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Systemic and Local Reactions of Bee Venom Immunotherapy in Iran

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ABSTRACT

Severe allergic reactions during specific immunotherapy may occur in the treatment of hymenoptera sting allergy. The objective of the present study was to examine the characteristics of allergic reactions during specific immunotherapy in patients with allergy towards hymenoptera venom in the Iranian population.

A prospective study was performed using the clinical reports of 27 patients with anaphylaxis to bee venom (Apis melifera, Geupes vespula and Geupes Polites). Ten patients treated with Cluster protocol during 2002 and 2006

After diagnosis of hymenoptera sting allergy according to history and intradermal tests, the patient were treated with Cluster protocol immunotherapy. The protocol lasted 6 weeks with an increase in the concentration of venom from 0.01μ g/ml to 100 μ g /ml. None of the patient received premedication. All patients with hymenoptera venom allergy received 120 injections. Anaphylactic reactions were classified according to the Mueller-classification.

The frequencies of systemic reactions during Cluster protocol were 8.33% and 5% for yellow jacket and honey bee venom respectively. No patient experienced severe systemic reaction.

Cluster protocol for hymenoptera immunotherapy is a reliable method for the treatment of anaphylactic reactions to bee venom. It is safe with low cost and do not need hospitalization.

Key words: Anaphylactic; Bee venum, Cluster Immunotherapy; Hymenoptera; Reactions

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INTRODUCTION

Anaphylactic reactions caused by hymenoptera stings predominantly bee, wasp or paper wasp stings

are a common medical problem and account for approximately 40 deaths per year in the United Sates.[1,2] These reactions are related to the most dramatic allergic diseases and may present with an acute onset of combined local and systemic symptoms. [3]

The prevalence of insect-sting allergies varies from 0.4 to 4%, [4] and the rate of mortality has been reported to be 0.09 to 0.45/1000000 people/year.[5] Allergen immunotherapy has been used in the management of allergic diseases for nearly 100 years. It is the only specific treatment for hymenoptera venom anaphylaxis.[6,7] Various immunotherapy schedules have been designed to treat hymenoptera-induced anaphylaxis.[8] The time required to reach the maintenance dose, varies depending on the protocol. Several months to weeks are needed for the conventional protocol, days for the rush protocol, and hours for the ultra-rush protocol.[9,10] Cluster protocols seem to be safe and slower protocols, with few systemic reactions that could be done on an outpatient clinic without hospitalization. The purpose of this study was to determine the efficacy and safety of this protocol in a population of hymenoptera venom allergic individuals in Iran.

MATERIALS AND METHODS

The present study included 27 patients who had history of anaphylaxis to bee venom. Ten patients were treated with EACCI protocol for hymenoptera sting allergy at the university hospital of Tehran (Children Hospital Medical Center) during the periods of 2002 to 2006. All study subjects were native Iranian. Hypersensitivity to honeybee, yellow jacket or wasp venom was confirmed by skin testing. The tests consisted of intradermal tests in concentrations of 0.001, 0.01, 0.1 and 1 µg/ml venom from honey bees (Apis melifera), wasps (Guepes polistes) or yellow jacket (Guepes vespula). Histamine dihydrochloride (1 mg/mL) and albumin 0.03% diluent were used as positive and negative controls, respectively. Prick test results were read after 15 minutes; a wheal diameter of 5 mm or greater produced by the solution was considered a positive reaction. The prick test was followed by an intradermal test on the forearm with increasing concentrations from 0.001µg/mL to 1 µg/mL. Intradermal tests were considered positive if reactions (wheal of at least 5 mm in diameter with erythema) occurred after 15 minutes at a concentration of 1 µg/mL or less.

Table 1. Cluster protocol for bee venom Immunotherapy (EAACI 1998).

Protocol cluster EAACI 1998			Concentration µg/ml	Dose in µg venom
Day	Hour	injected ml		
Day 1	0	0.1	0.01	0.001
	0.5	0.1	0.1	0.01
	1	0.1	1	0.1
Day 8	0	0.1	10	1
	1	0.5		6
	2	0.1	100	10
Day 15	0	0.2		20
	1	0.3		30
Day 22	0	0.5		50
	1	0.5		50
Day 29	0	1		100
Day 36	0	1		100

The venom immunotherapy regimen was completed within 6 weeks in outpatient clinics. The protocol began without premedication with an initial dose of 0.1 ml (0.01µg/mL, St-allergen, France). Every patient had six courses (one week apart) of immunotherapy injections. The first two courses included 3 injections and next two courses, consisted of two injections and the last course one injection (Table 1).

All injections were applied subcutaneously to the outside of the upper arm. Vital signs of all patients checked at first and then before and between each injection. Full emergency resuscitation equipment was readily available at all times. Venom extract dosage, local and systemic reactions, and treatment of side effects were recorded.

