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Original Article

An Overview of Bee Venom Acupuncture in the Treatment of Arthritis

Jae-Dong Lee[1,*], Hi-Joon Park[2,*], Younbyoung Chae[2] and Sabina Lim[2]

[1]Department of Acupuncture and Moxibustion and [2]Department of Meridian and Acupuncture, Seoul College of Korean Medicine, Kyung Hee University, Seoul, South Korea

Bee venom acupuncture (BVA), as a kind of herbal acupuncture, exerts not only pharmacological actions from the bioactive compounds isolated from bee venom but also a mechanical function from acupuncture stimulation. BVA is growing in popularity, especially in Korea, and is used primarily for pain relief in many kinds of diseases. We aimed to summarize and evaluate the available evidence of BVA for rheumatoid arthritis and osteoarthritis. Computerized literature searches for experimental studies and clinical trials of BVA for arthritis were performed on the databases from PUBMED, EMBASE and the Cochrane Library. In addition, two leading Korean journals (*The Journal of Korean Society for Acupuncture and Moxibustion* and *The Journal of Korean Oriental Medicine*) were searched for relevant studies. The search revealed 67 studies, 15 of which met our criteria. The anti-inflammation and analgesic actions of BVA were proved in various kinds of animal arthritic models. Two randomized controlled trials and three uncontrolled clinical trials showed that BVA was effective in the treatment of arthritis. It is highly likely that the effectiveness of BVA for arthritis is a promising area of future research. However, there is limited evidence demonstrating the efficacy of BVA in arthritis. Rigorous trials with large sample size and adequate design are needed to define the role of BVA for these indications. In addition, studies on the optimal dosage and concentration of BVA are recommended for future trials.

Keywords: acupuncture – analgesia – anti-inflammation – bee venom – osteoarthritis – rheumatoid arthritis

Introduction

Bee venom, as a therapeutic modality in use since at least the second century BC in Eastern Asia, has been extensively researched and practiced in Korea, focusing on clinical applications as a meridian therapy (1). Herbal acupuncture is a new method of acupuncture where a distilled herbal decoction is extracted, and purified to be administered on acupoints for stimulation (2). Bee venom acupuncture (BVA) is a kind of herbal acupuncture taking advantage of diluted bee venom instead of distilled herbal decoction (2). The bee venom once extracted and processed is utilized on the relevant sites according to specific diseases or acupoints. BVA simultaneously exerts pharmacological actions from the bioactive compounds isolated from bee venom and mechanical actions from the acupuncture stimulation. BVA has been considered as a promising therapeutic method for various diseases, especially in Korean medicine. BVA has long been used in a variety of conditions and good evidence for its effectiveness exists in pain syndrome, herniation nucleus pulpous, cervical disc protrusion and progressive muscle atrophy (3–6).

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology that is characterized by progressive joint destruction, deformity, disability and premature death in most patients. Osteoarthritis (OA) is characterized by degeneration of articular cartilage with proliferation and remodeling of subchondral bone. In complementary and alternative medicine

For reprints and all correspondence: Sabina Lim, Department of Meridian and Acupuncture, College of Korean Medicine, Kyung-Hee University, 1 Hoegidong, Dongdaemungu, Seoul 130–701, South Korea. Tel: +822 961 0324. Fax: +822 961 7831; E-mail: lims@khu.ac.kr
*The first two authors contributed equally to this article.

(CAM), acupuncture is one of the most common therapies used to treat a number of human inflammatory diseases including rheumatoid arthritis and osteoarthritis (7,8). Moreover, there are a sufficient number of studies using CAM therapies, including herbal therapy, glucosamine, chondroitin sulfate and *S*-adenosylmethionine, in these conditions despite claims often heard about the lack of evidence for CAM (9). It is notable that BVA demonstrated anti-inflammatory and analgesic actions in animal studies (10–19) as well as in clinical trials (20–23). However, the effectiveness of BVA for this indication is still not well known and no review of this subject exists.

The purpose of the present study was, therefore, to evaluate the data from experimental and clinical studies and to explore further ways to better comprehend the effectiveness of BVA on arthritis.

