Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Old Questions, new answers: real-world long-term efficiency of hymenoptera venom immunotherapy: prevalance of venom-induced anaphylaxis, risk factors, and field sting reactions

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Received 11 October 2024; Accepted 30 January 2025
Available online 1 March 2025

KEYWORDS
field sting;
honeybee venom;
venom immunotherapy;
venom-induced anaphylaxis;
vespid venom

Abstract
Background: Hymenoptera venom allergy is a potentially life-threatening allergic reaction. Venom immunotherapy (VIT) is recommended to prevent severe allergic reactions. Field stings indicate the effectiveness of immunotherapy.
Objective: The aim of this study was to investigate the prevalence of venom-induced anaphylaxis, risk factors, and field sting reactions during or after the completion of VIT.
Methods: In this study, the records of patients who underwent VIT between 2015 and 2023 at one of the largest referral hospitals in Turkey were retrospectively analysed. The protocol followed during the initiation of immunotherapy, adverse reactions, clinical characteristics of the patients (including demographic characteristics, allergic diseases, laboratory findings), and field sting reactions during and after completion of immunotherapy were analysed.
Results: A total of 194,526 unique patient files evaluated in the Allergy Outpatient Clinic between 2015 and 2023 were analysed. Of these, 384 patients were admitted with an allergic complaint following a bee sting. Among them, 113 patients (29.4%) were eligible for VIT. A total of 79 patients were included (F/M: 41/38). VIT was performed with honeybee venom in 39 patients, vespid venom in 36 patients, and both venoms in 4 patients. 62.0% (n=49) of the patients had been stung by a bee in the head and neck region. 69.6% (n=55) of the patients had a stage 3 reaction before VIT. The cluster scheme was applied to 54.4% (n=43) of all patients. There was no statistically significant difference in the number of field stings or the use of adrenaline autoinjectors between the VIT groups ($p>0.05$). Stage 3-4 reactions developed in 87.8% of patients stung in the head and neck region, compared to 53.3% of patients stung in other regions. During and after VIT, field stings were reviewed both from patient files and by follow-up inquiries during control visits. During VIT, field stings were observed

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https://doi.org/10.15586/aei.v53i2.1237

in 19 patients. Systemic allergic reactions developed in 5 patients, and local allergic reactions developed in 6 patients; no allergic complaints were observed in 8 patients. After VIT was discontinued, 56 field sting reactions developed in 25 patients. Local allergic reactions developed in 9 patients, but no systemic allergic reactions were observed. Mastocytosis was diagnosed in a patient whose tryptase level was 42.4 and whose c-kit mutation was positive following haematological evaluation.

Conclusions: This study confirms that the prevalence of venom-induced anaphylaxis was calculated to be 0.058%. Being stung in the head and neck region was identified as a risk factor for the development of stage 3-4 (severe allergic reactions).

Introduction

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a venom sting. Systemic allergic reactions to stings have been reported in up to 7.5% of adults. These reactions can range from mild and localized to the skin, to moderate or severe reactions with the risk of life-threatening anaphylaxis.[1] Venoms are the leading cause of anaphylaxis in adults, accounting for 55% of cases.[2] Patients should carry an emergency kit containing an adrenaline autoinjector (AAA). The only treatment to prevent further systemic reactions to stings is venom immunotherapy (VIT).[1] The clinical history, along with confirmatory skin or serum tests for venom-specific IgE, can help clarify the risk for future anaphylaxis and the need for VIT. VIT is recommended for patients with Grade 2 and above anaphylactic reactions according to the Ring and Messmer grading scale.[3,4] VIT is relatively safe, with a low incidence of systemic reactions, and it is recommended to continue VIT for at least three to five years. Follow-up of patients should continue even if immunotherapy is discontinued.[5,6] Adverse reactions are more common in patients receiving honeybee VIT (HBVIT) than in those receiving vespid VIT (VVIT).[7] Adverse reactions, which used to cause longer buildup phases of immunotherapy, have decreased due to increased experience and the development of new extracts.[8,9] Protection against anaphylaxis after discontinuation of VIT can be expected with an efficacy of 77-84% for honeybee venom and 91-96% for vespid venom.[9-11] Although there are paediatric experiences evaluating re-sting reactions in patients undergoing VIT who require long-term clinical follow-up, real-life data for adults, especially after discontinuation of VIT, are very rare.[10] An increased allergen-specific IgE response is expected after a venom sting. Due to the risk of reactivation of venom allergy with increased IgE, re-sting testing is not recommended.[12]

There is a paucity of data on the evaluation of field sting reactions in adult patients during VIT and, especially, after its discontinuation. The aim of this study was to evaluate cases of field stings during and after the discontinuation of immunotherapy, as well as anaphylactic reactions according to the Ring and Messmer grading scale, in adult patients who underwent VIT at our tertiary referral hospital.

