

Bee Venom Pharmacopuncture Responses According to Sasang Constitution and Gender

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Key Words

bee venom, sweet bee venom, skin test, Sasang constitution, sexual difference

Abstract

Objectives: The current study was performed to compare the bee venom pharmacopuncture skin test reactions among groups with different sexes and Sasang constitutions.

Methods: Between July 2012 and June 2013, all 76 patients who underwent bee venom pharmacopuncture skin tests and Sasang constitution diagnoses at Oriental Medicine Hospital of Sangji University were included in this study. The skin test was performed on the patient's forearm intracutaneously with 0.05 ml of sweet bee venom (SBV) on their first visit. If the patients showed a positive response, the test was discontinued. On the other hand, if the patient showed a negative response, the test was performed on the opposite forearm intracutaneously with 0.05 ml of bee venom pharmacopuncture 25% on the next day or the next visit. Three groups were made to compare the differences in the bee venom pharmacopuncture skin tests according to sexual difference and Sasang constitution: group A showed a positive response to SBV, group B showed a positive response to bee venom pharmacopuncture 25%, and group C showed a negative response on all bee venom pharmacopuncture skin tests. Fisher's exact test was

performed to evaluate the differences statistically.

Results: The results of the bee venom pharmacopuncture skin tests showed no significant differences according to Sasang constitution ($P = 0.300$) or sexual difference ($P = 0.163$).

Conclusion: No significant differences on the results of bee venom pharmacopuncture skin tests were observed according to two factors, Sasang constitution and the sexual difference.

1. Introduction

Animal poison is an evolutionary by-product that has maintained the species and protected it from external danger, and animal-based pharmacopuncture includes the use of the poisonous properties of bee venom, scolopendra and toad parts. In particular, bee venom pharmacopuncture is a therapeutic method that stimulates a meridian point physically, as well as chemically, and adds the oriental medical concept of '以毒治病' to acupuncture. Thus, it is a new therapeutic method that injects bee venom, an animal toxin that exists in nature, into meridian points of the body to treat diseases [1].

A toxin is a substance that can cause a deformity morphologically or functionally, leading to critical harm even in a small amount. Bee venom pharmacopuncture can have severe side effects in humans,

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and several reports have been published about these side effects [2-5]. Bee venom partner [6], anti-bee venom [7], and magnetic therapy [8] have been studied as ways to treat allergic reactions to bee venom pharmacopuncture. Also, sweet bee venom (SBV) which has hyper-molecular materials, such as the enzymes and the histamines that act as allergens in bee venom pharmacopuncture, removed, has been developed [9]. Clinical studies have shown that SBV has lower local immediate and systemic delayed hypersensitive reactions than bee venom pharmacopuncture and that it has an efficacy for preventing anaphylactic shock [10, 11]. In addition, Paull *et al.* reported that melittin was an allergen in some honey-bee venom-sensitive patients and that in an occasional patient, melittin might be a major allergen [12]. Still, SBV can cause anaphylaxis, as reported by Kwon *et al.* [13].

Because most allergens in SBV are removed through its manufacturing process, patients who experience a hypersensitive reaction to SBV are thought to have a tendency to be more hypersensitive to bee venom. We hypothesized that the sensitivity to bee venom is related with constitution as some patient groups have a hypersensitivity to SBV. The purpose of the present study was to identify the relevance of the Sasang constitution to bee venom pharmacopuncture reaction by analyzing the results of skin tests with bee venom pharmacopuncture for the patients who underwent bee venom pharmacopuncture therapy according to the patient's Sasang constitution and sex.

2. Materials and Methods

Between July 2012 and June 2013, 76 patients who underwent SBV skin tests and Sasang constitution diagnoses at the Oriental Medicine Hospital of Sangji University, were included in this study. Patients' information was obtained from the hospital's medical records, and target records were selected by reviewing the medical records with the diagnostic code search terms "skin test or allergy test, the constitution."

