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A Retrospective Study on the Clinical Safety of Bee Venom Pharmacopuncture at Craniofacial Acupuncture Points for the Treatment of Facial Disorders

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ABSTRACT

Background: This study was designed to evaluate the clinical safety of Bee Venom (BV) pharmacopuncture at craniofacial acupuncture points.
Methods: This was a retrospective study of 108 patients diagnosed with peripheral facial paralysis, trigeminal neuralgia, or facial spasm who were admitted to Kyung Hee University Korean Medicine Hospital at Gangdong, from April 1st, 2017 to August 30th, 2017. Patients were allocated into either, Group 1 (the non-allergy group of patients who did not have an allergic reaction to BV) or Group 2, the group who had allergic reactions to BV. To evaluate the clinical safety of BV pharmacopuncture after each treatment, several criteria were used to measure any side effects: outcome, Common Terminology Criteria for Adverse Events scale, Mueller HL scale, treatment decision after adverse reaction, causality, measures performed for patients with adverse reactions, and efficacy assessment.
Results: BV pharmacopuncture delivered in 0.1-0.2 mL at a concentration of 1:30,000 at the craniofacial acupuncture points, showed no statistically significant differences in baseline characteristics between non-allergy Group 1 and allergy Group 2. Amongst the 108 patients, 11 reported side effects after BV pharmacopuncture treatment. These adverse events included rash (n = 7), pruritus (n = 5), swelling (n = 1), vesicles (n = 1), erythema (n = 1), and hives (n = 1). All side effects resolved without sequelae.
Conclusion: In this study, BV pharmacopuncture delivered at low doses at the craniofacial acupuncture points, resulted in 10% of patients experiencing non serious side effects suggesting that BV pharmacopuncture was clinically well tolerated.

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Introduction

A number of patients who visit the Department of Acupuncture and Moxibustion suffer from facial disorders such as peripheral facial palsy or trigeminal neuralgia. Bee venom (BV) pharmacopuncture plays an important role in the treatment of such facial disorders.

BV pharmacopuncture is a treatment which uses the acupuncture effect of needling, combined with the pharmacological action of BV which is injected into the diseased area or meridian system associated with the disease being treated [1,2]. BV pharmacopuncture is commonly used in Korean medicine and is an effective treatment for facial disorders and musculoskeletal pain disorders [3-5].

Despite the effectiveness of BV pharmacopuncture, the pharmacological effects of BV may cause an allergic reaction in some individuals which may be mild or severe [6]. Mild symptoms are observed on the surface of the skin and in subcutaneous tissue. However, severe symptoms of an allergic reaction to BV include hypotension and hypoxia (anaphylaxis).

Although the safety of BV pharmacopuncture was investigated in a study by Jung et al [7] in 2013 (n = 130), there were only 3 patients who were treated specifically at the craniofacial acupuncture points. In the present study, BV pharmacopuncture at craniofacial acupuncture points, was retrospectively reviewed in 108 patients whose charts were used to evaluate the side effects of

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BV pharmacopuncture, to assess its clinical safety.

Materials and Methods

Participants

From April 1st, 2017 to August 30th, 2017, 108 patients were admitted to Kyung Hee University Korean Medicine Hospital at Gangdong with facial disorders such as peripheral facial paralysis, trigeminal neuralgia, or facial spasm and evaluated for suitability for treatment with BV pharmacopuncture Kyung Hee University Korean Medicine Hospital Gangdong. Prior to BV pharmacopuncture treatment, a BV skin test was performed to determine any possible allergic response. This was carried out by giving a 0.05 mL intracutaneous injection of BV solution [1:30,000 (BV: normal saline)] at LI-11 acupuncture points. All responses to the skin test were recorded 20 minutes later in the electronic medical record. Patients whose skin returned to normal without sequelae after mild edema or erythema, or who showed a negative response to BV were included in this study. Patients with cardiovascular disease (paroxysmal tachycardia, myocardial infarction, malignant hypertension, congenital heart disease, or arteriosclerosis), kidney disease (acute nephritis, diabetic nephropathy, acute or chronic renal failure), or had a moderate/severe allergic reaction to BV in the skin test were excluded from this study. Exclusion criteria were selected based on a previous study [7].

