing the title, author, and publication date.

The two reviewers extracted the data according to the databases based on the selection criteria. If two reviewers had disagreements, they were resolved by discussion. Also, if the title, author, and published date of the study were same, it was judged as a duplicate study. The data of the included studies were arranged according to the general characteristics (author, year of publication), patients' conditions (type of disease, mean age), sample size, interventions for experimental and control group, period of treatment, acupoint, outcome measures, summary of results, and adverse events.

### 2.5. Quality assessment

Two investigators assessed methodological quality by using the Risk of Bias (RoB) tool [13], which was developed by Cochrane. Each study was assessed for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. Disagreements were resolved by discussion between the two reviewers.

### 2.6. Data analysis

The meta-analysis and statistical analysis were performed using the RevMan 5.3 software of the Cochrane Collaboration. The effect size was calculated as weighted mean differences (WMDs) and standardized mean difference (SMD) with 95% confidence intervals (CIs). Summary estimates of the treatment effects were calculated using a random-effects model. Chi-squared and Higgins I<sup>2</sup> statistics were used to assess the heterogeneity of the data.

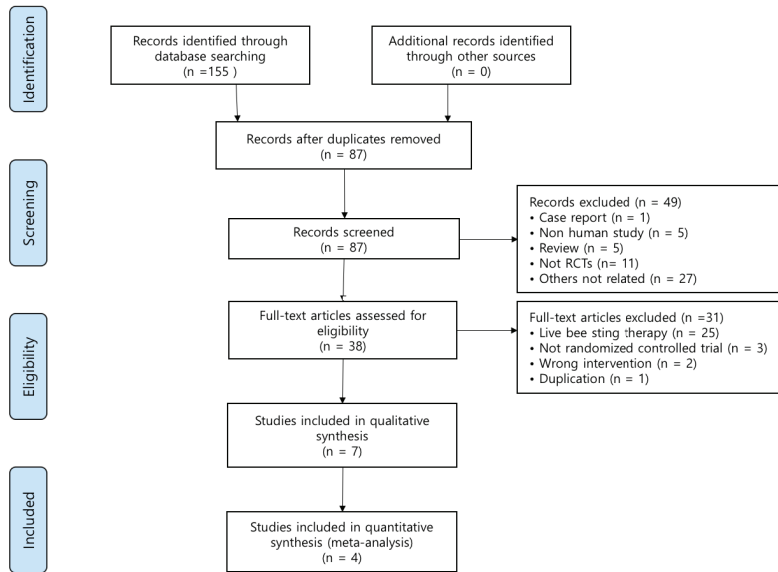


Figure 1 Flow chart of the study selection process.

Table 1 General characteristics of the included studies.

Author (year)	Types of disease	Participants age (mean ± SD)	Sample size (N = total)	Intervention group (dilution ratio)	Control group	Duration (frequency / total period)	Major Acupoints
Cho et al. (2005) [14]	Post-stroke hemiplegic shoulder pain	A: 58.55 ± 15.07 B: 61.50 ± 10.98	N = 23 A = 11 B = 12	A: BVA + CT (AT, PT, WM, HM) (1:20,000)	B: ZG + CT (AT, PT, WM, HM)	3 times a week / 2 weeks	LI15, TE14, GB21, SI10
Eom et al. (2006) [15]	Post-stroke hemiplegic shoulder pain	A: 69.2 ± 9.6 B: 67.3 ± 8.9 C: 67.7 ± 15.0	N = 30 A = 10 B = 10 C = 10	A: BVA (1:2,000)	B: AT with BV coating needle C: AT	3 times a week / 4 weeks	LI11, SI3, LI15, UE12, SI10
Ko et al. (2007) [16]	Shoulder pain after stroke	A: 64.33 ± 9.88 B: 67.50 ± 9.60	N = 46 A = 24 B = 22	A: BVA + CT (AT, HM, MT, PT) (1:10,000)	B: Saline injection + CT (AT, HM, MT, PT)	3 times a week / 2 weeks	LI15, TE14, GB21
Koh et al. (2013) [19]	Adhesive capsulitis	A: 54.95 ± 6.79 B: 56.18 ± 6.70 C: 55.13 ± 7.01	N = 68 A = 22 B = 23 C = 23	A: BVA + PT (1:10,000) B: BVA + PT (1:30,000)	C: Saline injection + PT	2 times a week / 12 weeks	LI15, LI16, TE14, GB21, SI11, 5 additional points around the shoulder
Lee et al. (2006) [17]	Shoulder pain patients in stroke sequelae	A: 62.45 ± 9.2 B: 68 ± 10.4	N = 40 A = 20 B = 20	A: BVA + CT (AT, WM, HM, MT, PT) (1:4,000 and 1:10,000)	B: CT (AT, WM, HM, MT, PT)	3 times a week / 3 weeks	LI15, TE14, GB21, SI9, SI10, LI11, SI11, additional ashi points
Park et al. (2011) [18]	Post-stroke hemiplegic shoulder pain	A: 62.52 ± 12.20 B: 64.26 ± 11.11	N = 40 A = 21 B = 19	A: BVA + CT (AT, HM, MT, PT) (Not reported dilution ratio)	B: Saline injection + CT (AT, HM, MT, PT)	3 times a week / 4 weeks	LI15, TE14, GB21, SI10, additional ashi points
Park et al. (2014) [20]	Adhesive capsulitis	A: 55.4 ± 6.8 B: 52.8 ± 7.3 C: 56.4 ± 7.9	N = 60 A = 20 B = 22 C = 18	A: BVA + PT (1:10,000) B: BVA + PT (1:30,000)	C: Saline injection + PT	2 times a week / 2 months one-year follow up	LI15, LI16, TE14, GB21, SI11, 5 additional points around the shoulder

