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A Study of the Initial Dose of Sweet Bee Venom for the Treatment of Patients with Lower Back Pain

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ABSTRACT

Sweet bee venom (SBV) causes less hypersensitivity reactions compared with whole bee venom. To determine the appropriate SBV initial dose for pharmacopuncture treatment of lower back pain, the initial dose, and the dose which caused hypersensitivity were retrospectively reviewed between January 1st, 2017 and December 31st, 2019. There were 523 first-visit patients who received SBV pharmacopuncture for lower back pain and 41 showed hypersensitivity. No systemic reactions were observed and localized reactions were not severe. Hypersensitivity was observed during the first (7 cases), and fifth treatments (8 cases). An initial SBV (10%) volume of 0.1 mL was used in 2 cases, 0.2 mL in 6 cases, 0.6 mL in 41 cases, and 1.2 mL in 474 cases. The hypersensitivity rate during the first and fifth treatment was 1.34% and 1.53%, respectively. As a result, 1.2 mL of SBV was considered the acceptable initial dose. However, for safer treatment, we recommend limiting the initial dose of SBV to 0.5 mL.

Introduction

Bee venom pharmacopuncture (BVP), which involves the use of bee venom [extracted from the sac of a live honey bee (Apis mellifera) and refined] during acupuncture, is frequently used and the most researched pharmacopuncture in Korean medicine [1,2].

Bee sting therapy or bee acupuncture therapy has been used for a long time to treat diseases in traditional Korean medicine. The technique involves placing the bee on the affected area or acupoint to treat disorders. Many apiarists still practice this technique in Korea. However, this traditional method has drawbacks, such as inaccuracy in location of acupoints, and variation in volume of venom injected. BVP compensates for these drawbacks and delivers bee venom that has undergone aseptic purification [3].

BVP has anti-inflammatory, analgesic, antipyretic, blood circulation activator, anticonvulsant, and immunity reinforcement effects, and is used in cases of autoimmune diseases, cancers, and arthritis [4,5]. The biggest drawback of using bee venom clinically is that it may cause an allergic reaction, which can range from localized hypersensitivity around the treatment site to systemic hypersensitivity that can cause respiratory and circulatory disorders, leading to death in severe cases. Therefore, before using BVP, the practitioner must know how to treat side effects caused by bee venom before its use in the clinic [3].

Sweet Bee Venom (SBV) is known to have fewer hypersensitivity reactions and have a superior therapeutic effect compared with BVP [3,6,7]. SBV is prepared by isolating melittin (molecular weight of 2,846), which is considered to be a therapeutic component of bee venom. This separation process removes the enzymes (molecular weight of ≥ 10,000) which may cause allergic reactions, and low-molecular substances such as histamine that causes inflammation and/or itching. However, in 2018, a fatal accident occurred in a patient undergoing BVP [8]. The exact dose and treatment schedule was not reported.

This study retrospectively analyzed the medical records of patients who received SBV pharmacopuncture in the Department of Acupuncture over the last 3 years to identify the initial dose and the dose at which hypersensitivity was caused by SBV.

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Materials and Methods

Research design

This was a retrospective study of 523 first-visit patients who underwent BVP for lower back pain in Acupuncture Department 2, the Korean Medicine Hospital, Sangji University, from January 1st, 2017 to December 31st, 2019. In this case report, the initial SBV volume used in all patients was reviewed. Hypersensitivity, and the dose used when hypersensitivity occurred, the treatment schedule which caused hypersensitivity, and the methods used to treat these reactions were investigated. This study was approved by the institutional review board (IRB) of Korean medicine hospital of Sangji University (no.: SJIRB - Human - 20 - 004).

Patients

This study was limited to patients with low back pain to exclude characteristics according to the treatment area, and various disease-specific differences. All 523 patients were enrolled according to the following inclusion and exclusion criteria.

