



Case Report

Bee venom acupuncture and herbal medicine for hand eczema: Two case reports and an in vivo study

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ARTICLE INFO

Keywords:

Eczema
Contact dermatitis
Bee venom acupuncture
San Wu Huangqin decoction

ABSTRACT

Introduction: Eczema and contact dermatitis are relatively common, non-life-threatening disease, but can reduce the patient's quality-of-life when it becomes chronic. This study describes two cases of bee venom acupuncture (BVA) and herbal medicine (San Wu Huangqin decoction; SWH) co-treatment for hand eczema and contact dermatitis, then confirms the effect of the combination therapy in an in vivo model of eczema.

Case presentation: A 56-year-old female (case 1) and a 33-year-old male (case 2) presented to the clinic with symptoms of itching and erythema (case 1), and scaliness (case 2) on both hands. Both were diagnosed with hand eczema and contact dermatitis based on examination of the erythema and scaliness. They were treated with BVA and SWH for three months. The lesions were healed and had not recurred after 1 and 3 years of follow-up. A mouse study was conducted by repeated application of 2,4-dinitrochlorobenzene (DNCB) to induce eczema-like contact dermatitis in Balb/c mice. In a DNCB-induced eczema-like contact dermatitis model, BVA and SWH co-administration synergistically improved clinical symptoms seen in eczema. Also, they improved histological changes of the skin, suppressed immune cell infiltration, and decreased inflammatory cytokines and immunoglobulin E in the serum.

Conclusion: This study suggests BVA and SWH could be an alternative treatment for eczema and contact dermatitis.

Introduction

Hand eczema (HE) is commonly used to describe inflammation of the hands characterized by redness, scaling, edema, vesicles, hyperkeratosis, fissures, and erosions.¹ Exogenous HE comprises of irritant contact dermatitis, atopic contact dermatitis, and urticaria/protein contact dermatitis; endogenous HE comprises atopic HE, hyperkeratotic, and acute recurrent vesicular.² Contact dermatitis is related to domestic or occupational exposures such as detergent, soap, diapers, dye, chemicals, cosmetics, or metal accessories.³ The range of HE prevalence in studies is

relatively wide. In a Norwegian cohort, the lifetime prevalence of HE was 11.3 %, and work-related HE was 4.8 %.⁴ Lifetime prevalence reached 15 % according to a review study.⁵ Among the ~22,000 patients who visited the dermatology department of 24 university hospitals in South Korea that were diagnosed with a skin disease of the hands, 36.3 % were irritant contact dermatitis, and 9.7 % were allergic contact dermatitis.⁶

HE is mainly treated by topical corticosteroids, UV light, and systematic therapy depending on the severity of symptoms.⁷ Avoiding risk factors and changing lifestyles are also needed. Unfortunately, the

Abbreviations: HE, hand eczema; BVA, bee venom acupuncture; SWH, San Wu Huangqin decoction.

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<https://doi.org/10.1016/j.explore.2024.03.002>

Received 8 January 2024; Received in revised form 5 March 2024; Accepted 18 March 2024

Available online 21 March 2024

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prognosis of HE is poor. According to a 15-year follow-up study in Sweden, 12 % of HE patients complained of continuous eczema during the period.⁸ In another study of occupational HE in Denmark, only 19.3 % of patients were completely healed at the 5-year-follow-up.⁹

Topical cream containing bee venom has shown a therapeutic effect on atopic dermatitis (AD) by reducing inflammation.^{10,11} This study hypothesized that bee venom acupuncture (BVA) is effective for eczema and contact dermatitis. With the two case reports here, we aim to suggest alternative treatments for HE by providing insights into the effectiveness of BVA and herbal medicine. Further, we conduct an animal study to verify the effect of BVA on eczema, especially focusing on the benefits of co-administration with herbal medicine.