Methods

Data Sources

Computerized literature searches for experimental studies and clinical trials of BVA for arthritis were performed on the databases from PUBMED, EMBASE and the Cochrane Library. In addition, two leading Korean journals (*The Journal of Korean Society for Acupuncture and Moxibustion* and *The Journal of Korean Oriental Medicine*) were searched for relevant studies. The search terms 'bee venom', 'bee venom therapy', 'acupuncture' and 'anti-inflammation', 'rheumatic arthritis' or 'osteoarthritis' were used. Further hand-searches were performed in the reference lists of all located articles.

Categorization of Studies

For experimental analysis, we focused on the animal research that have evaluated anti-inflammatory and anti-nociceptive effects. For clinical studies, we included all trials with rheumatoid arthritic and osteoarthritic patients. We included the papers in our review only when they applied bee venom treatment to acupoints. The search found 67 studies, of which 15 met our criteria.

Quality Assessment

The methodological quality of each randomized controlled trial (RCT) was rated according to the Jadad scale (24). Points were awarded as follows: the study was described as randomized, 1 point; the randomization scheme was described and appropriate, 1 point; the study was described as double blind, 1 point; the method of double blinding was appropriate, 1 point; there was a description of withdrawals and dropouts, 1 point. The maximum point-score available was 5.

Results

Anti-inflammatory and Anti-nociceptive Effects of BVA in Animals

The anti-inflammation and analgesic effects of BVA have been proven in various kinds of animal arthritic models, such as adjuvant, carrageenan or lipopolysaccharide (LPS)-induced arthritis.

Kwon *et al*. (10) and Seo *et al*. (12) conducted a comparative study of acupoint versus non-acupoint stimulation on an adjuvant induced RA animal model with BVA. Direct injection of bee venom into acupoint ST36 produced a potent anti-nociceptive effect, suggesting that this alternative form of acupoint stimulation using bee venom can be applied for relieving pain.

Kim *et al*. (14) and Choi *et al*. (13) conducted an experiment to show effectiveness of BVA at acupoint ST36 by inducing arthritis in rats by a mixture of type II collagen. It compared levels of proteolytic enzyme activities and free-radical-induced protein damage in synovial fluid from this animal model. BVA at acupoint BL23 significantly reduced proteolytic enzyme activities and level of reactive oxygen species (ROS)-induced oxidative damage to synovial fluid proteins in this model (14).

Doh *et al*. (17) observed anti-inflammatory effects on knee arthritis induced by carrageenan in rats. Numbers of white blood cells and red blood cells increased, and values of hemoglobin hematocrit also showed significant therapeutic effects. Lee *et al*. (18) administered bee venom at acupoint ST36 prior to carrageenan, and evaluated acute edema and heat on the paw and analyzed the Fos expression of the spinal cord quantitatively. Pretreatment with BVA prior to carrageenan administration inhibited both carrageenan-induced edema and heat on the paw, showing clear correlation between change rates of edema on the foot and the expression of Fos positive neutron on the spinal cord.

The effects of BVA at acupoint GB34 on LPS-induced arthritis were conducted to examine the therapeutic effects of BVA in mice (15,19). Bee venom decreased numbers of white blood cells, infiltration of leukocytes and fibroblasts into synovial joints, CD56, IL-1 β, IL-2R, CD54 and CD106 in synovial membrane when compared with controls.

Kim *et al*. (16) and Yim *et al*. (11) administered adult Sprague–Dawley rats with bee venom directly into acupoint ST36 or into an arbitrary non-acupoint located on the back. Pretreatment with bee venom into the ST36 acupoint significantly decreased paw-licking time in the late phase of the formalin test and also markedly inhibited spinal cord Fos expression induced by formalin injection.

Several studies suggest that the effects of BVA depend on the locations injected; acupuncture points exert much stronger effects than non-acupoints (10–12,16). The effects of bee venom might be intensified by acupuncture stimulations, which may help in reaching therapeutic goals.

