

Subcutaneous venom immunotherapy in children

Efficacy and safety



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ARTICLE INFO

Article history:

Received for publication October 29, 2017.

Received in revised form January 1, 2018.

Accepted for publication January 12, 2018.

ABSTRACT

Background: Venom immunotherapy (VIT) is safe in children, although adverse effects can occur.

Objective: To document adverse effects and to determine re-sting reactions and the efficacy of VIT in childhood.

Methods: We retrospectively analyzed data from children who had taken VIT from 2002 through 2015. These patients were queried by telephone to determine reactions after re-stings during or after VIT.

Results: In total 107 children with a systemic reaction after Hymenoptera sting and with proved immunoglobulin E-mediated sensitization were enrolled. Participants had a median age of 10.0 years (7.2–12.4 years) at the beginning of immunotherapy. Fifty-two participants had allergic reactions during VIT; 40 of these reactions were local (37.4%), 5 were large local (4.7%), and 7 were systemic (6.5%). Of the 52 patients with adverse reactions, most reactions were local ($n = 40$, 89%) and were observed mainly in dose-increase periods ($n = 25$, 60%; $P < .001$). Although local reactions were more frequently seen with *Vespula* treatment ($P = .047$), systemic reactions were common with *Apis* treatment ($P = .031$). Sixty-eight patients (63.5%) were queried for re-sting, 33 (48.5%) had a re-sting and 24 (72.7%) of these 33 patients developed allergic reactions. The reactions were local ($n = 19$), large local ($n = 1$), and systemic ($n = 4$). Risk analysis for local and systemic reactions during VIT showed pre-existing asthma as an independent risk factor (odds ratio 4.1, 95% confidence interval 1.3–12.7, $P = .016$).

Conclusion: In children, VIT appears to be safe and protective against severe reactions after re-sting. However, pre-existing asthma was identified as a risk factor for systemic and large local reactions during VIT in children.

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Introduction

Hymenoptera stings can cause allergic reactions ranging from insignificant local effects to severe anaphylaxis. The systemic reaction risk has been reported to be approximately 1% in children, 5% to 7.5% in adults, and as high as 32% in beekeepers.¹

Because of the possibility of allergic reactions and even fatal outcomes, insect venom induces high anxiety in many patients.² To date, venom immunotherapy (VIT) is the only treatment for venom allergies, and it is used in patients with previous systemic allergic reactions caused by venom stings and in those who have had positive venom diagnostic test reactions.³ Allergic reactions during VIT are mostly local,⁴ although intimidating systemic reactions are seen at the relatively low rate of 0.1% to 0.2%.^{3–5} Although adverse effect profiles of immunotherapy have been well documented in adults, data from children are limited. Moreover, risk factors that can be

used to predict systemic adverse reactions during VIT have not been fully defined. Adverse symptoms occurring during immunotherapy cause difficulties in treatment compliance and can lead to anxiety for the affected children and their parents.

The present study assessed the frequency and severity of adverse reactions during VIT in children and determined predictive factors for the development of adverse reactions. We present observations from children who received VIT in our outpatient clinic and their experiences with re-sting in the field.

Methods

Study Population

In this retrospective cross-sectional study, we analyzed data from children who received subcutaneous conventional VIT (SCIT) in our department from January 2002 through December 2015. All patients undergoing VIT had a history of at least 1 systemic reaction after *Apis mellifera* and/or *Vespula* stings⁶ and positive diagnostic test reactions (skin prick test [SPT] or specific immunoglobulin E [IgE]) for culprit insect venom.⁷ The data used in this study were collected from medical files filled out by physicians at each visit.

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Disclosures: Authors have nothing to disclose.

<https://doi.org/10.1016/j.anaai.2018.01.015>

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These files were unique for each patient and consisted of immunotherapy schedules, adverse effects during SCIT, and treatments administered after adverse reactions. Diagnostic test results (ie, SPT, intradermal tests [IDTs], *Vespula*-specific IgE, and honeybee-specific IgE), total IgE, and eosinophil numbers were recorded. We asked patients to describe their personal and family histories of aeroallergen and/or food atopy, allergic rhinitis (AR), asthma, and venom allergy. AR and asthma were defined according to international guidelines.^{8,9} Patients were administered VIT if they were at least 5 years old, had no severe uncontrolled asthma, and had no other systemic or autoimmune disorders. This study was approved by the ethics committee of the university, and written informed consent was obtained from the participating children and their parents.