BVA, bee venom acupuncture; AT, acupuncture therapy; PT, physiotherapy; ZG, Zingiberis Rhizoma acupuncture therapy; BV, bee venom; HM, herbal medicine; MT, moxibustion; WM, western medicine; CT, conventional therapy.

### 3. Results

#### 3.1. Study description

From 11 electronic databases, 155 potentially relevant articles were retrieved. Among them, 148 articles were excluded. Seven studies [14-20] (Korean: n = 5; English: n = 2) were included in the qualitative synthesis and four studies [16, 18-20] were included in the quantitative synthesis (meta-analysis) (Fig. 1). A total of 307 participants were included in these studies, 128 in the BVA group and 124 in the control group. Two [19, 20] of included studies assessed the effects of BVA on adhesive capsulitis and five [14-18] assessed the effects of BVA on post-stroke shoulder pain (Table 1). The duration of treatment varied from 2 to 12 weeks in the included studies. One study [20] was conducted one year follow up after 2 months of treatment.

#### 3.2. Characteristics of the bee venom intervention

The participants were intramuscularly injected with bee venom using a syringe at various acupoints. Dried bee venom powder was diluted in saline at various ratios: 1:10000 in 3 studies [16, 19, 20], 1:20000 in one study [14], 1:2000 in one study [15], 1:4000 and 1:10000 in one study [17]. One study [18] did not report dilution rates. To summarize the acupoints were injected with bee venom, LI15 was used in all studies [14-20], TE14 and GB21 in 6 studies [14, 16-20], SI10 in 4 studies [14, 15, 17, 18], SI11 in 3 studies [17, 19, 20], LI16 in 2 studies [19, 20], LI11 in 2 studies [15, 17], SI9 in one study [17], SI3 in one study [15], UE12 in one study [15], and ashi points in two studies [17, 18] (Table 1).

#### 3.3. Characteristics of the control intervention

In seven studies, control interventions were classified into four types. First, normal saline was used as control intervention in four studies [16, 18-20]. Two of them [19, 20] were given physiotherapy (PT), and the others [16, 18] were given CT such as classic acupuncture (AT), moxibustion, herbal medicine, PT. Secondly, AT was used in one study [15] as control intervention. Thirdly, Zingiberis Rhizoma herbal acupuncture therapy was used one study [14] as control intervention. In this study, all participants were treated with CT such as AT, herbal medicine, western medicine, PT. Fourthly, One study [17] did not provide any control intervention. In this study, all participants were treated with CT such as AT, herbal medicine, western medicine, moxibustion, PT (Table 1).

#### 3.4. Characteristics of outcome measures

In a total of seven studies, VAS was used in six studies [14-19]. In three of these studies [16-18], there were significant differences in the BVA group compared to control group and only one study [14] suggested no significant difference between the two groups. In addition, two studies [15, 19] did not report appropriate statistical data. Park et al. [20]

used VRS to evaluate shoulder pain, but there was no significant difference between the two groups ( $p > 0.05$ ). PRS was used in the two studies [16, 18], in which there were significant differences between two groups ( $p < 0.05$ ). SPA-DI was used in two studies [19, 20], both of which showed significant differences between the two groups ( $p < 0.05$ ) (Table 2).