Methods

Study design

This is a retrospective review and prospective survey, descriptive study. Ethics Committee approval was obtained prior to the study at Health Sciences University, Süreyyapaşa Training and Research Hospital (116.2017.R-335). Written informed consent was obtained from all participants.

Patient selection

The total number of unique patients admitted to our Allergy and Immunology Clinic between 2015 and 2023 was 194,526. This number was obtained from the hospital registry system. All patients aged 18 years and older who were evaluated for venom allergy in our Allergy and Immunology Clinic between 2015 and 2023 were included. The files of patients with ICD-10 diagnosis codes T78.2 (anaphylactic shock), X23 (contact with bees), L50 (urticaria), and T63 (contact with poisonous animals) were analysed.

A total of 384 patients were admitted to our hospital with any allergic complaint following a bee sting. Among these patients, 113 (29.4%) were eligible for VIT due to venom-induced anaphylaxis according to the Ring and Messmer grading scale. A total of 79 patients who underwent VIT between 2015 and 2023 were included (Figure 1). After file scanning, all patients were contacted by phone. One patient died due to comorbid diseases. Patients who agreed to participate were called for a follow-up. Field sting reactions of the patients were assessed both during and after the discontinuation of immunotherapy. Adrenaline autoinjector carrying habits and usage were also checked. A total of 78 out of 79 patients could be contacted. After VIT, the field sting timeline, number of stings, severity of reactions, and use of adrenaline autoinjectors were reviewed.

A validated questionnaire was not administered to the patients. Instead, a survey form that we created ourselves was applied to the patients. The survey form consisted of 8 questions.

1. Have you been stung by a bee after VIT?
2. How many times did a bee sting you after VIT?

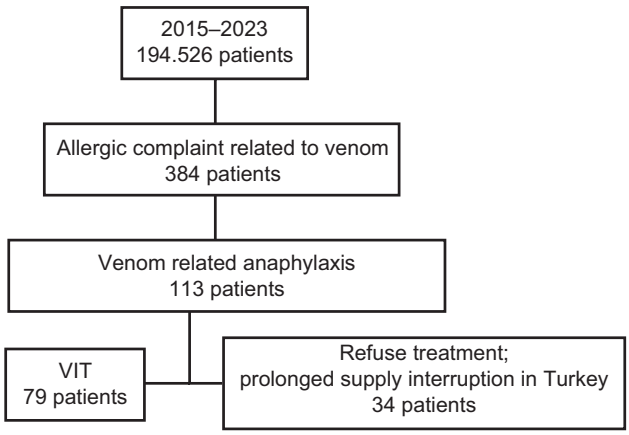

Figure 1 Patient selection process for the study.

3. Have LAR and/or SAR developed?
4. Was it necessary to administer adrenaline after the bee sting?
5. In what month did the bee sting develop after VIT was discontinued?
6. Is AAA still carried with you?
7. Was it necessary to provide training on AAA?
8. Does he feel anxious about bee stings?

Inclusion criteria: Patients who developed anaphylaxis from a Hymenoptera venom sting and underwent VIT were included. The following two criteria were required for diagnosis.

1. A history of Hymenoptera sting and the presence of Grade 2 or higher anaphylactic reactions according to the Ring and Messmer grading scale.
2. A positive skin test with Hymenoptera venom and/or documented increase in specific IgE antibodies (> 0.35kU/L) of honeybee venom and/or vespid venom. (Immuno-CAP, Pharmacia). For the skin prick test, a commercial venom extract with concentrations of 10,100,300 mcg/ml (ALK-Abelló A/S, Denmark) was used. Testing started with 10 mcg; if negative, 100 mcg was used; If still negative, up to 300 mcg was tested. Results were considered positive when the wheal diameter of the extract was greater than or equal to 3 mm after 15 minutes. IDT could not be performed due to the unavailability of the extract.

A standardized patient record form was created for each patient. The questionnaire form was analysed under five separate headings.