Diagnosis of Venom Allergy

Diagnosis of venom allergy was made based on European Academy of Allergy and Clinical Immunology guidelines.⁷ All participants had positive SPT and IDT reactions for *Vespula* species and honeybee and/or positive specific IgE (>0.35 kU/L) levels measured using the Pharmacia CAP (Pharmacia & Upjohn, Uppsala, Sweden) system for the 2 venom types. SPTs and IDTs were applied at least 4 to 6 weeks after systemic reactions.⁷ Saline solution and histamine were used as negative and positive controls, respectively, and venom extracts (100% *A mellifera* or *Vespula* species; Alutard SQ, ALK, Hørsholm, Denmark) were given at 15- to 20-minute intervals in incremental doses of 1, 10, 100, and 1000 ng/mL epidermally and intradermally.¹⁰ SPT and IDT reactions were considered positive when the mean wheal diameters were at least 3 and 5 mm, respectively, compared with the negative control, and the test reactions were accepted as positive at the lowest concentration of venom extract that produced a positive result.⁷

When assessing the culprit venom, we took into account venom-specific IgE levels, patient history, and social environment (eg, living in a wooded area, beekeeper in the family or neighbors).

Serum basal tryptase (sBT) levels were measured at the start of SCIT by the UniCAP method (System ImmunoCAP Tryptase, Pharmacia & Upjohn).

Venom Immunotherapy

All patients underwent conventional SCIT; 103 patients were given Alutard SQ 100% *A mellifera* or *Vespula* species and 4 patients were given Alyostal (Stallergenes, Antony Cedex, France). Doses were administered in 1-week intervals starting with 3 to 8 µg/dose and were gradually increased to the maintenance dose of 100 µg over 6 months.¹¹ After this “build-up” period, maintenance doses were administered every 4 to 6 weeks for up to 5 years.¹² The maintenance doses were decreased by 10% with each new bottle. All injections were administered to the lateral parts of the upper arm.

Adverse Reactions

Local, large local, and systemic reactions during the course of treatment were noted on each patient's immunotherapy card. Large local reactions were defined as those reactions having a diameter of induration larger than 10 cm. Reactions smaller than 10 cm were accepted as local reactions. Systemic adverse effects included widespread skin lesions, such as generalized urticaria, angioedema, and other system involvements.¹³ In addition, patients were queried by telephone to evaluate re-sting reactions during or after VIT. We verified sting reactions in the field first by phone calls and second by asking during routine visits and during VIT.

Statistics

The data were not normally distributed; therefore, results were expressed as median (interquartile range). Correlations were evaluated with Spearman correlation analysis. Statistical analyses included univariate and multivariate analyses. Odds ratios with relevant 95% confidence intervals were calculated to evaluate potential associations. *P* values less than .05 were accepted as significant.

Results

In total 107 patients (77 boys and 30 girls) with a median age of 10.0 years (interquartile range 7.2–12.4 years) at the start of VIT were enrolled in this study. The demographic and clinical features of patients are presented in Table 1. Immunotherapy was given to

Table 1
Characteristic Features of Study Group

	<i>Vespula</i> species (n = 81)	<i>Apis</i> species (n = 25)	<i>P</i> value
Age at first dose of VIT (y), median (IQR)	10.46 (7.75–12.46)	9.07 (7.18–11.92)	.49
Boys/girls (% boys)	58/23 (71.6)	18/7 (72.0)	.97
Total IgE (kU/L), median (IQR)	175 (84–484)	250 (132–660)	.16
Eosinophil number (mm ³ /mL), median (IQR)	200 (100–400)	300 (125–550)	.17
Eosinophils (%), median (IQR)	3.2 (1.8–4.5)	3.25 (1.87–5.94)	.61
Specific IgE, median (IQR)	8.54 (3.36–29.90)	19.2 (10.70–82.30)	.042
During IT, %			
Local reaction	42	20.0	.047
LLR	6.2	0	.20
SR	3.7	16.0	.03
Re-sting with responsible Hymenoptera during VIT (n = 68), %	42.3	50	
Reaction after exposure to Hymenoptera during IT, %	42.3	40	
No reaction or local reaction	81.8	80	.29
LLR	4.5	0	.76
SR	13.6	20	.19
Asthma, %	23.3	28.6	.68
Allergic rhinitis, %	23.0	30.8	.55
Allergy to foods, aeroallergen sensitization, asthma and allergic rhinitis, %	34.4	30.8	.80
Aeroallergen sensitization in family, %	42.4	27.3	.35
Family history of venom allergy (LLR + SR), %	37.3	36.4	.95