Favorable Effects of BVA on RA and OA Patients in Clinical Trials

One RCT and two uncontrolled clinical trials were found for RA (Table 1). Kwon (20) performed BVA on 10 patients diagnosed with RA. The results showed 90% validity with remarkable improvement in two cases, good improvement in five cases, and effective improvement in two cases. In Lee *et al*.'s

Table 1. The effects of bee venom acupuncture (BVA) on rheumatoid arthritis

Author (year)	Study design	Study quality*	Groups and interventions	Outcome measure and results
Lee SH, Hong SJ *et al*. (2003)	Randomized, controlled, two groups	1 + 0 + 1 + 1 + 1 = 4	• Rheumatic arthritis patients ($n = 80$): BVA group ($n = 40$) and control group ($n = 40$). • Treatment: twice a week for 2 months, BVA at proximal and distal phalangeal joints: SI5, LI5, PC7, TE4, LI11, TE10, HT3, SI8 ST36, GB34, SP9, EX-LE2, EX-LE4, GB40, BL62, SP5 and KI6, according to patients' symptomatic areas	• Tender joint count: BVA < control ($P < 0.05$) • Swollen joint count: BVA < control ($P < 0.05$) • Morning stiffness: BVA < control ($P < 0.05$) • Laboratory findings: • ESR: BVA < control ($P < 0.05$); • CRP: BVA < control ($P < 0.05$)
Lee SH, Lee HJ *et al*. (2003)	Uncontrolled	NA	• Rheumatic arthritis patients . ($n = 22$) • Treatments: twice a week for 3 months, BVA at proximal and distal phalangeal joints SI5, LI5, PC7, TE4, LI11, TE10, HT3, SI8, ST36, GB34, SP9, EX-LE2, EX-LE4, GB40, BL62, SP5 and KI6, according to patients' symptomatic areas	• Tender joint counts: before > after ($P < 0.01$) • Swollen joint counts: before > after ($P < 0.01$) • Analgesic effect with visual analogue scale: before > after ($P <0.001$) • Morning stiffness: before > after ($P < 0.01$)
Kwon KR *et al*. (1998)	Uncontrolled	NA	• Rheumatoid arthritis patients ($n = 10$)	• 90% clinical improvements in symptoms. Remarkable improvement, two cases; good improvement, five cases; effective, two cases

*Jadad score (randomization 1 point + appropriate randomization method 1 point + blinding 1 point + appropriate blinding method 1 point + describing withdrawals and dropouts 1 point = maximum 5 points).
ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

study (21), patients with RA who met ACR (American College of Rheumatology) 1987 revised criteria for diagnosis of RA were treated with BVA therapy twice a week for 3 months. Tender joint counts, swollen joint counts and duration of morning stiffness in patients after BVA therapy was significantly lower than those before BVA therapy. Lee *et al*. (22) also performed the RCT for evaluating effects of BVA in RA patients. RA patients were recruited and randomly divided into a BVA group and a control group by random selection. Each group was treated with BVA or normal saline injection on acupoints twice a week for 8 weeks. Tender joint count, swollen joint count, morning stiffness, pain, health assessment questionnaire, ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) were estimated and analyzed at baseline, at 1 month and 2 months after BVA therapy. Compared to the control group, the BVA group showed a significant decrease in tender joint count, swollen joint count, morning stiffness and health assessment questionnaire after 2 months. Pain, ESR and CRP also showed a significant decrease in the BVA group after 1 and 2 months.

One RCT and one uncontrolled trial were searched for OA (Table 2). Wang *et al*. (23) reported on treatment by BVA of 70 knee arthritis patients. The results were: excellent, 11 cases (15.7%); good, 31 cases (44.3%); and improved, 16 cases (22.9%). Kwon *et al*. (25) conducted an experiment to investigate whether direct administration of bee venom into an acupoint is a clinically effective and safe method for relieving pain of patients with knee OA as compared to traditional needle acupuncture. Four weeks of BVA treatment were followed by pain relief scores and computerized infrared thermography (IRT) for evaluation of efficacy of BVA. The group of subjects receiving BVA showed substantial relief of pain as compared to the group receiving traditional needle acupuncture, and the IRT score was significantly improved to parallel the level of pain relief. They demonstrated that a majority (82.5%) of subjects receiving BVA (33 out of 40 subjects) reported substantial pain relief as compared with traditional acupuncture therapy (55%). The therapeutic efficacy was favorable irrespective of disease duration (acute, subacute or chronic stage), arthritic type (unilateral or bilateral knee OA) and radiological severity.