#### 3.5. Risk of bias in the included studies

The risk of bias of included 7 studies was shown in Figure 2. All studies mentioned "randomization", but only 3 studies [16, 18, 19] reported adequate methods of sequence generation - a table of random numbers [18], stratified sampling [16], and the bloc randomization method [19]. None of the trials mentioned whether they had adequate allocation concealment methods. Four studies [16, 18-20] were assessed to be low risk for blinding of participants and personnel. The remaining three studies [14, 15, 17] compared BVA with AT, Zingiberis Rhizoma herbal acupuncture, and no control. Therefore, these studies were assessed to be at a high risk. Detection bias was low risk in four studies [16, 18-20], it was unclear in one study [14] because it did not mention the blinding of outcome assessment. Two studies [15, 17] were assessed to be at a high risk because blinding could affect the outcome assessment. Attrition bias was low risk in six studies [14-19], but it was high risk in one study [20] that did not report a complete set of baseline data. None of the trials reported information regarding the pre-registered protocol, therefore we assessed all trials to be unclear of reporting bias. We evaluated all of the studies as unclear of other bias because they had insufficient information to determine additional bias.

Figure 2 The summary of risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cho et al. 2005	?	?	+	?	+	?	?
Eom et al. 2007	?	?	+	+	+	?	?
Ko et al. 2007	+	?	+	+	+	?	?
Koh et al. 2013	+	?	+	+	+	?	?
Lee et al. 2006	?	?	+	+	+	?	?
Park et al. 2011	+	?	+	+	+	?	?
Park et al. 2014	?	?	+	+	+	?	?

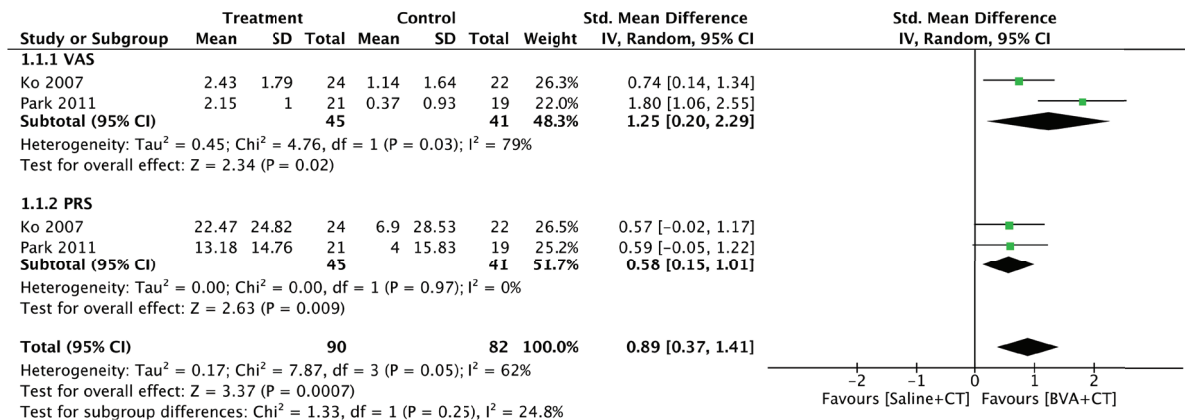
### 3.6. Meta-analysis

#### 3.6.1. Bee venom acupuncture versus saline injection

##### 3.6.1.1. Bee venom acupuncture plus CT versus saline injection plus CT

Four of included trials [16, 18-20] were classified into several subgroups according to the type of control intervention used. Two of the RCTs [16, 18] that compared the effectiveness of BVA plus CT and saline injection plus CT reported significant differences in the VAS of shoulder pain. The cause of shoulder pain in both studies was post-stroke shoulder pain. The meta-analysis suggested an effect in favor of BVA plus CT in VAS (SMD on 10-cm VAS, 1.25; 95% CI = 0.20 to 2.29,  $p = 0.02$ ,  $n = 86$ ; heterogeneity,  $p = 0.03$ ,  $I^2 = 79\%$ ; Fig. 3 [1.1.1]). Also, we found that shoulder pain was significantly lower for BVA plus CT than for saline plus CT, as assessed by the PRS (SMD, 0.58; 95% CI = 0.15 to 1.01,  $p = 0.009$ ,  $n = 86$ ; heterogeneity,  $p = 0.97$ ,  $I^2 = 0\%$ ; Fig. 3 [1.1.2]). Overall, the result showed pain reduction was significantly greater for BVA than for saline injection (SMD, 0.89; 95% CI = 0.37 to 1.41,  $p = 0.0007$ ,  $n = 172$ ; heterogeneity,  $p = 0.05$ ,  $I^2 = 62\%$ ; Fig. 3).

**Figure 3** Forest plot of shoulder pain in BVA plus conventional therapy versus saline injection plus conventional therapy. BVA, bee venom acupuncture.