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; IT, immunotherapy; LLR, large local reaction; SR, systemic reaction; VIT, venom immunotherapy.

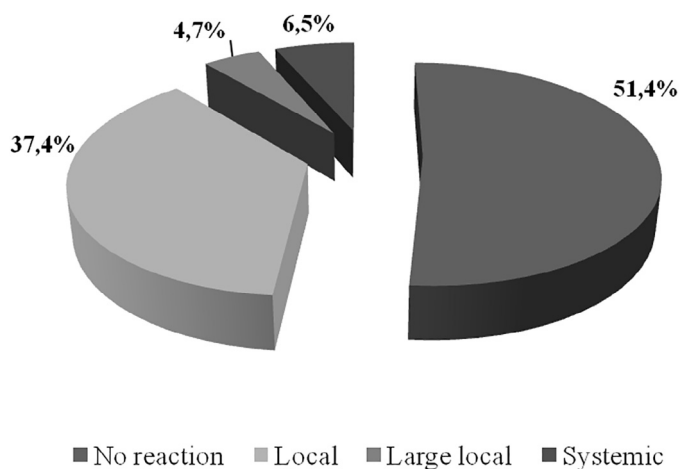


Figure 1. Distribution of reactions during venom immunotherapy.

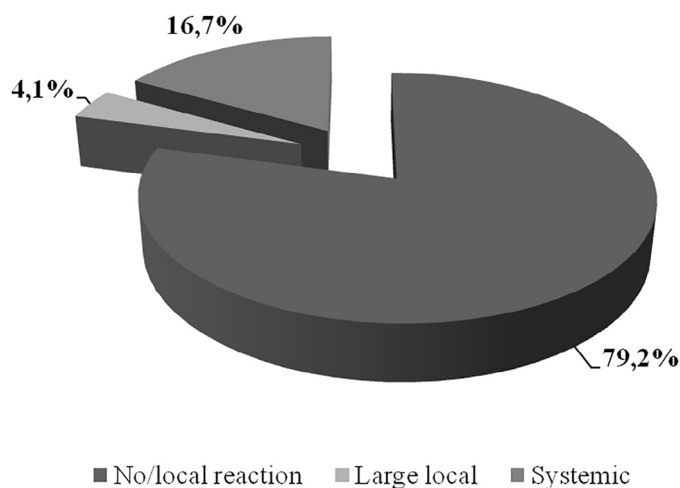


Figure 2. Reactions after exposure to bee during or after venom immunotherapy.

25 patients (23.3%) for *A mellifera* venom and to 81 patients (75.7%) for *Vespula* venom; 1 patient received treatment for *Apis* and *Vespula* venom. Seventeen participants did not complete treatment for familial or personal reasons, 51 completed treatment, and 39 continued to receive immunotherapy treatment during the course of the study.

In total 5,671 injections were administered during the course of immunotherapy, and local, large local, and systemic reactions were observed in 1.60%, 0.14%, and 0.17% of these injections, respectively. Fifty-two patients had allergic reactions (Fig 1). Local reactions constituted a significant proportion of these adverse effects ($n = 40$, 89%; $P = .103$), which were observed significantly more frequently in the dose-increase phase compared with the maintenance phase ($n = 25$, 62.5%; $P < .001$).

Large local reactions occurred in 5 patients, 2 of which were seen in the up-dosing phase, 2 of which were seen in the maintenance phase, and 1 that was observed in these 2 periods of immunotherapy.