1. Characteristics of the patients: Age, gender, allergic diseases and atopy status.
2. Venom species and allergic reactions: The venom species to which the patient had allergic complaints, skin prick test and/or venom specific IgE results to determine the responsible venom type; the severity of anaphylaxis as described by the patient according to the Ring and Messmer grading scale.[3] Skin, respiratory, gastrointestinal and cardiovascular symptoms were recorded.
3. Venom immunotherapy details: The type of venom immunotherapy applied to the patient, the scheme used during the build-up phase, and any premedication administered.
4. Immunotherapy duration and field stings: The duration of immunotherapy, whether there was a bee sting during or after the discontinuation of immunotherapy.
5. Adrenaline autoinjector (AAA) usage: AAA usage training was checked, and their files were examined for mastocytosis.

Venom immunotherapy

Conventional or cluster venom immunotherapy protocols were applied depending on the severity of the patient's index reaction. Conventional VIT was given as weekly injections until the maintenance dose was reached. A weekly cluster regimen, involving one additional injection per visit, was applied during the up-dosing phase over a 7-week period, followed by monthly maintenance injections of 100,000 SQ-U/mL. Biologically standardized extracts were applied in the depot (ALK-Abello, Madrid, Spain). All injections were administered subcutaneously under the supervision of a physician and nurse. After VIT was administered, patients were observed for 2 hours following each injection. If a local or systemic reaction occurred, it was recorded.

Statistical analysis

The data obtained from the study were transferred to a computer and analysed using the SPSS (Statistical Package for Social Sciences) version 22.0 program. In descriptive analyses, frequency data were expressed as numbers (n) and percentages (%), while numerical data were expressed as the median (interquartile range). The Fisher Exact test was used to compare categorical data. The normality distribution of the numerical data was assessed using the Shapiro-Wilk test. The Kruskal–Wallis test was used to compare the numerical data from more than two independent groups that did not follow a normal distribution.

Statistical significance level was set at $p<0.05$ for all tests.

Results

The total number of patients admitted during the study was 194,526. Of these, 384 patients were admitted with an allergic complaint related to venom, and 113 patients were admitted with venom-related anaphylaxis. In other words, the prevalence of venom-induced anaphylaxis was calculated to be 0.058%.

The study included 79 patients who underwent venom immunotherapy. The demographic characteristics of the patients are provided in Table 1. Venom immunotherapy (IT) was performed with honeybee venom in 39 patients, vespid venom in 36 patients, and both venoms in 4 patients.

Table 1 Demographic Characteristics of the patients.

		Total (n=79)	Honeybee VIT (n=39)	Vespid VIT (n=36)	Double (n=4)	P
Year		52,0 (42,0-60,0)				0,998
Gender	Female	41 (51,9)	12 (30,8)	26 (72,2)	3 (75,0)	-
	Male	38 (48,1)	27 (69,2)	10 (27,8)	1 (25,0)	
Atopy	Positive	23 (29,1)	10 (25,6)	12 (33,3)	1 (25,0)	-
	Negative	34 (43,0)	16 (41,0)	16 (44,4)	2 (50,0)	
Comorbidity	Asthma(A)	4 (5.1)	-	4 (11.1)		-
	Rhinitis(R)	2 (2.5)	2 (5.1)	-	-	
	A+R	6 (7.6)	3 (7.7)	3 (8.3)	-	
	Urticaria(U)	2 (2.5)	-	2 (5.6)	-	
	U+A	1 (1.3)	-	1 (2.8)	-	
Eosinophil count		110,0 (97,5-252,5)	130,0 (100,0-270,0)	100,0 (50,0-160,0)	270,0 (200,0-)	0,060
Eosinophil percentage		2,1 (0,7-3,0)	2,0 (1,2-3,5)	1,7 (0,7-2,7)	3,3 (2,7-)	0,241
Total IgE		74,0 (33,5-200,5)	77,0 (30,5-291,0)	72,5 (30,7-199,7)	55,5 (32,0-)	0,847
Triptase		5,6 (4,1-8,0)	5,7 (4,3-7,7)	4,8 (3,4-7,7)	23,7 (5,0-)	0,507
Sting Area	Head/neck	49 (62,0)	25 (64,1)	22 (61,1)	2 (50,0)	-
	Other	30 (38,0)	14 (35,9)	14 (38,9)	2 (50,0)	

Median (IQR), n(%).