We requested the contents of the data anonymously, extracted and analyzed data such as sex, age, diagnostic name, skin test result, and diagnosed Sasang constitution from the selected chart records. This study was approved by Institutional Review Board of the Oriental Medicine Hospital of Sangji University.

All the bee venom pharmacopuncture used in this study was produced at the Korean pharmacopuncture Institute. The types are SBV 10% and Bee venom pharmacopuncture 25%.

Skin tests were carried out according to the methods of Lee [14] and Biló *et al.* [15]. The tests were performed on the forearm intracutaneously with 0.05 ml of SBV at admis-

sion or on their first visit. If the patients showed positive response, the test was discontinued. On the other hand, if the patient showed a negative response, the test was performed on the opposite forearm intracutaneously with 0.05 ml of bee venom 25% on the next day or the next visit.

The diagnosis of constitution was determined by use of QSCC-II questionnaires, analysis of the results of the Phonetec System for Sasang Constitution (Voice one Co., Korea) and the results of a questionnaire made by a specialist in Sasang constitution medicine.

The patients were divided into three groups:

Group A, the SBV positive group;

Group B, the Bee venom pharmacopuncture 25% positive group;

Group C, the bee venom pharmacopuncture negative group.

After the patients had been divided into the three groups, the bee venom pharmacopuncture skin test reactions according to Sasang constitution and sex were compared and evaluated. For the comparison of the bee venom pharmacopuncture skin test reactions according to Sasang constitution and sex, Fisher's exact test was used. Significance was set at a level of 0.05 with associated 95% confidence intervals. The SPSS software package (version 19.0; SPSS, Inc, an IBM Company, Chicago Illinois) was used for the statistical analysis.

3. Results

76 patients were included in the current study (Table 1), including 31 men and 45 women. The mean age was 60.34 ± 17.33 (mean \pm SD) yrs. Of the 31 men, 8 were in group A, 19 in group B, and 4 in group C, and their mean age was 57.68 ± 15.94 yrs. Of the 45 women, 4 were in group A, 33 in group B, and 8 in group C, and their mean age was 62.18 ± 18.17 yrs. No statistically significant difference was observed in the distribution of the results of the skin tests between men and women ($P = 0.163$). Male patients seemed to have more positive reactions than the female patients but that possible difference was not significant statistically ($P = 0.060$); 25.8% (8 of 31) of the male patients and 8.9% (4 of 45) of the female patients showed positive reactions.

Among 76 patients, there were 46 Tae-eum people, 13 So-yang people, and 17 So-eum people (Table 2). Of the Tae-eum people, 9 were in group A, 30 in group B, and 7 in group C. Of the So-yang people, 3 were in group A, 8 in group B, and 2 in group C. Of the 17 So-eum people, no patient was in group A, 14 were in group B and 3 in group C. Consequently, the distribution of skin test results according to Sasang constitutional showed no significant difference ($P = 0.300$).

Table 1 Patients characteristics and skin test reactions between males and females

	Group A	Group B	Group C	Total	Age*
Males	8	19	4	31	57.68 ± 15.94
Females	4	33	8	45	62.18 ± 18.17
Total	12	52	12	76	60.34 ± 17.33

Fisher's Exact Test; $P > 0.05$ ($P = 0.163$, Distribution of all groups; $P = 0.060$, Group A only)

*Mean ± SD

Table 2 Distribution of skin test reactions among Sasang Constitution

	Group A*	Group B [†]	Group C [‡]	Total
TE [§]	9	30	7	46
SY	3	8	2	13
SE [¶]	0	14	3	17
Total	12	52	12	76

Fisher's Exact Test; $P > 0.05$ ($P = 0.300$)