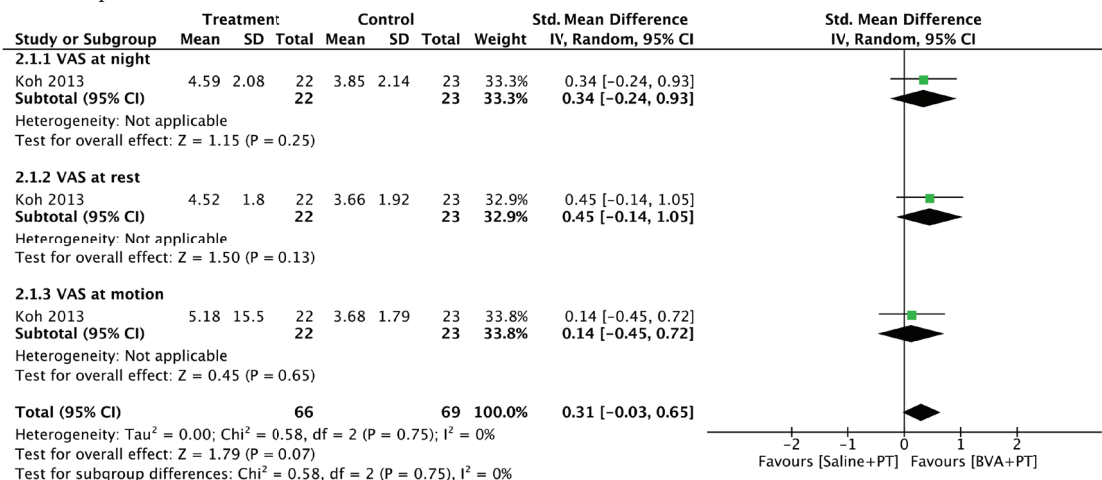


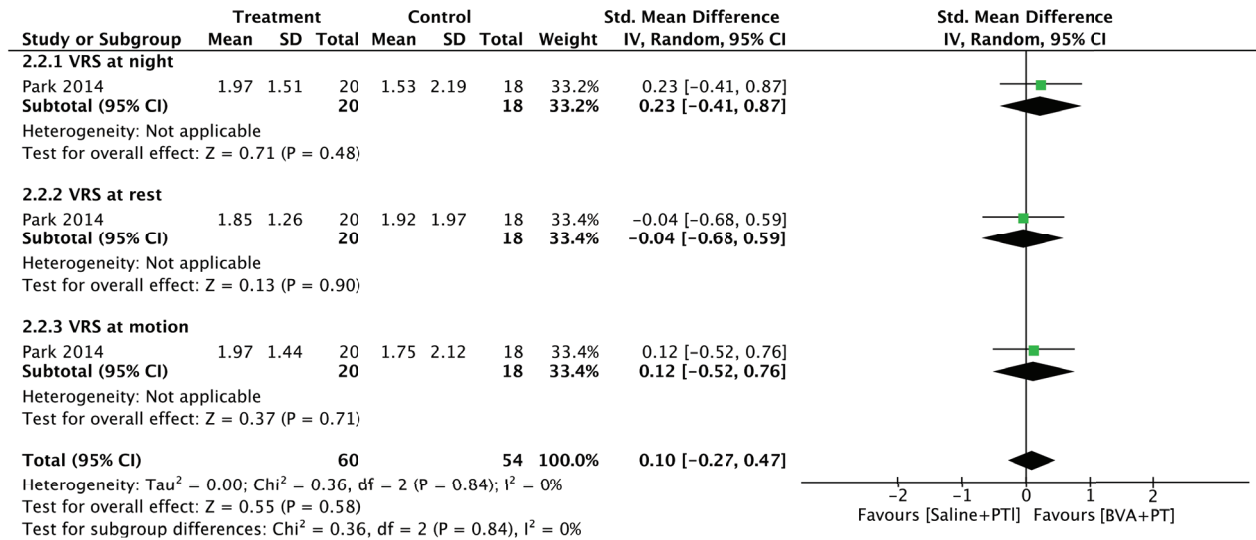
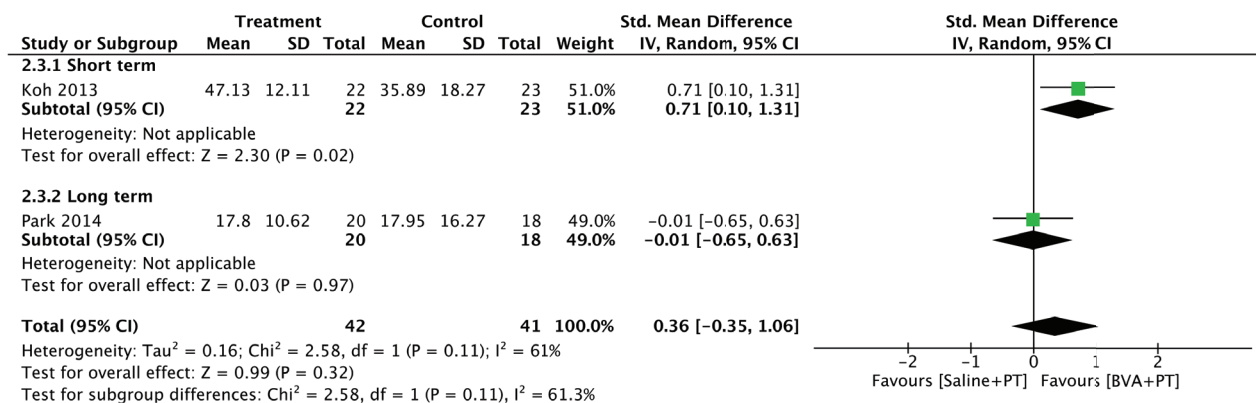
##### 3.6.1.2. Bee venom acupuncture plus PT versus saline injection plus PT