Systemic reactions were graded according to the modified classification system of Mueller.³ Systemic reactions occurred in 7 patients as grades I ($n = 2$), II ($n = 2$), III ($n = 2$), and IV ($n = 1$). Three of these systemic reactions were seen in the up-dosing phase and 4 were seen in the maintenance phase.

Of the 52 patients with allergic reactions, adverse effects were frequently observed during the up-dosing period ($n = 25$, 60%; $P < .001$). One patient had adverse effects in the maintenance and up-dosing phases. Sex, age, and laboratory parameters did not appear to significantly affect the type of allergic reaction or the treatment period in which the reaction occurred.

Patients receiving *Vespula* immunotherapy ($n = 34$, 85%) had significantly more adverse local effects than those receiving *Apis* immunotherapy ($P = .047$). In contrast, patients receiving *Apis* immunotherapy had more adverse systemic effects (16%) than those receiving therapy for *Vespula* immunotherapy (3.7%; $P = .031$).

Sixty-eight participants (63.5%) were contacted and asked whether they were stung in the field during or after VIT; 33 (48.5%) were exposed to re-sting by the culprit Hymenoptera. The median interval from the starting date of VIT to re-sting was 34 months (interquartile range 24–46 months). Reactions occurred after re-sting in 24 (72.7%) of the 33 patients (19 local, 1 large local, and 4 systemic) with a significant frequency of local adverse effects and a mild grade of systemic reactions (Mueller grades I and II; Fig 2). Further, no risk factors appeared to be related to adverse reactions after re-sting in the field.

The type and risk of reactions occurring during VIT did not differ for eosinophil count, total IgE, venom-specific IgE, sex, or age (Fig 3). Moreover, sBT levels were not correlated with the severity of the adverse effect or the type of the insect venom used for treatment.

The starting age at VIT, pre-existing asthma or AR, atopy in the family, and local reactions during the course of VIT appeared to correlate with large local and systemic reactions in univariate analysis; however, only pre-existing asthma was determined to be a risk factor for the development of large local and systemic adverse effects in multivariate analysis (odds ratio 4.1, 95% confidence interval 1.3–12.7, $P = .016$; Table 2).

Discussion

Results of the present study showed that pre-existing asthma was an independent predictor for large local and severe reactions during VIT in children. Further, local symptoms were the most frequently observed type of reaction, and the adverse effects were mostly observed in the up-dosing period. In addition, patients receiving treatment for *Apis* species had significantly more systemic reactions than those treated for *Vespula* species. VIT appears to be protective for severe systemic re-sting reactions.

Table 2
Predictive Factors for Large Local and Systemic Reactions During VIT

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age at first dose of VIT (y)	1.167	0.982–1.387	.080	1.268	0.975–1.648	.077
Asthma	1.946	0.847–4.469	.117	4.072	1.301–12.744	.016
Allergic rhinitis	3.786	0.840–17.066	.083			
Atopy in family	0.214	0.024–1.884	.165	0.065	0.040–1.105	.059
Local reaction during VIT	2.630	0.774–8.935	.121			

Abbreviations: CI, confidence interval; OR, odds ratio; VIT, venom immunotherapy.