* Who showed positive response of SBV skin test

[†] Who showed positive response of bee venom pharmacopuncture 25% skin test

[‡] Who showed negative response in all bee venom pharmacopuncture skin test

[§] Tai-eum person

^{||} So-yang person

[¶] So-eum person

4. Discussion

The bee venom pharmacopuncture is the most popularly used pharmacopuncture presently. The Neo-acupuncture, which uses a toxin abstracted from a toxin-pouch in a live sweet bee and purified during manufacturing process, is injected into a diseased site or a meridian point to use a combination of the acupuncture effect and the biochemical pharmacologic effects to treat diseases. Bee venom is known to have an anti-inflammatory effect, to regulate the immune system, to facilitate circulation, to have an antibiotic effect, and to reduce resistance to radiation, so it is used in treating immune, musculoskeletal, neurologic and other numerous intractable diseases [1]. However, as like most toxins, bee venom might cause a hypersensitivity immune reaction, the most difficult point is in using bee venom clinically being anaphylaxis [16].

Hypersensitivity to insect poison is displayed in 0.5%-2.0% or 4%-5% of the population. The difference is due to the range of objects and the scope of hornets and honey bees, hypersensitivity being less for a honey bee. One study suggests that less than 5% of all adverse reactions from an insect bite come from the honey bee. The epidemiological distribution of systemic acute hypersensitivity

to bee venom is 2-3 per 100,000. Hypersensitive reactions from a bee sting are manifested as a drop in blood pressure, systemic lethargy, skin rash, pale complexion, nausea and vomiting, abdominal pain, tachycardia, and aversion to cold. Dyspnea, syncope, or even death is seen in more advanced stages [1]. These severe responses are called "anaphylactic shock," which is an acute systemic allergic reaction occurring as a result of the release of chemical mediators after an immunologic reaction, typically an IgE-mediated reaction [17]. IgE antibody production mediates most human anaphylaxis by increasing the target cell's responsiveness to vasoactive mediators. In the human body, human complement is a complex network of soluble and membrane-associated serum proteins that participate in highly regulated humoral and cellular immune responses to infectious organisms, to tissue damage by chemical, physical, or radiation exposure, and to substances not recognized as self [18].

To eliminate these problems, bee venom in which the enzymes that act as allergens and that have molecular weights of more than 10,000 have been removed through a protein separation technique using gel filtration was developed. SBV is another name for the pure melittin pharmacopuncture obtained from the bee venom [9].

Removal of the allergens inhibits the hypersensitive re-

action to bee venom pharmacopuncture significantly, so local allergic reactions for SBV are remarkably lower than those for bee venom pharmacopuncture. In addition, high-dose therapy is possible even in the early period of treatment and has an advantage of shortening the therapeutic period, with SBV having therapeutic effect equivalent to that of bee venom pharmacopuncture. Also, treatment with SBV is as effective, or better, than that with bee venom pharmacopuncture, so more aggressive treatment is possible for hard-to-cure disorders [1].

Melittin is a well-known water-soluble toxic peptide present in the venom of *Apis mellifera* and is the dominant component of bee venom constituting 40%-50% of the dried weight. This peptide is able to disrupt membranes, having many effects on living cells. It is a low-molecular-weight peptide with a weight of 2836 and is made of 26 amino acids. A three-dimensional analysis has revealed that four sets of melittin combine in a helical structure [19].

Because the allergens were removed in the manufacturing process and the hypersensitivity is inhibited significantly in SBV, patients who have a hypersensitivity reaction to SBV seem to be more sensitive to bee venom. Also, if a patient with a specific constitution has higher rate of hypersensitivity, with the corresponding constitution can be said to be vulnerable to stimulation with bee venom. Hypersensitivity to bee venom is manifested in several different fashions based on one's constitution and the amount of venom. Adverse reactions from a large volume of bee venom is not caused by clinical injections of bee venom for therapy, thus, the patient's constitution is more of a determining factor [1]. Especially, because bee venom has hot properties, the stimulating effects or side effects of bee venom occur relatively rapidly when the bee venom pharmacopuncture is administered in a Yang pattern or to a Yang person [20]. So, we hypothesize that a Yang person like Tae-yang person or So-yang person, will have more risk to develop a hypersensitivity reaction than an Eum person like a Tae-eum person or a So-eum person, [21] and that a more positive reaction to the skin test will occur in a Yang person.