In two studies [19, 20] on adhesive capsulitis disease, VAS (at night, rest, and motion), VRS (at night, rest, and motion), and SPADI were measured for BVA plus PT and saline plus PT. One trial [19] reported that there was no significant difference in VAS pain reduction at night (SMD on 10-cm VAS, 0.34; 95% CI = -0.24 to 0.93,  $p = 0.25$ ,  $n = 45$ ; Fig. 4 [2.1.1]), at rest (SMD on 10-cm VAS, 0.45; 95% CI = -0.14 to 1.05,  $p = 0.13$ ,  $n = 45$ ; Fig. 4 [2.1.2]), and at motion (SMD on 10-cm VAS, 0.14; 95% CI = -0.45 to 0.72,  $p = 0.65$ ,  $n = 45$ ; Fig. 4 [2.1.3]). Overall, the result showed pain reduction in VAS had no significant difference between BVA and saline injection (SMD, 0.31; 95% CI = -0.03 to 0.65,  $p = 0.07$ ,  $n = 135$ ; heterogeneity,  $p = 0.75$ ,  $I^2 = 0\%$ ; Fig. 4).

The other trial [20] reported that there was no significant difference in VRS of pain reduction at night (SMD, 0.23; 95% CI = -0.41 to 0.87,  $p = 0.48$ ,  $n = 38$ ; Fig. 5 [2.2.1]), at rest (SMD, -0.04; 95% CI = -0.68 to 0.59,  $p = 0.90$ ,  $n = 38$ ; Fig. 5 [2.2.2]), and at motion (SMD, 0.12; 95% CI = -0.52 to 0.76,  $p = 0.71$ ,  $n = 38$ ; Fig. 5 [2.2.3]). Overall, the result showed pain reduction in VRS had no significant difference between

**Figure 4** Forest plot of VAS in BVA plus physiotherapy versus saline injection plus physiotherapy. VAS, visual analog scale; BVA, bee venom acupuncture.



**Figure 5** Forest plot of VRS in BVA plus physiotherapy versus saline injection plus physiotherapy. VRS, verbal rating scale; BVA, bee venom acupuncture.**Figure 6** Forest plot of SPADI in BVA plus physiotherapy versus saline injection plus physiotherapy. SPADI, shoulder pain and disability index; BVA, bee venom acupuncture.

BVA and saline injection (SMD, 0.10; 95% CI = -0.27 to 0.47,  $p = 0.58$ ,  $n = 114$ ; heterogeneity,  $p = 0.84$ ,  $I^2 = 0\%$ ; Fig. 5).

In 12-week short-term observations [19], BVA group showed significantly better outcomes in SPADI than the control group (SMD = 0.71; 95% CI = 0.10 to 1.31,  $p = 0.02$ ;  $n = 45$ ; Fig. 6 [2.3.1]). In a one-year long-term observation [20], SPADI had no significant difference between the two groups (SMD = -0.01; 95% CI = -0.65 to 0.63,  $p = 0.97$ ,  $n = 38$ ; Fig. 6 [2.3.2]). Overall, the result showed pain reduction in SPADI had no significant difference between BVA and saline injection (SMD, 0.36; 95% CI = -0.35 to 1.06,  $p = 0.32$ ,  $n = 83$ ; heterogeneity,  $p = 0.11$ ,  $I^2 = 61\%$ ; Fig. 6).