Materials and methods

Case reports

Interventions

Both patients with HE and contact dermatitis were treated with BVA (Beeplus, Chilgok, Gyeongsangbuk-do, Korea). BVA treatments were for a total of 19 and 16 sessions, respectively, using a sterile hypodermic syringe (31-gauge, 0.8 mL; ShinaMed, Anseong, Korea). On the first day of treatment a BVA skin test was conducted (0.3 mL BVA diluted to 10 % in case 1, 0.2 mL BVA diluted to 10 % in case 2). The BVA dose was increased to 2.4 mL (case 1) or 0.9 mL (case 2) on the last day of treatment. San Wu Huangqin decoction (SWH) was prescribed in both cases.

Principles of BVA treatment

The concentration and dose of BVA were the most important factors in the BVA procedure. To maximize the therapeutic effect, doctors should select the safest and the most appropriate concentration and dose according to the patient's condition, constitution, and the severity of the disease. For mild and local lesions, low-dose BVA may be effective, but for severe symptoms, it is challenging to expect satisfactory treatment effects with low-concentrations of BVA alone. The concentration of BVA is selected according to the patient's medical history, such as those that have never been exposed to BVA or have had a high exposure to BVA. In the case of treatment on sensitive areas such as the face or the extremities, the first treatment concentration of BVA was 10 %. It is recommended to conduct the treatment procedure after inducing the hypersensitivity reaction to a minimum.

Herbal medicines (concomitant treatment)

SWH consists of Rehmanniae Radix (地黃) 6 g, Scutellariae Radix (黃芩) 3 g, Sophorae Radix (苦參) 3 g based on daily dose. Each patient was administered this decoction twice a day during the treatment period.

Outcome measures

Photographs were used to compare the degree of dermatitis and cracked skin before and after treatment of the patient, and a visual analogue scale (VAS) was used to indicate changes in itching and lesions, which are the main symptoms. The criteria for the VAS score are as follows; 0 score for no symptoms; 1 to 2 score for mild symptoms; 3 to 6 score for moderate symptoms; 7 to 8 score for severe symptoms; 9 to 10 score for very severe symptoms.

In vivo study

Experimental design

Eczema-like contact dermatitis was induced using 2,4-dinitrochlorobenzene (DNCB) as previously described.¹² Six-week-old Balb/c mice were exposed to 1 % DNCB once per week for 4 weeks. From the second week, mice were injected with BVA (50 µg/kg diluted in PBS) or saline and SWH (200 mg/kg, 3 times/week) was orally administered (Supplemental file 1).

Hematoxylin & eosin (H&E) and toluidine blue staining

Skin tissues were stained with H&E for histological examination and toluidine blue to identify mast cells. Representative pictures were obtained using EVOS M7000 Imaging System (Thermo Fisher Scientific, Waltham, MA, USA).

Serum analysis

Serum levels of interleukin (IL)-4, IL-5, IL-13, and immunoglobulin E (IgE) were measured using enzyme-linked immunosorbent assay kits (BD Biosciences, San Jose, CA, USA). Serum levels of aspartate transaminase (AST), alanine transferase (ALT), creatinine and blood urea nitrogen (BUN) were measured using the Cobas c502 with ISE system by the Seoul Clinical Laboratories Healthcare (Yongin-si, Gyeonggi-do, Korea).

Western blot

Western blot assays were performed as previously described.¹² The membranes were incubated with the following primary antibodies (1:1000) at 4 °C overnight: Antibodies for thymic stromal lymphopoietin (TSLP), signal transducer and activator of transcription 5 (STAT5), phospho-STAT5 and phospho-nuclear factor kappa B (NFκB) were purchased from Cell Signaling Technology (Danvers, MA, USA). STAT3, phospho-STAT3 and Bcl XL were purchased from Abcam Inc. (Waltham, MA, USA). Antibodies for NFκB and glyceraldehyde-3-phosphate dehydrogenase were purchased from ABclonal (Woburn, MA, USA). Next day, membranes were incubated with secondary antibodies. Chemiluminescence signals were detected by the Davinch In Vivo System (Davinch K, Seoul, Korea).