Ethics

This study was approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital at Gangdong (File no.: 2019-09-008), and the requirement for informed consent was waived due to use of electronic medical records.

Past medical history

Past medical history included previous allergies (asthma, allergic rhinitis, atopic dermatitis, or food allergy), and other health conditions (hypertension, diabetes, heart disease, respiratory disease, or skin disease), exposure to stings, current use of oral antibiotics (cefotiam, rifampin, cefaclor, ampicillin, amoxicillin, quinolone, vancomycin, erythromycin, or aminoglycoside), aspirin, nonsteroidal anti-inflammatory drugs [6], angiotensin-converting enzyme inhibitor drugs, and beta blockers or alpha blockers. All these factors may contribute toward the development of an allergic reaction to BV [8,9].

Laboratory tests

The basic blood tests were performed to screen for hematological problems in patients who were admitted to hospital. In patients that received BV pharmacopuncture treatment, the concentration of IgE was measured to determine whether BV would be an allergy risk. [10,11] (Table 1).

Table 1. Blood Tests.

White blood cell (WBC) count	Absolute neutrophil count (ANC)
Red blood cell (RBC) count	Neutrophil segment
Hemoglobin (Hb)	Lymphocyte segment
Hematocrit (Hct)	Monocyte segment
Platelet (PLT) count	Eosinophil segment
Erythrocyte sedimentation rate (ESR)	C-reactive protein (CRP)
Hemoglobin A1c (HbA1c)	Immunoglobulin E (IgE)

BV pharmacopuncture treatment

BV solution was made by dissolving 10 vials of freeze-dried BV powder (Daehan purified BV, Korea) into 300 mL of normal saline solution which was sterilized using a 0.22 μm syringe filter. The BV solution was capped and stored at 4°C.

There were 108 patients who received BV pharmacopuncture treatment. The subcutaneous injection was performed using 1 mL, 30-gauge needle in a disposable syringe (Hwajin) which was applied to a depth of 0.4-0.6 cm.

Selection of acupuncture points differed based on each practitioner. These acupuncture points included CV-24, LI-20, TE-17, ST-2, ST-4, ST-7, GB-3, GB-14, EX-HN4, GV-26, SI-18, TE-23, ST-3, ST-6, BL-2, EX-HN5, and EX-HN8.

The total injection volume was 0.1 mL, and approximately the same amount of BV was administered at each acupuncture point. Patients were treated with BV pharmacopuncture once a day during hospitalization. If side effects occurred, the treatment was discontinued or substituted with appropriate treatments until the patient returned to normal health.

Evaluation

During hospitalization, medical staff monitored each patient every morning for side effects. If side effects occurred after treatment, they were recorded in the electronic medical record. Based on the recorded side effects, several criteria were used to quantitatively evaluate adverse reactions. These included outcome, severity grade (Mueller HL scale) [12], Common Terminology Criteria for Adverse Events (CTCAE) scale [13], causality [14], treatment decision after adverse reaction, measures performed for patients with adverse reactions, and efficacy assessment.

Outcome

Adverse reactions after BV pharmacopuncture treatment were classified into 5 categories: 1 = complete healing (no sequelae), 2 = healing (with sequelae), 3 = in progress, 4 = permanent damage, 5 = death.

Severity grade

The grade of severity was quantified using 2 scales (CTCAE and Mueller HL) which are associated with adverse drug responses. CTCAE and Mueller HL scale grades are shown in Tables 2 and 3.

Causality

The World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (WHO-UMC) causality was used to determine the relationship between BV pharmacopuncture treatment and adverse events. The causality scale is shown in Table 4.

Treatment decision after an adverse reaction to BV pharmacopuncture

When an adverse reaction occurred following BV pharmacopuncture treatment, the practitioner's decision regarding treatment was categorized into 5 responses: 1 = discontinued, 2 = reduced, 3 = increased, 4 = no change, 5 = unknown.