### 3.7. Adverse events

Two [16, 19] of the seven studies reported adverse events. Both studies used saline injection as the control intervention. One study [16] included pruritus (8 in the BVA group and 2 in the control group), burning sensation (3 in the

BVA group and 1 in the control group), and pain (2 in the BVA group and 3 in the control group). All of these adverse events were Mueller Grade 0, and symptoms were relieved after using ice packs. In the other study [19], among the 45 patients in the BV1 and BV2 groups who received BVA, 30 patients experienced slight pruritus, local swelling, and or redness (under 20mm in diameter), which were Mueller Grade 0. One patient showed mild, generalized swelling and aching (in BV1 group), which were classified as Mueller Grade 1 reactions, and 3 patients showed slight redness and pruritus (in control group). The rest five studies [14, 15, 17, 18, 20] did not mention any information about adverse events (Table 2).

### 4. Discussion

This is a systematic review and meta-analysis to investigate the efficacy and safety of BVA for shoulder pain. The results of the systematic reviews and meta-analyses

**Table 2** The outcome of included studies.

Author (year)	Outcome	Results	Adverse events
Cho et al. (2005) [14]	1. MMT 2. VAS 3. PROM	1. No differences between the two groups ( $p > 0.05$ ). 2. No differences between the two groups ( $p > 0.05$ ). 3. In PROM, ZG had some effectiveness on abduction and flexion, but BV had effectiveness on all movement	Not reported
Eom et al. (2006) [15]	1. VAS 2. FMMA 3. PROM 4. Modified ashworth scale	1. Ratio of VAS showed significant decrease in BVA and BV coating needle groups compared to the AT group ( $p < 0.05$ ) 2. FMMA showed significant increase in all groups ( $p < 0.05$ ), No differences between the three groups. ( $p > 0.05$ ) 3. PROM showed significant increase in all groups ( $p < 0.05$ ), No differences between the three groups. ( $p > 0.05$ ) 4. No differences between the three groups. ( $p > 0.05$ )	Not reported
Ko et al. (2007) [16]	1. VAS, PRS 2. FMMA 3. PROM	1. VAS: A > B ( $p = 0.022$ ), PRS: A > B ( $p = 0.034$ ) 2. No differences between the two groups. ( $p > 0.05$ ) 3. No differences between the two groups. ( $p > 0.05$ )	1. Pruritus: A (n = 8), B (n = 2) 2. Burning sensation: A (n = 3), B (n = 1) 3. Pain: A (n = 2), B (n = 3)
Koh et al. (2013) [19]	1. SPADI 2. VAS 3. PROM	1. A > C ( $p < 0.05$ , at 8 and 12 weeks), No differences between the A and B groups. ( $p > 0.05$ ) 2. A > C ( $p < 0.05$ , at 8 weeks (at rest) and 12 weeks (during motion)), No differences between the A and B groups. ( $p > 0.05$ ) 3. No differences between the three groups. ( $p > 0.05$ )	1. Slight pruritus, local swelling, redness (Mueller Grade 0): A and B (n = 30) 2. Mild, generalized swelling, aching (Mueller Grade 1): A (n = 1). 3. Slight redness and pruritus: C (n = 3) 4. No SAEs.
Lee et al. (2006) [17]	1. VAS 2. PROM	1. A > B ( $p < 0.05$ ) 2. No differences between the two groups. ( $p > 0.05$ )	Not reported
Park et al. (2011) [18]	1. VAS, PRS 2. PROM 3. FMMA	1. VAS: A > B ( $p < 0.05$ ); PRS: A > B ( $p < 0.05$ , after 4 weeks treatment) 2. No differences between the two groups. ( $p > 0.05$ ) 3. No differences between the two groups. ( $p > 0.05$ )	Not reported
Park et al. (2014) [20]	1. SPADI 2. VRS	1. A > C ( $p = 0.043$ ) 2. No differences between the three groups. ( $p > 0.05$ )	Not reported

MMT, manual muscle test; VAS, visual analog scale; PROM, passive range of motion; FMMA, fugl-meyer motor assessment; PRS, pain rating score; SPADI, shoulder pain, VRS, verbal rating scale.

showed the benefit of BVA on shoulder pain. However, there were insufficient information, small sample size, and small RCTs to draw firm conclusions.

There has been one systematic review and meta-analysis of RCTs concerning BVA efficacy in reducing shoulder pain. Lim et al. [8] reviewed and meta-analyzed the effectiveness of BVA in alleviating post-stroke shoulder pain. However, this review was limited to shoulder pain after the occurrence of a stroke, so it failed to show the efficacy of BVA in treating shoulder pain by other causes.