The mean age was 49.77±14.16 years in patients who underwent IT with honeybee venom and 50.47±13.18 years in patients who underwent IT with vespid venom. Age distribution was statistically similar across the IT groups (p=0.998). Of the patients who underwent IT with honeybee venom, 30.8% (n=12) were female, while 72.2% (n=26) of the patients who underwent IT with vespid venom were female. Atopy (aeroallergen sensitivities) was positive in 29.1% (n=23) of all patients. There was no statistically significant difference in the distribution of eosinophil count, eosinophil percentage, total IgE, and tryptase levels between the VIT groups (p>0.05). Additionally, 62.0% (n=49) of the patients had been stung by a bee in the head and neck region.

The distribution of characteristics related to the IT applied to the patients is presented in Table 2. It was recorded that 69.6% (n=55) of the patients had a stage 3 reaction before VIT. The cluster scheme was applied to 54.4% (n=43) of all patients, 61.5% (n=24) of patients who underwent VIT with honeybee and 44.4% of patients who underwent VIT with vespid. During the IT build-up phase, 20.3% (n=16) of the patients developed a reaction. During the IT maintenance period, 19.0% (n=15) of the patients developed a reaction. LAR developed in 10 patients during the VIT maintenance period. LAR was prevented by dividing VIT doses and giving antihistamines before VIT. SAR developed in 5 patients. In one patient, VIT was discontinued by making a decision together with the patient. In the other four patients, the decision was made to continue with the patient. In one patient, omalizumab was administered before VIT and VIT doses were divided. In one patient, methylprednisolone, antihistamine, and acetylsalicylic acid were given before VIT. Vaccine doses were divided. In the other two patients, antihistamine and acetylsalicylic acid were given before vaccination. VIT doses were divided. The VIT dose was not increased. There was no statistically significant difference in the number of field stings and adrenaline autoinjectors use in VIT groups (p>0.05). IT could not be continued in 36.7% (n=29) of all patients because they did not come for follow-up and in 35.4% (n=28) because of IT supply problems. Anxiety due to field sting occurred in 82.3% (n=65) of all patients. 82.3% (n=67) of the patients had adrenaline autoinjectors with them. The VIT scheme and tests performed in the patient groups are presented in Figure 2. Specific IgE test was performed in 18, prick test in 8, and both tests were performed in 16 of the VIT application groups who underwent VIT with honeybee.

Stages 3 and 4 of the reactions that developed before VIT were combined and the severity of the reaction was compared according to the site of field sting. Stage 3-4 reactions developed in 87.8% of patients sting from the head and neck region and in 53.3% of patients sting from regions other than the head and neck region. The distribution of these rates was statistically significantly different (p=0.001).

While applying VIT and after VIT, field sting was checked both from their files and asked when they were called for control. Field sting was observed in 19 patients while VIT was being applied. Systemic allergic reactions developed in 5 patients and local allergic reactions in 6 patients; no allergic complaints were observed in 8 patients. After VIT was discontinued, 56 field sting reactions developed in 25 patients. While local allergic reactions developed in 9 patients, systemic allergic reactions were never observed. Mastocytosis was diagnosed in a patient whose tryptase value was 42.4 and ckit mutation was positive as a result of haematological evaluation. A patient with a tryptase value of 15.1 and a ckit mutation negative was diagnosed with mast cell activation syndrome.

Table 2 Characteristics of immunotherapy in the study groups.