Table 2. CTCAE Scale (version 4.0).

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL†
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and ambulation.
ADL, Activities of Daily Living; CTCAE, Common Terminology Criteria for Adverse Events

Table 3. Classification of Allergic Reactions According to Mueller HL [12].

Grade	Description
0	Swelling at site with diameter > 10 cm and lasting > 24 h
I	Generalized urticaria, itching, malaise, or anxiety
II	Any of the above plus 2 of the following: angioedema, constriction in chest, nausea, vomiting, diarrhea, abdominal pain, dizziness
III	Any of the above plus 2 or more of the following: dyspnea, wheezing, stridor, dysphagia, dysarthria, hoarseness, weakness, confusion, fear of death
IV	Any of the above plus 2 or more of the following: drop in blood pressure, collapse, loss of consciousness, incontinence (urine, stool), cyanosis

Table 4. WHO-UMC Causality Assessment Scale.

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

WHO-UMC, World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre.

Measures performed for patients with an adverse reaction to BV pharmacopuncture

The relief measures given to patients who had an adverse reaction after BV pharmacopuncture treatment were divided into 4 types: 0 = none, 1 = ice pack, 2 = liquid gel (including antihistamine), 3 = oral medication (including antihistamine), 4 = other (sambaek-e-hwang-go ointment).

Monitoring of serious adverse events

The effect of BV pharmacopuncture treatment on serious problems, such as physical deformities or life-threatening conditions, was classified as 0 = not applicable, 1 = death, 2 = life threatening, 3 = extended hospital stay, 4 = continuous impairment or decreased physical function, and 5 = other medically important situation.

Statistical analysis

Non-allergy patients, Group 1, and BV allergy patients, Group 2 were assessed to determine whether a patient's underlying condition was associated with the side effects caused by BV. The baseline characteristics between the 2 groups were analyzed using IBM SPSS Statistics version 18.0 (IBM Co, Armonk, NY, USA), and the values were expressed as mean ± SD. The Independent *t* test or the Mann-Whitney *U* test was used for continuous variables. The Chi-Square test or Fisher's exact test was used for categorical

variables to compare differences in general characteristics between the groups.

Results

Baseline characteristics

Of the 108 patients, there were 97 in the non-allergy, Group 1, and 11 patients in the allergy, Group 2. The gender distribution in Group 1 was 34 males and 63 females, and in Group 2 it was 3 males and 8 females. The mean age in Group 1 was 47.2 ± 14.3 years and in Group 2 it was 52.2 ± 11.3 years. The duration of admission in Group 1 was 15.4 ± 6.78 days and in Group 2 it was 18.6 ± 5.4 days.

There were 56 patients with a positive BV skin test in Group 1 and 6 patients in Group 2 (these patients presented with mild erythema or swelling, without sequelae). No severe allergic reactions to BV in the skin test were observed. There were 19 patients in Group 1 and 3 patients in Group 2 with a history of allergies such as food or drug allergy. The mean number of injections per group was 12.7 ± 3.1 in Group 1 and 12.8 ± 4.2 in Group 2. The concentration of total IgE was 154.22 ± 307.51 IU/mL in Group 1 and 113.41 ± 153.02 IU/mL in Group 2. No statistically significant differences in baseline characteristics were observed between the 2 groups (Table 5).

Table 5. Baseline Characteristics.

	Non-allergy patients (Group 1)	BV allergy patients (Group 2)	*p*
Gender (male/female)	97 (34/63)	11 (3/8)	0.606*
Age (y)	47.2 ± 14.3	52.2 ± 11.3	0.286†
Hospitalization period (d)	15.4 ± 6.78	18.6 ± 5.4	0.053†
BV skin test (+) (mild edema or erythema)	56 (57.7%)	6 (54.5%)	0.839*
Allergy history	19 (19.6%)	3 (27.3%)	0.549*
Mean acupuncture points	12.7 ± 3.1	12.8 ± 4.2	0.127†
Total IgE level (IU/mL)	154.22 ± 307.51	113.41 ± 153.02	0.666†

* *p* value based on chi-square test. $p < 0.05$ was considered statistically significant.
† *p* value based on independent *t*-test.
BV, bee venom.