Inclusion criteria [9,10]

① First-visit patients over 19 years of age
② BVP is used during treatment
③ If the condition/disease is due to lower back pain
a) Spondylosis (M478 or M479)
b) Spinal stenosis (M480)
c) Lumbar intervertebral disc disorders (M51)
d) Lumbago with sciatica (M544)
e) Lower back pain (M545)
f) Fracture of lumbar vertebra (S320 of S327)
g) Sprain and strain of lumbar spine (S335 or S337)

Exclusion criteria

① Patients who have had BVP treatment previously
② Treatment under coverage of car insurance
③ When hospitalized for lower back pain

Bee venom

SBV (Kirin Korean medicine extramural herbal dispensary facility, Wonju, Korea) pharmacopuncture was used for treatment for lower back pain patients. Firstly, SBV 10% (1:10,000) was used, followed by SBV 50% (1:2,000) when the usage capacity of SBV 10% was increased. When SBV 50% was used, the dose was calculated by converting it to the SBV 10% dose.

Hypersensitivity reaction criteria

If there were findings of systemic reactions or severe pruritus, redness, and/or edema of the local area noted in the medical records, it was judged as a hypersensitivity reaction. If there was a record of pruritus, edema, and/or redness, it was not judged as a hypersensitivity reaction if a similar dose was used in the next treatment visit. If it was reduced to less than half in the next treatment visit, it was judged as a hypersensitivity reaction, even if there was no record of reactions.

Statistical methods

Mean and standard deviations are presented for continuous variables, and frequency and ratio (*n*; %) are presented for nominal variables including age, sex, SBV use, and the number of hypersensitivity reactions (Microsoft Excel Professional Plus 2016, Santa Rosa, USA).

Table 1. Patient Characteristics and the Distribution of Hypersensitivity Reactions According to Age.

Age (y)	Sex	*N*		No. of reactions	%
≤ 30	Female	10	41	1	2.44
	Male	31			
31 - 40	Female	25	69	3	4.35
	Male	44			
41 - 50	Female	49	101	4	3.96
	Male	52			
51 - 60	Female	80	136	10	7.35
	Male	56			
61 - 70	Female	56	102	16	15.69
	Male	46			
≥ 71	Female	39	74	7	9.46
	Male	35			
Sum		523		41	7.84

Results

The distribution of hypersensitivity reactions according to age among the 523 patients is shown in Table 1. A total of 41 hypersensitivity reactions occurred, all of which were localized and no systemic reactions were observed. The greatest number of patients (16) were in the 61-70 age group.

When the 41 cases of hypersensitivity reactions were classified according to the treatment visit number, 8 cases (19.51%) occurred during the fifth visit and 7 cases (17.07%) occurred in the first visit. Out of the 41 cases, 31 cases occurred before the fifth visit (Table 2).

During the first treatment visit for lower back pain, 0.1 mL of SBV (10%) was used in 2 cases, 0.2 mL in 6 cases, 0.6 mL in 41 cases, and 1.2 mL in 474 cases (Table 3). Among them, hypersensitivity reactions occurred once during the second visit when 0.2 mL SBV (10%) was used. Hypersensitivity reactions were observed 3 times when 0.6 mL of SBV (10%) was used, with 1 occurrence in the first and 2 occurrences in the seventh visit. All of the remaining 37 hypersensitivity reactions occurred when the initial volume of SBV (10%) was 1.2 mL.

Of the 41 hypersensitivity reactions, all were localized hypersensitivity reactions and systemic reactions were not observed. As a result, the only treatment prescribed was that of a single oral antihistamine. Of the 41 cases, 31 cases occurred before the fifth treatment visit, with the most occurrences at fifth treatment visit (8 cases).

Discussion

Skin testing is recommended prior to BVP to ensure safety. Taking 'Apitoxin' as an example, skin test is performed using a

Table 2. Hypersensitivity Reactions (n = 41) Classified According to the Number of Treatments Visits.

Visit (N)	Occurrences (N)	Occurrences (%)	% of total patient No. (%)	Average accumulated volume (mL) mean ± SD
1	7	17.07	1.34	1.86 ± 0.38
2	6	14.63	1.15	2.50 ± 1.38
3	6	14.63	1.15	3.67 ± 1.51
4	5	12.20	0.96	6.63 ± 1.97
5	8	19.51	1.53	9.69 ± 5.12
6	4	9.76	0.76	11.88 ± 2.39
7	2	4.88	0.38	8.80 ± 1.77
8	1	2.44	0.19	12.50 ± 0.00
9	2	4.88	0.38	10.00 ± 0.00
10	1	2.44	0.19	22.50 ± 0.00

Table 3. The Amount of SBV Used During the First Visit for Lower Back Pain Treatment.