Statistical analysis

Results are expressed as mean ± standard error (S.E.) of three or more separate experiments. Statistical analyses were performed using one-way ANOVA followed by Tukey's post-hoc test (GraphPad Software, Inc., Boston, MA, USA). Probability values <0.05 are considered statistically significant.

Results

Case reports

Case 1

A 56-year-old woman complained of continuous dermatitis on the face and both dorsal hands with symptoms of itching and erythema (Fig 1a, 1b); VAS for itching was 7 score and for lesions was 8 score. The patient had worked as a hairdresser for 20 years and had been continuously exposed to cosmetics and creams throughout. Three years ago, the patient had displayed red spots on both wrists and the area under the lower lip and had been diagnosed with contact allergic dermatitis and treated for two months in a local dermatology clinic. With the improvement of symptoms, the patient had stopped treatment. Steroids had been used whenever the symptoms of itching or erythema had appeared. The symptoms reappeared four months ago, and the patient had been reluctant to use steroids without firstly quitting their occupation. During a physical examination at the Wonjae Korean Medicine clinic, erythema on the hands and the area under the lower lip (Fig 1c, 1d) were revealed. Neither biopsies or patch tests were conducted. Based on these features and occupation, HE and contact dermatitis were diagnosed. A Korean medicine doctor with 20 years of experience diagnosed this patient using Korean Medicine (KM) theory; based on the symptoms, including flushing, etc.

The patient underwent treatment with BVA and herbal medicine, based on KM theory. BVA was injected in the area under the lower lip and both hands. She was treated with BVA 19 times for three months using a sterile hypodermic syringe. 0.3 mL of BVA diluted to 10 % was used on the initial day of treatment, and this was increased to 2.4 mL by the final day. San Wu Huangqin decoction was also prescribed. The

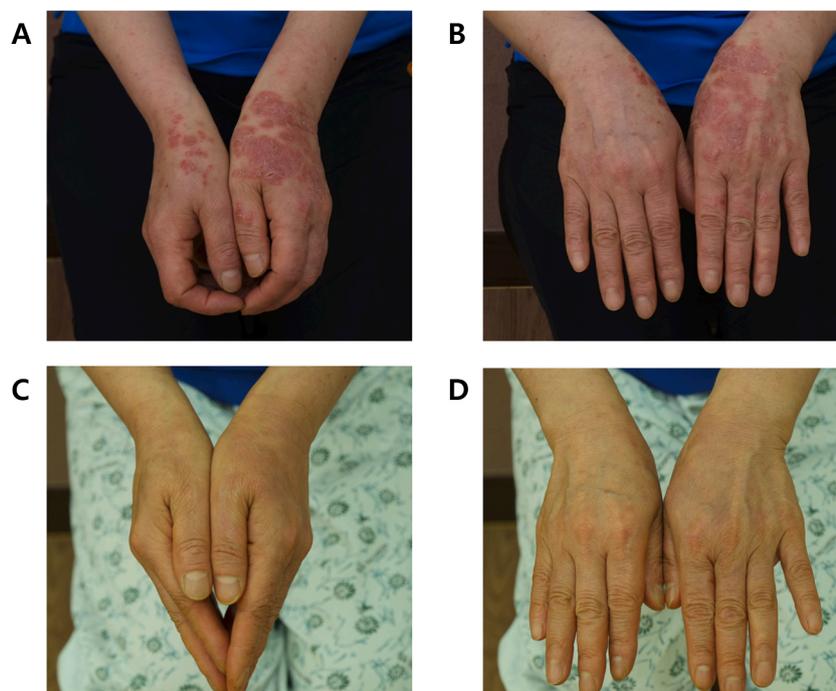


Fig. 1. Hand eczema and contact dermatitis before and after treatment in Case 1. (a, b) before, and (c,d) after treatment.

treatment was well-tolerated with no adverse events reported. Itching (VAS 1) and erythema (VAS 0) symptoms were decreased after therapy. The lesions were healed after three months and have not recurred after one year. The timelines of case 1 and case 2 are presented in Supplemental file 2.