Adverse reactions

Amongst the 108 patients, 11 patients reported side effects after BV pharmacopuncture treatment. These included adverse events of rash ($n = 7$), pruritus ($n = 5$), swelling ($n = 1$), vesicles ($n = 1$), erythema ($n = 1$), and hives ($n = 1$). The reported side effects occurred in the treatment area, and the patients had no history of bee stings. All the reported side effects were transient, lasting between 24 to 168 hours, and all 11 patients recovered without sequelae. The CTCAE and Mueller HL scales showed the severity of side effects in 10 patients as Grade I, and Grade II in 1 patient whose side effects included a rash, swelling, and nausea.

Side effects were mild in 6 patients, and their BV dose remained unchanged. However, the side effects in 5 patients were severe and required discontinuation of BV pharmacopuncture treatment. After the severe symptoms alleviated, treatment was performed at

Table 6. Reported Side Effects after BV Pharmacopuncture Treatment.

Side effects	Duration (h)	Outcome	CTCAE	Mueller HL	Causality	Treatment decision	Relief measures	Efficacy	BV skin test result	Onset of adverse reactions
Pruritus	140	1	1	1	3	4	2	0	+ (swelling & rash)	3rd treatment
Rash/ pruritus	24	1	1	1	3	1	0	0	-	9th treatment
Rash/ swelling	10	1	1	1	3	1	4	0	-	17th treatment
Pruritus/ vesicle	48	1	1	1	3	1	4	0	+ (swelling & rash)	7th treatment
Rash	24	1	1	1	3	1	0	0	-	9th treatment
Rash/ swelling	60	1	2	1	2	1	1	0	+ (swelling and rash)	5th treatment
Rash/ pruritus	120	1	1	1	3	4	4	0	+ (swelling & rash)	3rd treatment
Rash/ swelling	168	1	1	1	2	1	0	0	-	4th treatment
Erythema	40	1	1	1	2	4	0	0	+ (rash)	8th treatment
Rash/ pruritus	96	1	1	1	2	4	4	0	+ (swelling & rash)	8th treatment
Pruritus/ hives	72	1	1	1	2	4	4	0	+ (swelling & rash)	4th treatment

BV, bee venom; CTCAE, Common Terminology Criteria Adverse Events.

the original dose. Among the 11 patients who reported side effects, 4 underwent observations until the side effects subsided. The other 7 patients with side effects received symptom relief treatment; 1 ice pack, 1 liquid gel (to relieve itching), and 5 had sambaek-e-hwang-go (to treat skin symptoms). Based on the WHO-UMC criteria, causality due to BV pharmacopuncture was probable/likely in 5 patients and possible for 6 patients. None of the 11 patients had serious side effects such as physical deformities or life-threatening conditions. In total, 7 patients had a positive (mild swelling or erythema) BV skin test, and all patients who had an adverse reaction, showed symptoms on the third treatment or later (the last side effects were reported at the 17th treatment ; Table 6).

Discussion

The BV used in pharmacopuncture is obtained through the purification of BV (*Apis mellifera*). It has anti-inflammatory and analgesic properties. The main components of BV are melittin, phospholipases A1 and A2, phosphatase, and hyaluronidase. After these antigens enter the human body and combine with IgE antibodies, histamine, serotonin, and catecholamine may be released. The allergic reaction results in vascular permeability, local edema, pain and a range of mild to severe symptoms such as anaphylaxis [20], which is caused by vasodilation [15-19].