Discussion

Collective evidence from *in vivo* experiments shows that BVA has a potent analgesic and anti-inflammatory effect. Two clinical studies on degenerative arthritis and three clinical studies on RA suggest that BVA may become a promising treatment for both RA and OA. The number of controlled studies of BVA in arthritis is quite small, and their quality is limited. However, it would be worth considering BVA as an applicable treatment for arthritis in CAM.

Many animal investigations cited in this review have shown that BVA is capable of producing anti-nociception and anti-inflammatory actions in several animal models (10–19). Several studies suggested that the effects of bee venom were intensified by acupuncture stimulations, which may help in reaching therapeutic goals. The anti-nociceptive property of

Table 2. The effects of bee venom acupuncture (BVA) on osteoarthritis

Author (year)	Study design	Study quality*	Groups and interventions	Outcome measure and results
Kwon YB *et al*. (2001)	Randomized, controlled, two groups	1 + 0 + 0 + 0 + 0 = 1	• Knee osteoarthritic patients (n = 60): BVA (n = 40) and acupuncture (n = 20) Treatments: • BVA: twice a week for 4 weeks at Ex-LE2, and Ex-LE5 and LR8. • Acu: once a day needles were selected within five points (or 10 bilaterally) among acupoints SP10, ST34, ST36, GB34, LR3, Ex-LE2 and Ex-LE5 considering individual symptoms for 20 min. • Deqi sensation was induced.	• Subjective pain relief score • Excellent improvement: BVA (37.5%), Acu (5%) • Good improvement: BVA (45%), Acu (50%) • Fair: BVA (17.5%), Acu (40%) • Poor: BVA (0%), Acu (5%) • Comparison of the effects between BVA and Acu: BVA > Acu (P < 0.01 by Mann-Whitney U-test).
Wang OH *et al*. (2001)	Uncontrolled	NA	• Knee osteoarthritic patients (n = 70) • Treatments: BVA once or twice a week at EX-LE2, EX-LE4, LR3 and ST34	• Lysholm and Karsson's knee joint evaluation scale: • Limp: Pretreatment < Posttreatment • Assitive device: NS • Up stair: Pretreatment < Posttreatment • Giving way: Pretreatment < Posttreatment • Squat: Pretreatment < Posttreatment • Sit down and up: Pretreatment < Posttreatment • Crepitation: Pretreatment < Posttreatment • Swelling: Pretreatment < Posttreatment • Pain: Pretreatment < Posttreatment

*Jadad score (randomization 1 point + appropriate randomization method 1 point + blinding 1 point + appropriate blinding method 1 point + describing withdrawals and dropouts 1 point = maximum 5 points).
Acu, acupuncture; NA, not applicable; NS, not significant.

BVA may be explained by the process of counter irritation; that is, when noxious stimuli are applied to body regions, these stimuli increase the pain thresholds and reduce pain rating scores through the body. For centuries, pain has been relieved by counter-irritation methods such as moxibustion (a method of burning herbs to stimulate acupuncture points) on arthritic limbs (25).

The two uncontrolled investigations (20,21) and one RCT study (22) from the above search results showed that bee venom therapy was very effective in the treatment of RA. The treatment goal for RA can be summarized as follows: first, pain and inflammation should be prevented, since it can lead to pain in the joints, disformity of the joints, or loss of functions; second, chronic inflammation is inhibited so that loss of function in the joints is prevented or minimized to help patients back to normal life. The RCT study of Lee *et al*. (22) observed that BVA treatment improved the number of painful joints, swollen joints, morning stiffness and hematological indices. Utilizing the Korean health-related questionnaire, it also showed that BVA treatment could contribute to improvement of patients' quality of life.