Pharmacopuncture is a new acupuncture treatment method with the combination of herbal medicine and

acupuncture. BVA is one of the most common pharmacopuncture, which has been used in clinic for many years. BVA is to inject diluted bee venom into an acupoint using a syringe, and treat a patient through both the pharmacologic effects and acupuncture effect. Previous studies have shown that bee venom has many effects such as anti-inflammatory, anti-cancer, and regulating immunity and so on [21, 22]. Based on these pharmacological effects, BVA is often used to treat various diseases such as rheumatoid arthritis, low back pain, and cancer [23-25]. In vivo experiments, BVA showed a potential analgesic effect [26]. Choi et al. [27] observed that BVA has significant analgesic ef-

fects in rats with paclitaxel-induced neuropathic pain.

The diseases causing shoulder pain in this review are adhesive capsulitis in two studies and post-stroke in five studies. Adhesive capsulitis usually refers to the inflammation of articular capsule, characterized by a painful stiff shoulder, and is one of many conditions that progressively limit shoulder motion [28, 29]. Shoulder pain is one of the most common complications following stroke and may delay recovery of stroke [30]. Shoulder pain is usually experienced during rest or exercise, restricting shoulder mobility and affecting quality of life. Regardless of the cause of the shoulder pain, there is no universally effective treatment for shoulder pain, and most of them are accompanied by varying degrees of side effects. Therefore, it is necessary to find an effective and safe complementary and alternative therapy.

Two [16, 18] of the included studies compared the effectiveness of BVA plus CT with saline injection plus CT for treating shoulder pain. The meta-analysis suggested an effect in favor of BVA plus CT in VAS and PRS. Two [19, 20] of the included studies compared BVA plus PT with saline injection plus PT. VAS and VRS were used to measure pain at night, rest, and motion, respectively. Meta-analysis showed that there was no significant difference in VAS and VRS between the two groups. In addition, SPADI was used to measure the quality of life. During the 12-week short-term observation [19], there was a significant difference in SPADI scores between the BVA and control groups. However, during the long-term follow-up [20], there was no significant difference between BVA and control groups.

Based on currently available evidence, our meta-analysis found that BVA was an effective option for shoulder pain relief. This kind of therapy could benefit shoulder pain, especially as an adjunctive therapy. In Korea, BVA therapy is already widely used for shoulder pain and is becoming an important treatment option.

This systematic review has several limitations. First of all, the included studies exhibited various degrees of bias susceptibility. Among the included 7 studies, only 3 studies [16, 18, 19] reported an adequate method of random sequence generation. Allocation concealment was not described in the included 7 studies. 3 studies [14, 16, 17] had a high risk in blinding of participants and personnel. Secondly, all included studies were conducted in Korea. Although extensive research and practice has been conducted in Korea, this might indicate a publication bias and limit the external generalization of the evidence. Thirdly, the sample size of the included studies were small and calculation methods were not reported. This means that statistical power of each study is unknown even though pooled estimate indicated significant effect of BVA. Fourthly, since BVA administration is likely to cause discomfort, some participants who had previously experienced BVA treatment may have known what they were received with. This issue can interfere the patient blinding. Fifthly, only 2 of the 7 studies [16, 19] reported adverse events, while the other 5 studies [14, 15, 17, 18, 20] did not mention adverse events. In some case reports, severe adverse events after BVA treatment have been reported, such as severe ulnar nerve injury and immune thrombocytopenia [31, 32]. Although no severe adverse events were reported in this

review, the evidence was limited. Finally, this review only included studies published in journals except for dissertation papers and conference papers. Thus, a global and complete summary of all the evidence may not have been gathered. Future researchers are encouraged to register the protocols of clinical trials to ensure the research can be conducted according to the pre-defined protocol. Furthermore, it is necessary to calculate the appropriate sample size for statistical power, frequency, duration of treatment, and ideal follow-up. Also, appropriate study design, such as adequate randomization methods or double blinding, must be developed.

## 5. Conclusion

The results of this systematic review and meta-analysis suggest that BVA might be beneficial as an adjuvant treatment for shoulder pain. However, considering that the total number of included RCTs and sample size were too small, and most of the studies included in the review were assessed as a high methodological risk, so definitive conclusions cannot be drawn. In the future, more large-scale, rigorous RCTs should be conducted.

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## Conflict of interest

The authors declare that there are no conflicts of interest.