The initial volume (mL)	N	No. of occurrences	%	Note
0.1	2	0	0.00	
0.2	6	1	16.67	2nd visit
1	41	3	7.32	once in 1st, twice in 7th
2	474	37	7.81	
Sum	523	41	100.00	

SBV, sweet bee venom.

sterile disposable syringe on the forearm flexor surface. After inserting the needle into the epidermal layer of the skin, 0.05 mL (equivalent to 0.05 mg dry honey bee venom) is slowly injected. If wheal reaction of 0.5-1 cm in diameter or an erythematous area of 2.5-4 cm in size surrounding the injection site appears and there are no signs of a systemic reaction 15 to 30 minutes after injection, it is judged as a negative reaction [11]. The skin test dose of Apitoxin is 0.05 mg in dry honey bee venom, it corresponds to 0.5 mL for SBV 10%.

Of the 523 patients in this study, 1.2 mL was used as a treatment volume in 474 cases and since SBV was used instead of whole bee venom, the initial dose in 1.2 mL caused only 8 cases of mild hypersensitivity, therefore it was considered an acceptable initial dose. There were 41 hypersensitivity, which accounted for 7.84% of the total 523 patients. As a result of mild hypersensitivity, a single oral antihistamine tablet was prescribed. Hypersensitivity reactions occurred in 1 out of the 6 cases (16.67%) when 0.2 mL was used as the initial dose, in 3 out of the 41 cases (7.32%) with 0.6 mL as the initial dose, and in 37 out of the 474 cases (7.85%) with 1.2 mL as the initial dose. Considering that the rate of incidence was similar regardless of whether 0.6 mL or 1.2 mL of SBV was used, the likelihood of hypersensitivity did not change with the initial dose.

Pharmacopuncturology [3] has been reported as hypersensitivity reactions that have not been observed in the early stages of SBV pharmacopuncture, but as the treatment progressed with more treatment visits, localized reactions (such as itching and edema) were observed between the fifth and tenth treatment. This is because melittin has been recognized as a foreign antigen due to the secondary immune response that occurred as a result of repeated antigenic stimulation. In the present study, hypersensitivity reactions occurred more frequently between the first and fifth treatment visit because the initial dose was large and dosing was increased aggressively.

Although not included in this study, anaphylactic reactions due to SBV that have occurred in clinic were due to an increase in the dose during the course of the treatment.

Generally, anaphylaxis is caused by the action of IgE. Phospholipase A2 (PLA2) is the component in bee venom that stimulates IgE antibodies [12,13]. Although PLA2 and histamine are removed from SBV through gel filtration, pure melittin that is retained in SBV [14], can cause an IgE response, even though it is a smaller compound than PLA2 [15]. Hence, SBV also needs to be used cautiously.

It is known that low levels of IgE antibodies and high levels of IgG antibodies are seen in beekeepers, who do not have major problems with bee stings or in patients who are well adapted to immunotherapy. In particular, IgG4 antibodies which are known to compete with allergen-specific IgE to induce resistance and protect patients prone to allergies from anaphylactic reactions [13,16]. The relationship between SBV or melittin and IgG4 with respect to this needs to be investigated.

In this study, the rate of incidence of hypersensitivity reactions was the highest at 15.69% in patients belonging to the 61-70 years age group. Overall, the rate of hypersensitivity reaction was higher in the age groups over 50 years than in the younger patients. This reflects the contents of the previous study [17], in which the patient's health status has more influence on the hypersensitivity reaction than the patient's constitution.

Although most of the hypersensitivity reactions occurred during the initial treatment visits, the proportion of hypersensitivity

reaction during the first treatment visit was only 1.34%, and the degree of hypersensitivity was not severe. Accordingly, using 1.2 mL of SBV 10% as the initial dose is acceptable, however it is better to be cautious because the number of subjects analyzed in this study was only 523 in 3 years and the records were insufficient due to various limitations. Therefore, if the allergy test is not performed it is considered to limit the volume to 0.5 mL of SBV 10% for low back pain patients, which corresponds to the skin test volume of Apitoxin as the initial dose, and more data should be accumulated to verify the safe initial dose of SBV. In addition, since allergy testing is considered to be important when using bee venom, I hope that there will be a study to investigate the relationship between allergy testing and initial dose of SBV in the future.

Conflicts of Interest

The author has no conflicts of interest to declare.

Acknowledgments

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