One RCT investigations (25) and one uncontrolled trial study (23) demonstrated that herbal acupuncture using bee venom for knee arthritis was effective. Previous studies have established the effectiveness of acupuncture treatment both in relieving pain and recovering dysfunction of knees in elderly patients with OA in comparison to non-acupuncture treated control groups (26). Kwon *et al*. (25) compared therapeutic effects of acupuncture by hand manipulation with herbal acupuncture using bee venom. BVA is more effective than acupuncture. Computerized IRT objectively displayed changes in skin temperature in the painful region. Computerized IRT is a method of examination whereby infrared rays naturally emitted from the body are detected, displaying minute changes in body temperature on painful or other diseased parts on the computer monitor. It is a widely employed method of examination, now used for evaluation of pain and prognosis. Kwon *et al*. (25) showed that the temperature on the knee region significantly decreased after treatment with bee venom. However, significant change was examined in all groups with severe, moderate or mild degrees of degenerative arthritis.

RA is a typical autoimmune disease, of which exact causative factor have not yet been verified various aspects. The pathogenesis and pathophysiology of RA are being investigated. Until now, there are no methods recommended from perfect prevention or perpetual extermination after onset of RA. Existing methods of treatment for RA can be categorized as medication, surgery, rehabilitation and physical therapy. Medication therapy used in most cases utilizes various kinds of medicine such as NSAIDs, adrenal cortical hormone,

anti-rheumatic drugs and immunosuppressive agents, which can cause severe adverse effects such as depression, peptic ulcers, enterohemorrhage, liver malfunction and renal disorders. OA is the most commonly examined arthritis, also known as 'degenerative arthritis' or 'degenerative arthritic disease'. Mostly occurring in middle-aged or elderly people, it attacks the weight-bearing joints—mostly the knee joint—and causes local degenerative changes in cartilage, hypertrophy of subchondral bones, excessive bone formation around osteochondral regions and disformity of joints. Clinically, it shows repetitive pain, ankylosis and gradual dysfunction of movement with inflammatory changes occurring only in a few patients. Western medical treatment of knee arthritis utilizes conservative methods such as medication therapy, rest and exercise, and physical therapy, and surgical methods like arthroscopic debridement, osteomy, arthroscopic surgery and total knee arthroplasty. Patients with mild symptoms should be provided with teaching, physical therapy, and non-narcotic medication and when these do not improve symptoms, prescription of non-steroidal drugs can be considered only when patients have no contraindications for the drug. Steroids are administered to patients with exudative knee arthritis. These treatments have certain adverse effects in RA, calling for safer and more effective methods of treatment (27,28).

In general, in order to determine the appropriateness of using CAM therapy in various conditions, it is necessary to consider the relevant problems such as: the severity and acuteness of illness; curability of the illness by conventional forms of treatment; degree of invasiveness, associated toxicities and side effects of conventional treatment; availability and quality of evidence of utility and safety of desired CAM treatments; level of understanding of risks and benefits of CAM treatments combined with the patient's understanding and voluntary acceptance of those risks; and the patient's persistence of intention to use CAM therapies (29). A number of complications or adverse effects of conventional treatment call for safer and more effective methods of treatment (7). There have been investigations on the effects of acupuncture treatment on RA and OA (7,26). Recently, bee venom therapy has been proposed as another approach. Several clinical trials have demonstrated that BVA could improve arthritis-related symptoms. However, evidence for BVA is still scarce. In order to enlarge the clinical therapeutic field of BVA throughout the world, rigorous trials of well-organized design are urgently required to determine the role of BVA in treatming of arthritis. A greater understanding of the risks and benefits of BVA is also needed.

Safety intervention is important for estimating its risk–benefit framework. Serious adverse events such as anaphylaxis and non-serious adverse effects such as local swelling or itching are reported with BVA treatment but are infrequent provided that it is practiced according to established safety rules in appropriate anatomic regions (30). Similarly, there is concerned about the extra cost of BVA. At present no conclusive cost-effectiveness of BVA for arthritis is available, but it requires consideration from an economic point of view. In addition, the determination of acupoints, amount and concentration of bee venom should be carefully considered. Studies on the standardization of such measurements are also required.