Case 2

A 33-year-old male complained of continuous seborrheic dermatitis of the scalp and both fingers with scaliness symptoms, despite the sporadic usage of steroid ointments for one year (VAS for lesions was 10 score, Fig 2a). Based on these features, HE and contact dermatitis were diagnosed. As in case 1, the patient was diagnosed using KM theory and received BVA and herbal medicine in the same manner. BVA was injected into both fingers and scalp. On the initial day of treatment, 0.2 mL of BVA diluted to 10 % was used, and the amount of BVA had increased to 0.9 mL by the final day of treatment. Treatment was terminated after three months of herbal medicine administration and 16 sessions of BVA treatment. Symptoms of cracked skin had disappeared, and dead skin cells had begun to fall off within a week. The skin partially returned to normal, and the dead skin continued falling off in a serious lesion by three weeks. VAS for lesions was 2 in 7 weeks, and VAS for lesions was 1 in 8 weeks of treatments. Only the lesion on the right hand's first and fifth finger slightly remained (Fig 2b). The patient's alcohol intake reduced the recovery rate, but the lesions were healed after three months and have not recurred after three years. In addition, any adverse event was reported in case 2.

In vivo studies

We exposed the dorsal skin of Balb/c mice to 1 % DNCB to induce eczema-like contact dermatitis. Body weight was slightly decreased upon DNCB application, with no significant changes in food or water intake. While BVA treatment alleviated dermatitis symptoms, combination treatment of BVA and SWH exhibited better effect in scratching and SCORAD index (Supplemental file 3). BVA plus SWH co-treatment reduced the serum expression of IgE and ILs 4, 5 and 13 comparable to the normal levels. The normalization of serum IL levels indirectly indicates a balanced immune response. Hepatic toxicity and renal toxicity were determined by the serum levels of ALT, AST, creatinine, and BUN. BVA or BVA plus SWH co-treatment did not induce notable toxicity (Supplemental file 3).

Induction of eczema-like contact dermatitis with 1 % DNCB results in epidermal thickening. However, combination treatment with BVA and SWH leads to alleviation of keratosis and restoration of the skin thickness comparable to those of normal mice. Epidermal and dermal thickness were measured after H&E staining. BVA injection reduced the thickness of the dermis, however the change in epidermal thickness was not significant. Infiltration of eosinophils and mast cells were suppressed by both BVA injection or BVA and SWH co-administration (Supplemental file 4).

The spleen size and weight can be used as a marker to determine immune activation and inflammation. DNCB application for 4 weeks resulted in a significant increase of spleen weight. Importantly, while BVA injection could not suppress the increase of spleen, SWH co-

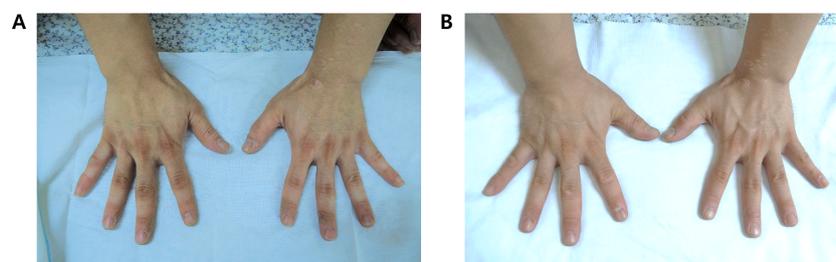


Fig. 2. Hand eczema and contact dermatitis before and after treatment in Case 2. (a) before, and (b) after treatment.

administration showed notable decrease of the spleen size and weight. This suggests the anti-inflammatory effect of SWH can potentiate the effect of BVA on eczema (Supplemental file 4E). Next, we investigated skin tissues of mice to identify factors involved in the effect of BVA and SWH (Supplemental file 4D), to see that co-treatment of BVA and SWH suppressed TSLP-STAT3-STAT5 pathway and NFκB phosphorylation, the key factors in eczema pathogenesis