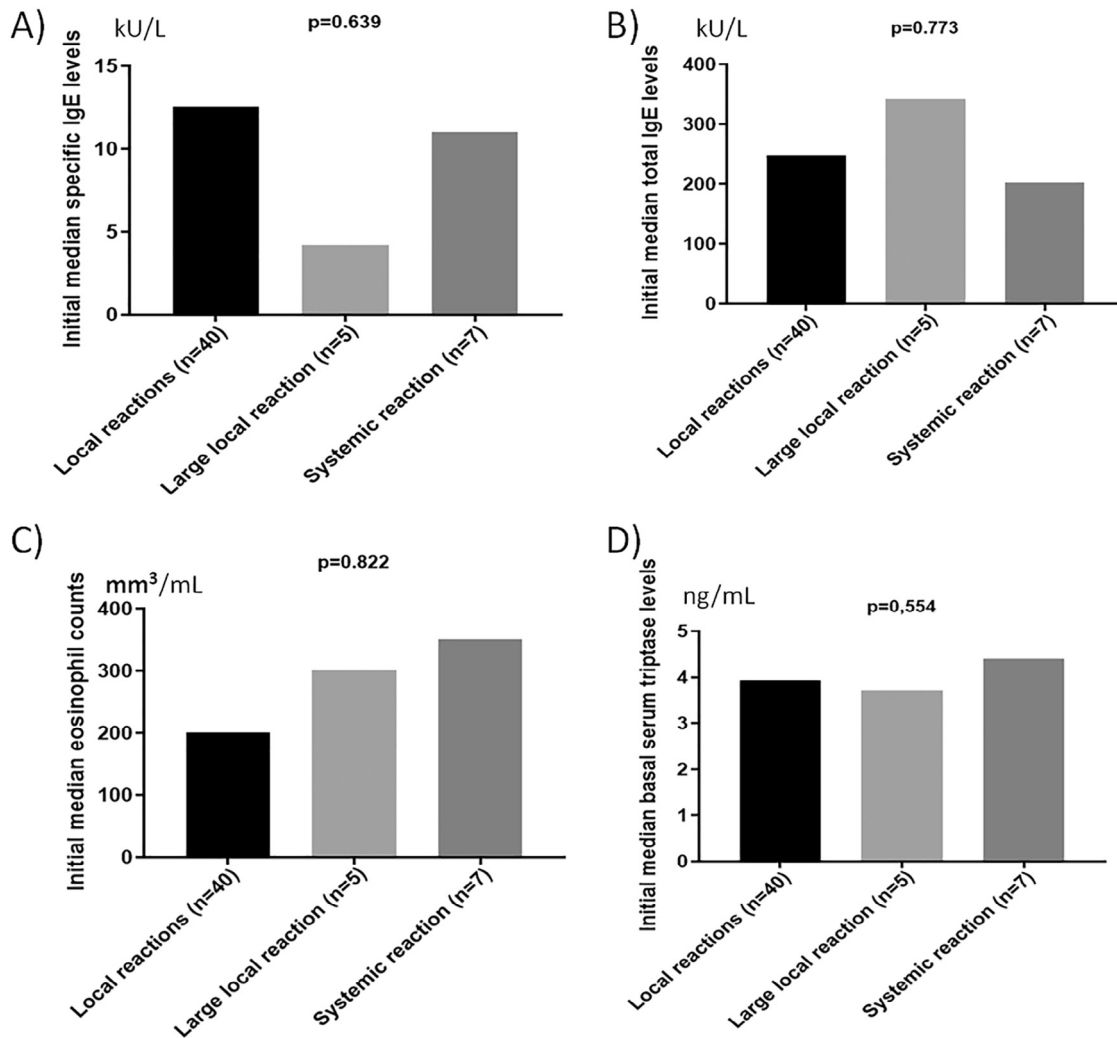


Figure 3. (A) Serum specific immunoglobulin E (IgE), (B) serum total IgE, (C) eosinophil counts, and (D) serum basal tryptase levels before initiation of venom immunotherapy.

In contrast to the literature, the present study identified pre-existing asthma as an independent predictor for childhood VIT. Although asthma is a well-known risk factor in pollen immunotherapy,¹⁴ it has not been previously related to VIT. In a study by Mosbech and Müller,¹³ asthma was determined to be unrelated to VIT, but AR was reported to be an independent risk factor for VIT. In the present study, pre-existing asthma increased the risk of adverse reaction 4 times and was the only determining risk factor for systemic and large local reactions. In contrast to the study by Mosbech and Müller,¹³ we did not find any correlation between AR and immunotherapy.

During VIT, allergic adverse effects are frequently observed, and it has been shown that most of these are the local type.^{15,16} Systemic symptoms, which are mostly mild, have been observed in 10% to 15% of patients receiving VIT.² In the present study, most patients developed local reactions, especially in the dose-increase period, and large local systemic symptoms were observed much less frequently. Systemic reactions were seen in 6.5% of the present study group, and systemic reactions were seen in 13.5% of patients experiencing adverse effects during VIT; these results are consistent with those of previous publications.^{13,17–20} However, previous data were mostly attained from studies in adults, and there are few data related to adverse effects in children.^{21,22} However, the present study indicated that the frequency of systemic allergic re-

actions observed during VIT is very low in children, which is consistent with the literature on adults.