We determined the incidence and nature of side effects during the initial phases of the treatment. If a patient developed a systemic allergic reaction during a dose increase, treatment was interrupted until complete recovery was obtained, and then restarted with a dose reduced by 2 steps. In case of large local reaction with pronounced erythema and/or swelling (>8 cm in diameter) of both upper arms, the protocol continued without dose reduction.

RESULTS

During July 2002 and November 2006, 10 patients with a hymenoptera venom allergy (5 females, 5 males) ranging in age from 21 to 47 years (mean, 31.70±7.52 years) were administered venom immunotherapy. Five

patients were vaccinated with honeybee venom and five with yellow jacket venom. Throughout the entire immunotherapy period, 10 patients received a total of 120 injections within 6 weeks; 60 of the injections (50%) were honeybee venom extracts and the remaining were yellow jacket extracts. Systemic reactions that occurred during immunotherapy were dyspnea (1.6%), headache (1.6%) and vertigo (1.6%) (Table 2). Dyspnea was more common in 2nd and 7th injection. Three late local reactions were observed (Mean; 2.5%). There were not any differences between systemic reactions due to honeybee or yellow jacket immunotherapy but local wheal were more common with honeybee than yellow jacket (P=0.003).The most common local reactions were local erythema and local wheal (66.6%). All the systemic reactions were transient and ceased spontaneously without using any medications and none was life threatening or fatal. The patients did not receive injections of adrenaline, antihistamines, and corticosteroids due to the systemic reaction. Itchy distal part of injection site or itchy lower extremities or scortum developed in six injections (5%). No dose adjustments were required for large local reactions, and local reactions did not require therapy but one patient received antihistamine (Loratadine) and short course of prednisolone due to severe large local reaction.

Table 2. Frequency of side effects following immunotherapy.

Reactions due to immunotherapy	Maximum	Minimum	Mean
Local erythema	90%	0	65%
Local wheal	90%	40%	66.6%
Local pain or burning	10%	0	6.66%
Local itching	30%	0	10%
Diffuse erythema	30%	0	6.66%
Diffuse itching	30%	0	9.1%
Diffuse pain	10%	0	0.8%
Diffuse induration	10%	0	0.8%
Distend complications	10%	0	5%
Dyspnea	10%	0	1.6%
Headache	10%	0	1.6%
Vertigo	20%	0	1.6%
Late complications	10%	0	2.5%

DISCUSSION

Venom immunotherapy (VIT) is established as a highly effective and specific form of treatment to prevent life-threatening reactions in hymenoptera allergies. The goals of venom immunotherapy are to reach an allergen dose inducing tolerance to hymenoptera venom with the lowest rate of systemic reactions.[8] However, many VIT schedules for build-up and maintenance have been proposed. They range from very slow protocols to 1-day rush protocols. With a rush protocol, the time required to reach the maintenance dose ranges from 1 to several days instead of weeks or months, [11] but it needs hospitalization. In addition, their safety is controversial because of a potentially higher frequency of severe systemic reactions.[12] In this study, we evaluated the early clinical safety of VIT through focusing on local, large local and systemic reactions. Ten patients with a history of severe systemic reactions after an insect sting were treated with VIT using a 6 weeks protocol. They were all able to tolerate a subcutaneous injection of 100µg of venom as early as treatment day 29. In the literature, 17.9% to 45% of VIT applications have been reported to cause side effects.[13] Up to 20% to 40% of patients may develop systemic allergic reactions particularly against honeybee VIT.[14] Frequencies of reactions 40%-46% with honeybee venom and of 12%-25% with yellow jacket venom have been noted with the conventional weekly build-up regimens.[15,16] In our Study; we recorded a mild systemic reaction in patients (6.66% of all injections). None of the reactions were life-threatening, and adrenaline or any other medications for reactions never used. Sturm et al, also reported a 0.47% risk per injection in their 4-day rush regimen.[17] Hence, the risk for systemic reaction to VIT was shown to be much more related to the nature of the venom than to the regimen used. Immunotherapy with honeybee venoms is evidently better tolerated than treatment with yellow jacket venom, but it has not been elucidated why VIT with yellow jacket venom causes more systemic reactions. An explanation for this could be due to nature of reaction to bee sting that were more severe in patients with allergic to yellow jacket. In conclusion; various protocols are currently used to induce tolerance to hymenoptera venom in order to eliminate the risk of anaphylaxis during a subsequent sting. The adverse effect rate is an important factor to consider when selecting a protocol and maintenance

dose. We suggest that if a relatively fast and safe protocol is required, the utilization of Cluster protocols can reduce the cost and time for clinics as well as patients. Our patients are still under observation and treatment. We are also aiming to study the long-term effectiveness of this protocol.

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