Most systematic reviews of therapeutic interventions include only RCTs, which are generally considered as the gold standard for evaluation. However, the medical literature is full of non-randomized and uncontrolled studies. It is certainly highly problematic to draw conclusions on causal effects from non-randomized or uncontrolled studies. However, RCTs also have flaws in other aspects. First, they often recruit only a small and non-representative sample of patients who are then treated and monitored under man-made conditions (31,32). As a result, the degree to which the results can be generalized and are externally valid is unclear. Second, RCTs in chronic conditions have limited observation periods because of ethical reasons, feasibility or resources (33,34). If the number or quality of available randomized trials is not sufficient to draw conclusions, non-randomized studies might be useful to give a better overview of what is known so far and to inform future research. It is obvious that the number of subjects and the quality of the studies in this review have limitations. However, BVA is considered to be highly promising in the treatment of arthritis.

Conclusion

A sufficient number of animal studies have shown that BVA has significant anti-inflammatory and analgesic effects. Due to paucity and methodological flaws in the existing clinical studies, it is premature to draw any firm conclusions at this time. However, the effectiveness of BVA for arthritis is likely to be a promising area of future research. Rigorous trials with large sample sizes and adequate design are required to define the role of BVA for these indications.

References

1. Yin CS, Koh HG. The first documental record on bee venom therapy in Oriental medicine: 2 prescriptions of bee venom in the ancient Mawangdui books of Oriental medicine. *J Kor Acup Mox Soc* 1998;15:143–7.
2. Lee HJ. *Principle of herbal acupuncture and clinical application*. Seoul: Iljoongsa, 1999.
3. Lim JK, Cho GC, Park YN, Wang WH, Jang HS. A clinical study on the patient of sequestrated disc treated by bee venom therapy—according to a radiological change. *J Kor Acu Mox Soc* 2002;19:256–63.
4. Cha JD, Jeong SM, Kim GO, Kim GS, Kim NO. The comparison of effectiveness between acupuncture and its cotreatment with bee venom acua-acupuncture therapy on the treatment of herniation of nucleus pulpous. *J Kor Acu Mox Soc* 2004;21:149–58.
5. Kim CH, Lee BH, Seo JC, et al. A case of the reduction of cervical disc protrusion on the CT scanning after 5 months by oriental medical treatments added by bee venom acupuncture. *J Kor AM Meridian Pointology Soc* 2001;18:141–8.
6. Kim YH, Yook TH, Song BY, Lee DH. Clinical report of oriental medicine treatment with bee venom therapy of progressive muscle atrophy 1 patient. *J Kor Inst Herbal Acu* 2000;3:119–40.
7. Berman BM, Swyers JP, Ezzo J. The evidence for acupuncture as a treatment for rheumatologic conditions. *Rheum Dis Clin North Am* 2000;26:103–15, ix–x.
8. Ezzo J, Hadhazy V, Birch S. Acupuncture for osteoarthritis of the knee: a systematic review. *Arthritis Rheum* 2001;44:819–25.