Published data have shown that children receiving *Apis* immunotherapy have many more systemic adverse effects (14.2–24%) than those receiving *Vespula* immunotherapy (2.8–19%).^{13,23} Previous studies have shown that honeybee venom is related to a high frequency of systemic reactions but not to the severity of adverse effects.¹³ In agreement with published data, the present study showed that 19% of patients undergoing *Apis* immunotherapy experienced systemic reactions, whereas this rate was only 3.7% for those undergoing *Vespula* immunotherapy. In a study including adults and children, *Apis* immunotherapy was determined as an independent risk factor for developing adverse reactions during VIT.¹³ Previously, the difference in systemic reaction frequency between *Apis* and *Vespula* immunotherapy has been hypothesized to be due to the difference in venom extract quality.^{18,24} The investigators concluded that *Vespula* venom extract is diluted by nonallergenic proteins, but that *Apis* venom is a purified extract with a lower concentration of nonallergenic proteins.^{17,18} However, the current preparations of allergen extracts are much more standardized, and the patients in the present study used products from the same company; therefore, we believe that the differences cannot be explained by the allergen concentrations.

Laboratory parameters cannot provide as clear implications for the assessment of VIT efficacy as can re-sting in the field. In previous reports, most reactions after a bee sting after completion of VIT were observed as mild systemic reactions that were less severe than the original insect sting reactions before immunotherapy.^{3,18,23,25} Although there are few studies related to VIT in childhood, studies have shown a lower risk of systemic reactions after re-sting in adults and children.^{23,26} In the present study, 33 patients (48.5%) were exposed to re-sting in the field during or after immunotherapy, and adverse effects developed in 72.7% of them, most of which were local (79%). A study by Stritzke and Eng²⁷ reported that the frequency of systemic reaction after re-sting was 16.6%, and the reactions were mostly mild grade. The result of our study was higher than the ratio of 3% reported by Golden et al.²³ There are few publications related to venom sting after VIT in childhood; more studies are needed to more concretely define the risk of systemic reactions after re-sting. In this report, we presented the real-life experiences of patients exposed to re-sting during or after immunotherapy; the present study demonstrated the protective effect of VIT against severe reactions in children after a bee sting in the field.

Apis immunotherapy, the dose-increment phase, mastocytosis, and increased sBT levels have been documented as risk factors for the development of adverse effects in VIT.^{1,17,18} We found that systemic adverse reactions were frequently observed in children receiving *Apis* immunotherapy and during the up-dosing period, which is consistent with the literature.¹³ Although publications have documented the relation among sBT level, systemic adverse effects, and type of venom extract used in immunotherapy, we did not find such correlations in the present study.^{17,28}

Although the present study brings much new data to the field, it had some limitations. First, this is a retrospectively designed study, and there are some missing data related to mild adverse reactions during VIT and in the patients' medical histories. Second, we could not contact all the participants to ask whether they were exposed to venom sting after VIT completion. Third, the patients might have confused or misidentified the exact species of bee that stung them during or after VIT. Therefore, it was not possible to determine the precise efficacy of a given immunotherapy against the main allergen venom type. However, we also showed photos of the Hymenoptera species to minimize misunderstandings. Fourth, this study includes only conventional immunotherapy outcomes and does not reflect the adverse effect and efficacy profiles of other immunotherapy procedures. Despite these limitations, the present study had the benefits of a long-term clinical follow-up and a large study population consisting of only children. Furthermore, because there are limited studies on the adverse effects of VIT in children, this study is important in showing the efficacy and safety profile of immunotherapy in children.

In conclusion, the present study indicates that adverse effects during VIT were frequently local; systemic reactions occurred less frequently and were of mild grade. According to the outcomes of this study, we conclude that VIT is safe in children. In addition to the known predictors shown in previous publications, the present study showed that asthma is a risk factor contributing to systemic and large local reactions in the course of immunotherapy. In consideration of these implications, we suggest that physicians should pay attention to the adverse effects of VIT, especially in patients with asthma, in those receiving therapy for *A mellifera*, and in the dose-increase phase.

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