Discussion and conclusions

This study reports the medical histories and treatment processes of two cases of hand eczema, including contact dermatitis that were cured by BVA combined with herbal medicine. Both patients had suffered from eczema for a long time, with case 1 specifically related to their occupation as a hairdresser. Hairdressers are at risk of contact dermatitis due to working conditions involving activities such as hair washing, hair dyeing, and the use of permanent wave chemicals.¹³ In Italy's case-control study, the prevalence of occupational dermatitis was significantly higher among hairdressers (44.1 %) than controls (10 %) as a result of patch testing (Odds ratio 7.1 95 % CI: 5.7–9.0).¹⁴ In a small study in Bangkok, thirty-two (75 %) of forty-four hairdressers were positive after skin patch testing.¹⁵ Both patients were very satisfied with bee venom therapy after their symptoms were much improved, having previously suffering from HE for a long time.

BVA is an injection of purified bee venom for therapeutic purposes. Bee venom contains mast cell degranulation peptide, melittin, histamine, phospholipase A2, hyaluronidase, acid phosphatase, and non-peptide components (glucose, fructose).¹⁶ Bee venom is used to treat musculoskeletal diseases (i.e. arthritis, arthralgia) and immune-related diseases for its anti-inflammatory and analgesic effects.¹⁷ In vivo studies verified the beneficial effect of bee venom in several mouse models of allergic skin diseases. Such effect was shown in a compound 48/80-induced,¹⁸ a trimellitic anhydride-induced,¹⁹ and a house dust mite-induced model.²⁰ Melittin, its major component, has anti-bacterial, anti-viral, and anti-inflammatory activities.²¹ Previously, the anti-inflammatory effect of bee venom and melittin has been shown in ovalbumin-induced²² or DNCB-induced AD.¹⁰

Bee venom should be dealt carefully; since although rare, it can cause hypersensitivity reactions or anaphylaxis. Bee venom for BVA is generally diluted to a ratio of less than 1:10,000 to minimize the side effects while providing therapeutic effects.¹⁷ Initially, low concentrations are used, and once the patient accustoms, the dose is gradually increased. Therefore, it is important to control dose while balancing the therapeutic effect and safety. There are several types of bee venom treatment: live bee stings, BVA, and externally applied bee venom ointments.¹⁷ Usually bee venom is given topically for eczema, but in cases here, BVA was injected directly into the affected lesions.

SWH decoction, an herbal medicine prescribed to treat prolonged fever, was administered with BVA in both cases. SWH decoction has been proven to have anti-inflammatory, anti-swelling, and anti-itching effects.^{23,24} It consists of *Rehmanniae Radix* 6 g, *Scutellariae Radix* 3 g, *Sophorae Radix* 3 g based on a daily dose. Each herb was effective for improving allergic contact dermatitis in mice. *Rehmanniae Radix* suppressed inflammatory skin lesions in NC/Nga mice.²⁵ *Scutellariae Radix* showed anti-allergic effects in DNCB-induced contact dermatitis by suppressing serum IgE and IL-4 expression in the skin.²⁶ *Sophorae Radix* inhibited mast cell degranulation and improved contact dermatitis induced with dinitrofluorobenzene.²⁷

Our study also confirmed the effect of BVA and SWH co-treatment in an eczema-like dermatitis mouse model. DNCB is a chemical which induces type IV hypersensitive reactions.²⁸ DNCB increases IgE or Th2 cytokines such as IL-4 or IL-13,²⁹ thus DNCB application is a widely used method for eczema animal research. BVA alleviated DNCB-induced eczema-related clinical symptoms such as inflammatory skin lesions, altered scratching and SCORAD index.