9. Soeken KL. Selected CAM therapies for arthritis-related pain: the evidence from systematic reviews. *Clin J Pain* 2004;20:13–8.
10. Kwon YB, Lee JD, Lee HJ, et al. Bee venom injection into an acupuncture point reduces arthritis associated edema and nociceptive responses. *Pain* 2001;90:271–80.
11. Yim YK, Seo JC, Kim YS, Kim CH, Lee YH, Choi DY. The effect of bee venom acupuncture into Chok-samni (ST36) formalin—induced pain behavior. *J Kor Acu Mox Soc* 2000;17:139–52.
12. Seo DM, Park DS, Kang SG. The analgesic effect of bee venom aqua-acupuncture and its mechanism in the rat model with adjuvant-induced arthritis. *J Kor Acu Mox Soc* 2003;20:85–97.
13. Choi DY, Lee JD, Kim TW. The effect of bee venom on type 2 collagen-induced arthritis. *J Kor Acu Mox Soc* 2002;19:92–104.
14. Kim MJ, Park SD, Lee AR, Kim KH, Jang JH, Kim KS. The effect of bee venom acupuncture on protease activity and free radical damage in synovial fluid from collagen-induced arthritis in rats. *J Kor Acu Mox Soc* 2002;19:161–75.
15. Do WS, Kim KH, Kim KS. Effects of aqua-acupuncture (*Cortex Pumilae, Ramulus Cinnamomum, Radix Achyranthis, Apitoxin, Calculus Bovis, Fel Ursi, Moschus* compound) in mice with lipopolysaccharide. *J Kor Acu Mox Soc* 2001;18:157–69.
16. Kim HW, Kwon YB, Ham TB, et al. Acupoint stimulation using bee venom attenuates formalin-induced pain behavior and spinal cord fos expression in rats. *J Vet Med Sci* 2003;65:349–55.
17. Doh WS, Jang JH, Kim KH, Yoon JW, Kim KS. Effects of bee venom therapy on inflammatory edema on knees of rats. *J Kor Acup Mox Soc* 1995;12:211–20.
18. Lee JH, Kwon YB, Han HJ, et al. Bee venom pretreatment has both a antinociceptive and anti-inflammatory effect on carageenan-induced inflammation. *J Vet Med Sci* 2001;63:251–9.
19. Lee SD, Kim KS. Effects of *Achyranthes japonica* and bee venom acupuncture on the cell immunity of LPS-induced arthritis in rats. *J Kor Acu Mox Soc* 1999;16:287–316.
20. Kwon GR. Clinical study on treatment of rheumatoid arthritis by bee venom therapy. *Proc Congress Kor Med* 1998:130–131.
21. Lee SH, Lee HJ, Baek YH, et al. Effects of bee venom on the pain, edema, and acute inflammatory reactant of rheumatoid arthritic patients. *J Kor Acu Mox Soc* 2003;20:77–84.
22. Lee SH, Hong SJ, Kim SY, et al. Randomized controlled double blind study of bee venom therapy on rheumatoid arthritis. *J Kor Acu Mox Soc* 2003;20:80–8.
23. Wang OH, Ahn KB, Lim JK, Jang HS. Clinical study on effectiveness of bee venom therapy on degenerative knee arthritis. *J Kor Acu Mox Soc* 2001;18:35–47.
24. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
25. Kwon YB, Kim JH, Yoon JH, et al. The analgesic efficacy of bee venom acupuncture for knee osteoarthritis: a comparative study with needle acupuncture. *Am J Chin Med* 2001;29:187–99.
26. Berman BM, Singh BB, Lao L, et al. A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. *Rheumatology* 1999;38:346–54.
27. Zochling J, March L, Lapsley H, Cross M, Tribe K, Brooks P. Use of complementary medicines for osteoarthritis—a prospective study. *Ann Rheum Dis* 2004;63:549–54.
28. Baumrucker SJ. Complementary medicine and the scientific method: mainstreaming proven 'alternative' therapies. *Am J Hosp Palliat Care* 2002;19:369–71.
29. Adam KE, Cohen ME, Eisenberg D, Jonsen AR. Ethical Considerations of Complementary and Alternative Medical Therapies in Conventional Medical Settings. *Ann Intern Med* 2002;137:660–4.
30. Hwang YJ, Lee BC. Clinical study of anaphylaxis on bee venom acupuncture. *J Kor Acu Mox Soc* 2000;17:149–59.
31. Charlson ME, Horwitz RI. Applying the results of randomised trials to clinical practice: impact of losses before randomisation. *Br Med J* 1984;289:1284–8.
32. Mant D. Can randomised trials inform clinical decisions about individual patients? *Lancet* 1999;353:743–6.
33. Feinstein AR. An additional basic science for clinical medicine: II. The limitations of randomized trials. *Ann Intern Med* 1983;99:544–50.
34. Pincus T. Limitations of randomized clinical trials to recognize possible advantages of combination therapies in rheumatic diseases. *Seminar Arthrit Rheumatism* 1993;23:2–10.

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