## Appendix 1. Search strategy

### 1. MEDLINE-Pubmed

#1 bee venoms [MeSH Terms]

#2 apitoxin

#3 apitherapy

#4 apipuncture

#5 bee venom therapy

#6 bee venom acupuncture

#7 bee sting

#8 wasp venom

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

#10 shoulder pain [MeSH Terms]

#11 bursitis [MeSH Terms]

#12 shoulder impingement syndrome

#13 rotator cuff

#14 adhesive capsulitis

#15 tendinitis

#16 tendonitis

#17 frozen shoulder

#18 shoulder\*

#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR

#17 OR #18

#20 #9 AND #19

### 2. EMBASE

#1 'bee venoms'/exp

#2 apitoxin



#3 apitherapy  
 #4 apipuncture  
 #5 bee venom therapy  
 #6 bee venom acupuncture  
 #7 bee sting  
 #8 wasp venom  
 #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #7 OR #8  
 #10 'shoulder pain'/exp  
 #11 'Bursitis'/exp  
 #12 shoulder impingement syndrome  
 #13 rotator cuff  
 #14 adhesive capsulitis  
 #15 tendinitis  
 #16 tendonitis  
 #17 frozen shoulder  
 #18 shoulder\*  
 #19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR  
 #17 OR #18  
 #20 #9 AND #19

### 3. Cochrane Central Register of Controlled Trials

#1 MeSH descriptor: [Bee Venoms] explode all trees  
 #2 apitoxin  
 #3 apitherapy  
 #4 apipuncture  
 #5 bee venom therapy  
 #6 bee venom acupuncture  
 #7 bee sting  
 #8 wasp venom  
 #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #7 OR #8  
 #10 MeSH descriptor: [Shoulder pain] explode all trees  
 #11 MeSH descriptor: [Bursitis] explode all trees  
 #12 shoulder impingement syndrome  
 #13 rotator cuff  
 #14 adhesive capsulitis  
 #15 tendinitis  
 #16 tendonitis  
 #17 frozen shoulder  
 #18 shoulder\*  
 #19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR  
 #17 OR #18  
 #20 #9 AND #19

### 4. CiNii

(bee venom OR apitoxin OR apitherapy OR apipuncture  
 OR bee venom therapy OR bee venom acupuncture OR  
 bee sting OR wasp venom) & (shoulder OR shulder pain  
 OR Bursitis OR shoulder impingement OR rotator cuff OR  
 adhesive capsulitis OR tendinitis OR tendonitis OR frozen  
 shoulder)

### 5. CNKI

SU=('蜂针'+ '蜂针穴位治疗'+ '蜂针穴位注射'+ '蜂毒'+  
 '蜂毒穴位治疗'+ '蜂毒穴位注射') AND SU=('肩痛'+ '肩  
 周炎'+ '肩关节周围炎'+ '肩手综合征'+ '颈肩痛'+ '颈肩  
 综合症'+ '冻结肩'+ '五十肩')

### 6. Wanfang

主题: ("蜂针"+ "蜂针穴位治疗"+ "蜂针穴位注射"+ "蜂  
 毒"+ "蜂毒穴位治疗"+ "蜂毒穴位注射") AND 主题: ("肩

痛"+ "肩周炎"+ "肩关节周围炎"+ "肩手综合征"+ "颈肩综  
 合症"+ "冻结肩"+ "五十肩")

### 7. VIP

M=(蜂针+蜂针穴位治疗+蜂针穴位注射+蜂毒+蜂毒穴位治  
 疗+蜂毒穴位注射)\*M=(肩痛+肩周炎+肩关节周围炎+肩手  
 综合征+颈肩综合症+冻结肩+五十肩)

### 8. Kmbase

((([ALL=오십견] OR [ALL=유착성관절낭염]) OR [ALL=  
 견관절주위염]) OR [ALL=동결견]) OR [ALL=어깨통증])  
 AND ((([ALL=벌침] OR [ALL=벌독]) OR [ALL=봉독약  
 침]) OR [ALL=봉약침]) OR [ALL=봉침])

### 9. RISS

(오십견 OR 유착성 관절낭염 OR 견관절 주위염 OR 동결  
 견 OR 어깨통증) AND (벌침 OR 벌독 OR 봉독 OR 봉약  
 침 OR 봉침)

### 10. OASIS

(오십견 OR 유착성 관절낭염 OR 견관절 주위염 OR 동결  
 견 OR 어깨통증) AND (벌침 OR 벌독 OR 봉독 OR 봉약  
 침 OR 봉침)

### 11. NDSL

(오십견 OR 유착성 관절낭염 OR 견관절 주위염 OR 동결  
 견 OR 어깨통증) AND (벌침 OR 벌독 OR 봉독 OR 봉약  
 침 OR 봉침)

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