IgE level rises in allergic sensitization and atopic disorders, as well as

in eczema. IgE was overexpressed in control mice but was restored to the normal level following BVA and SWH co-treatment. Then, we measured several cytokine levels in the serum including IL-13, IL-4 and IL-5. Level of IL-13 is implicated in Th2-mediated inflammation in AD, while IL-4 interacts with IL-13 in atopic lesions.³⁰ IL-5 is involved in eosinophil migration during inflammation.³¹ IgE and IL levels were suppressed by BVA and SWH co-administration. Pathological eosinophil infiltration causes an upregulation of various inflammatory mediators.³² Augmented influx of eosinophils into the dermis was seen in DNCB-induced contact dermatitis. Administration of SWH potentiated the inhibitory effect of BVA injection on eosinophil influx.

Histology analysis also confirmed decreased dermal/epidermal thickening and immune cell infiltration by BVA and SWH co-administration. Mast cells secrete histamine and play a crucial role in immune activation. They exhibit high-affinity binding to the IgE receptor. Increased mast cell infiltration signifies a heightened autoimmune response, exacerbating atopy.³³ The extent of mast cell infiltration was determined using toluidine blue staining, and infiltrated mast cells decreased in the combination group.

TSLP is an epithelial cell-derived cytokine which plays an initiative role of the development of 'Atopic march'. TSLP protein is highly expressed in the lesion with AD,³⁴ and is related to IL-4, IL-5 and IL-13 levels.³⁵ We find that TSLP expression is decreased by BVA injection or BVA plus SWH co-treatment.

TSLP-STAT5 pathway transcribes various target genes including IL-4, IL-5, and IL-13.^{36,37} Along with TSLP, phosphorylation STAT5 decreased after administering BVA and SWH to the DNCB-induced disease control group. Activation of STAT3 leads to upregulation of various proinflammatory cytokines,³⁸ and we observed the phosphorylation level of STAT3 was suppressed by co-treatment of BVA and SWH. NFκB plays a key role in inflammation. Phosphorylated NFκB enters cellular nucleus and act as a transcription factor for several inflammatory mediators. Thus increased NFκB phosphorylation indicates an inflammatory state,³⁹ which was seen in the DNCB-induced dermatitis group. However, BVA and SWH co-treatment inhibited the activation of NFκB by suppressing phosphorylation, suggesting the role of NFκB in the mechanism of action of the effect of BVA and SWH on eczema.

There are some limitations in these case reports. First, patients were diagnosed as eczema without conducting a patch test during the initial consultation. Patch testing is recommended in patients with eczema; however, in clinical practice, eczema and contact dermatitis are often judged only by skin observation and patient history. In case 2, the cause of eczema was not clearly identified through the patient's history. Second, there were only photos to evaluate the therapeutic effect of BVA. Measured indexes such as changes in skin flaking or discomfort may have helped. Third, careful consideration is required to apply BVA and herbal medicine to other patients. Herbal medicine here is chosen based on traditional Korean medical theory and scientific research.

Overall, bee venom therapy combined with herbal medicine is safe and effective for patients with HE. Since chronic HE is hard to treat, BVA may be an alternative treatment. Further studies are needed to confirm the efficacy of bee venom for eczema.

Declaration

Ethics statement

All two patients had been informed of this study signed consent forms voluntarily and agreed to the publication of their cases reports with associated images.

This case report was approved by the institutional review board of the Korea Institute of Oriental Medicine (No. I-2109/008-006). Animal studies were performed according to the mouse-related guidelines approved by the Kyung Hee University Animal Care Center (approval number: KHSASP-22-191).

Availability of data and materials

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

Funding

The authors are grateful to all patients who allowed the publication of their cases. This article was supported by the Korea Institute of Oriental Medicine (KSN2022210) and the National Research Foundation of Korea (NRF-2020R1C1C1009721).

CRediT authorship contribution statement

Soobin Jang: Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Hyo In Kim:** Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jae Woo Jung:** Investigation, Methodology, Resources. **Minna Boo:** Investigation. **Soo-Hyun Sung:** Investigation. **Jinbong Park:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Sungha Kim:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Supplemental materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.explore.2024.03.002](https://doi.org/10.1016/j.explore.2024.03.002).

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