		Total (n=79)	Honeybee VIT (n=39)	Vespid VIT (n=36)	Double (n=4)	P
Reaction severity developed before VIT	Stage II	20 (25.3)	8 (20.5)	12 (33.3)	-	-
	Stage III	55 (69.6)	29 (74.4)	23 (63.9)	3 (75)	
	Stage IV	4 (5.1)	2 (5.1)	1 (2.8)	1 (25)	
VIT application scheme	Conventional	24 (30.4)	9 (23.1)	14 (38.9)	1 (25)	-
	Clustered	43 (54.4)	24 (61.5)	16 (44.4)	2 (50)	
	Clustered to conventional	12 (15.2)	5 (12.8)	6 (16.7)	1 (25)	
VIT total duration	<1 year	9 (11.4)	4 (10.3)	5 (13.9)	-	-
	1-3 year	31 (39.2)	12 (30.8)	18 (50)	1 (25)	
	3-5 year	23 (29.1)	16 (41)	7 (19.4)	-	
	>5 year	16 (20.3)	7 (17.9)	6 (16.7)	3 (75)	
Reaction during build-up phase	Yes	16 (20.3)	8 (20.5)	7 (19.4)	1 (25)	-
	No	63 (79.7)	31 (79.5)	29 (80.6)	3 (75)	
Severity of reaction VIT build-up phase (n=16)	LAR	10 (62.5)	5 (62.5)	5 (71.4)	-	-
	SAR	6 (37.5)	3 (37.5)	2 (28.6)	1 (100)	
Reaction during VIT	Yes	15 (19)	7 (17.9)	8 (22.2)	-	-
	No	64 (81)	32 (82.1)	28 (77.8)	4 (100)	
Severity of reaction to VIT (n=15)	LAR	10 (66.7)	4 (57.1)	6 (16.7)	-	-
	SAR	5 (33.3)	3 (42.9)	2 (5.6)	-	
Field sting after VIT started	Yes	25 (31.6)	16 (41)	8 (22.2)	1 (25)	-
	No	54 (68.4)	23 (59)	28 (77.8)	3 (75)	
Number of field stings after VIT		2.2±2.1	2.5±2.6	1.7±0.4	2	0,63
Number of AAA use after VIT		0.1±0.4	0.1±0.3	0.1±0.4	0	0,835
Time after completion VIT (months)		51.1±36.1	49.7±33	55.2±40.2	26.5±11.8	0,471
Severity of field sting reaction after VIT	LAR	9 (11.4)	5 (12.8)	4 (11.1)		-
	SAR	-	-	-		
Reason for VIT stopped	Discontinued VIT earlier voluntarily	29 (36.7)	17 (43.6)	12 (33.3)	-	
	Prolonged supply interruption	28 (35.4)	13 (33.3)	13 (36.1)	2 (50)	
	5 years completed	17 (21.5)	8 (20.5)	7 (19.4)	2 (50)	
	Side effect	3 (3.8)	1 (2.6)	2 (5.6)	-	
	Death	1 (1.3)	-	1 (2.8)	-	
	Pregnancy	1 (1.3)	-	1 (2.8)	-	
Anxiety due to field stings	Yes	67 (84.8)	31 (79.5)	33 (91.7)	3 (75)	-
	No	12 (15.2)	8 (20.5)	3 (8.3)	1 (25)	
Carrying AAA	Yes	65 (82.3)	31 (79.5)	30 (83.3)	4 (100)	-
	No	14 (17.7)	8 (20.5)	6 (16.7)	-	
New training requirements for AAA	Yes	43 (54.4)	24 (61.5)	19 (52.8)	-	-
	No	36 (45.6)	15 (38.5)	17 (47.2)	4 (100)	
Test used in diagnosis	Specific IgE positive	49 (62)	18 (46.2)	30 (83.3)	1 (25)	-
	Skin Prick positive	8 (10.1)	5 (12.8)	2 (5.6)	1 (25)	
	Both	22 (27.8)	16 (41)	4 (11.1)	2 (50)	

Median (IQR), n(%); *LAR*, local allergic reaction; *SAR*, systemic allergic reaction; *AAA*, adrenaline autoinjectors.

Discussion

In this retrospective study, the prevalence of venom-induced anaphylaxis was calculated as 0.058%. During a lifetime, approximately 3 percent of the general population is expected to develop SAR following a Hymenoptera sting.[13] In our study, the prevalence of honeybee and vespid-induced anaphylaxis was calculated as 0.058%. The prevalence of anaphylaxis due to these two venoms could be calculated because both honeybee and vespid are

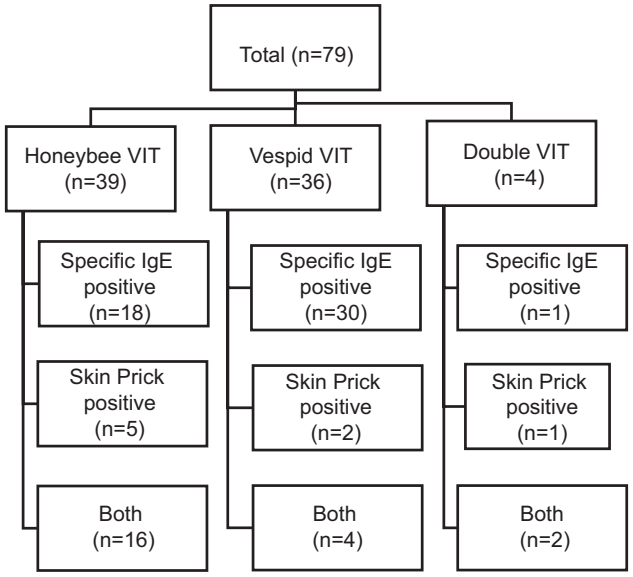

Figure 2 Tests used for diagnosis.

present in our country. This is the reason why our prevalence is lower.