The severity of an allergic reaction is classified according to the system proposed by Mueller HL. Grade 0 is swelling at the site, Grade I is symptoms such as itching, urticaria, anxiety, and malaise, Grade II refers to digestive symptoms, angioedema, chest constriction, and dizziness, Grade III is respiratory symptoms and confusion, and Grade IV is severe cardiovascular symptoms (systolic blood pressure < 90 mmHg, hypoxia, cyanosis), incontinence, or loss of consciousness. Generally, anaphylaxis is Grade III and Grade IV according to the Muller HL classification.

Among the 7 patients who received symptom relief treatment for their BV allergic reaction, 5 were treated with sambaek-e-hwang-go ointment, a topical dermatological drug that reduces fever and inflammation, and is clinically used for local burns, erythema, and papules on the skin. The ointment is composed of Alumen, *Mentha arvensis*, *Angelica dahurica*, *Phellodendron amurense*, and *Dryobalanops aromatica*.

The allergic reaction caused by BV pharmacopuncture may be associated with various factors such as gender, history of BV allergy, allergic disease, angiotensin-converting enzyme inhibitor use, antibiotic intake, and total IgE concentration [21]. In a previous study by Sturm GJ et al, mild to moderate allergic reactions were more frequent when the total concentration of IgE was > 250 IU/mL [22]. However, in the present study, 1 of 11 patients who showed a mild to moderate allergic reaction had a total IgE concentration > 250 IU/mL. There was no statistically significant difference between the 2 groups for the total IgE concentration (both groups were < 250 IU/mL), with a mean IgE serum level of 113.41(IU/mL) in Group 2. The number of patients with allergic reactions was too small to compare with a previous study.

In the study reported by Lee et al [21], amongst the 23 patients with an acute allergic reaction following BV pharmacopuncture treatment, 6 had mild symptoms, 10 had moderate symptoms, and 7 had severe symptoms. In addition, reclassification of patients based on the patient's symptoms showed 19 skin symptoms, 10 respiratory symptoms, 10 cardiovascular symptoms, and 6 gastrointestinal symptoms. Among these patients, 15 were treated with an epinephrine injection. In the present study, all adverse reactions were mild to moderate, with no severe adverse reactions requiring administration of epinephrine. The present study may differ from the previous study [21] because the BV was diluted (30,000:1, normal saline: BV) in the present study but the exact BV concentration and dose were not described in the previous study.

The present study had several limitations firstly, the average hospitalization period was approximately 14 days, and monitoring of the reoccurrence of side effects after discharge with a follow-up appointment, was not carried out. Allergic reactions resulting from BV pharmacopuncture can occur within seconds or minutes, but delayed-type hypersensitivity can occur days or weeks later. Secondly, based on a previous study [22], the total IgE concentration was expected to be associated with allergic reactions caused by BV pharmacopuncture. However, there was no difference in the total IgE concentrations between Group 1 and Group 2 in the present study. The total IgE concentration is influenced by other factors including clinical history, the environment, and an individual's age [23] and is not specific to BV. BV-specific IgE is an immunoglobulin that specifically recognizes BV. In the study by Guan K et al [24], the BV-specific IgE concentration was significantly higher in the systemic reaction group than in the common localized skin reaction group (showing redness or swelling less than 10 cm in diameter) and the control group. In addition, the specific IgE/Total-IgE (sIgE/T-IgE) ratio was used to better predict allergic reactions to BV [24]. As a result of measuring this ratio, significant differences were observed between the systemic reaction group and the localized skin reaction group and control group. Based on Guan's study [24], if the sIgE/T-IgE ratio had been measured in the present study, significant differences may have been observed between the 2 groups. Accordingly, studies including measurement of specific IgE level are needed.

Despite the limitations, this study is valuable in demonstrating the clinical safety of BV pharmacopuncture used at craniofacial acupuncture points.

Conclusion

In the present study, the use of BV pharmacopuncture at craniofacial acupuncture points caused an allergic reaction in 11 patients. However, the reactions were mild with no sequelae, and anaphylaxis did not occur. BV pharmacopuncture used at low volumes and concentrations (0.1-0.2 mL, 1:30,000) at craniofacial acupuncture points was determined to be well tolerated.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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