The IgE-mediated allergic reaction of the skin immediately results in a dermal response that is marked by a wheal and flare reaction and that depends on both chemical and neurogenic mediators (immediate reaction). Although this is often, but not always, followed by a late phase reaction developing over the next 3-5 h, peaking at 6-12 h, and resolving in approximately 24 h. The late phase reaction appears as an ill-defined edematous reaction that is related temporally to an influx of inflammatory cells [22].

For the above reasons, we analyzed the results of the skin tests according to constitutions of the 76 patients who underwent bee venom skin test and had a diagnostic record

of Sasang constitution at the Oriental Medicine Hospital of Sangji University, between July 2012 and June 2013.

Of the 46 Tae-eum people, nine (19.6%) showed positive reactions to the SBV skin test, and of the 13 So-yang people, three (23.1%) showed such positive reactions; no positive reactions occurred in the So-eum people. Most patients showed bee venom pharmacopuncture 25% positive reactions, including SBV skin test positive reactions; 38 Tae-eum people (82.6%), 11 So-yang people (84.6%), and 14 So-eum people (82.4%). On the other hand, 8 Tae-eum people (17.4%), 2 So-yang people (15.4%) and 3 So-eum people (17.6%) showed negative reaction to all bee venom pharmacopuncture. In our opinion, more positive reactions to skin tests seem to have occurred in So-yang people, one type of the Yang people, but the distribution of skin tests according to constitutions did not have a significant relation statistically ($P = 0.300$). The distribution of skin tests according to sexual difference also did not show any significant difference ($P = 0.163$).

In the study of bee venom pharmacopuncture and Sasang constitutions, Lee *et al.* [23] reported that the stimulation by bee venom pharmacopuncture induced different reactions according to the constitution, in the pulse wave and the cerebral blood flow velocity; on the other hand, Lee [21] reported that Sasang constitution did not have an influence on the occurrence of bee venom pharmacopuncture hypersensitivity reactions. In this study, the positive reaction to skin tests also did not show a significant relation with Sasang constitution. Although Lee [21] reported that the probability of the hypersensitivity reaction is higher in female than in male patients, no significant difference between male and female patients was observed for the skin test reactions in the present study, but rather a tendency was observed for the hypersensitivity reactions to occur more frequently in male patients.

About skin tests, Golden *et al.* reported that systemic reactions in patients with negative venom skin test responses may reflect limited diagnostic sensitivity of the skin test for IgE-mediated sensitivity or could indicate nonallergic reactions, such as anxiety and panic, conditioned reflex reactions, or toxic reactions. Low levels of venom-specific IgE antibodies can be associated with severe anaphylaxis. Nevertheless, venom skin test responses are still relevant and useful because they are positive in at least 65% of adults with positive histories and in only 17% of adults with negative histories [24].

Therefore, caution and skin tests are always needed when bee venom pharmacopuncture is used regardless of the Sasang constitution or sex of the patient. However, this study has limitation; the numbers of the materials and the patients are small in the study of the relationship of bee venom pharmacopuncture to Sasang constitution, and

the diagnostic accuracy of the Sasang constitution may be a factor that need further consideration. Consequently, because in this study, the relationship of the bee venom pharmacopuncture reaction to the constitution was not evaluated accurately, a study with more accurate diagnoses of the patients' constitutions and with more large numbers of patients and materials is needed.

5. Conclusion

Between July 2012 and June 2013, 76 patients who underwent bee venom pharmacopuncture skin tests and Sasang constitution diagnoses in the Oriental Medicine Hospital of Sangji University were analyzed; the results are as follows:

1. No significant differences in the results for the bee venom pharmacopuncture skin test reactions were observed according to Sasang constitution ($P = 0.300$).
2. No significant differences in positive reactions on the bee venom pharmacopuncture skin tests were observed according to the sexual difference ($P = 0.163$).

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