Venom stings from well-vascularized areas of the body, such as the head and neck, have been reported to cause large local reactions.[13] In our study, 49 (62.0%) patients were stung in the head and neck region. Stages 3 and 4 of the reactions that developed before VIT were combined, and the severity of the reaction was compared according to the site of the sting. Stage 3-4 reactions developed in 87.8% of patients stung in the head and neck region and in 53.3% of patients stung in regions other than the head and neck. The distribution of these rates was statistically significantly different (p=0.001). In other words, being stung in the head and neck region was considered a risk factor for more severe allergic reactions according to the Ring and Messmer grading scale, but studies with larger numbers of patients are needed.

Allergic reactions during the VIT build-up phase varied according to the scheme used, but in our study, SAR developed in 6 patients, and the rate was calculated as 7.5%. Due to the number of patients, it was not possible to identify which dose in particular was a risk factor for SAR. The rate was similar to the rates defined with both cluster and rush protocols.[14-16] Six (37.5%) patients developed SAR in the VIT build-up phase, and 5 (33.3%) in the VIT maintenance phase. These reactions were generally milder than the index reactions. Although this rate appears to be higher than in some studies,[17] it is similar to studies using the same VIT.[18]

According to Parke et al., 3-year compliance with VIT was 92.4% and 5-year compliance was 84.1%.[19] Only 28.6% of patients purchased AAI after early termination of VIT. In our study, 3-year compliance with VIT was 49.4% and 5-year compliance was 20.3%, which is significantly lower than the literature. The most important reason for this situation is that immunotherapy has not been available in our country since 2022. It was discontinued for this reason in 35.4% of patients.

VIT was applied to our patients because of grade 2, 3, and 4 reactions according to the Ring and Messmer classification. After VIT was discontinued, LAR was observed in 9 (11.4%) patients after field sting reactions, while SAR was not observed. Before VIT, it is noteworthy that SAR developed in 4 patients, leading to cardiac arrest and resuscitation. Koleczek et al. also reached similar results for field stings after VIT.[20] Additionally, two studies conducted in our country, when evaluating field sting reactions after VIT, confirmed that the severity of field sting reactions decreased after VIT.[21,22]

In our study, the two data sets overlap. These are the patients who completed 5 years of VIT and the patients who carried AAA with them. The percentage of patients who completed 5 years of VIT was 21.5%, while the percentage of patients with AAA was 82.3%. We believe that this situation is related to the fact that the patients were followed up in 3-6 month intervals, even if VIT was not applied in our clinic.

The major risk factor for a more severe anaphylactic sting reaction is a high basal serum tryptase level[23,24] and/or mastocytosis.[13,-25] The serum tryptase level of all patients was 7.8±8. The serum tryptase level of the patients in whom both honeybee and vespula VIT were applied was 23.7±26.4. Although it did not reach statistical significance due to the small number of patients, especially basal serum tryptase levels should be examined in patients who develop anaphylaxis due to both venoms, and further investigations should be performed for mast cell diseases. While it used to be asked 'what is the frequency of anaphylaxis in patients with clonal mast cell activation syndrome? It is now thought that the correct question is: 'How many patients with anaphylaxis have clonal mast cell disease?[26] In one of our patients who developed anaphylaxis due to both venoms, the basal serum tryptase level was 42.4, and mastocytosis was diagnosed through haematological evaluation.

The limitation of our study is that there is no control group that has not received or has not yet completed VIT.

Conclusion

This study confirms that the prevalence of venom-induced anaphylaxis was calculated as 0.058%. Being stung in the head-neck region was identified as a risk factor for the development of stage 3-4 (severe allergic reaction) (p=0.001). Patients did not develop SAR after the discontinuation of VIT, and patients tolerated the field stings. This confirms that VIT is highly effective.

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