
Latex sublingual immunotherapy: can its safety be predicted?

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Background: Complete avoidance sometimes cannot be possible in latex-allergic health care workers. So far, very few double-blind placebo-controlled studies revealed the efficacy of sublingual latex immunotherapy (SLIT) in those patients.

Objective: Our aim was to evaluate the efficacy and safety of latex SLIT in health care workers.

Methods: 30 patients (all health care workers) diagnosed as latex allergic were advised to avoid latex exposure and were given information about the prevention measures and asked to return two months later. 24 patients who were still symptomatic despite prevention measures were informed about the latex SLIT study and asked to participate. However, only 12 gave approval and were randomized to receive sublingual latex extract or placebo. Symptom scores and latex cutaneous provocation test scores were recorded at baseline and at the 6th and 12th months of the study.

Results: Two patients experienced anaphylaxis, 1 patient showed severe bronchial obstruction during dose incremental phase and were excluded from the study. The differences of the symptom and provocation scores between baseline and the 12th month of the treatment were significant in the active group ($p = .042$, $p = .038$, respectively). Also the symptom and provocation scores at 12 months were significantly lower in the active group than in the placebo group ($p = .035$, $p = .013$, respectively).

Conclusion: Latex SLIT can be used as an effective treatment for latex-allergic health care patients having difficulties in applying adequate avoidance measures. However, the risk of systemic reactions should be kept in mind and sufficient precaution measures must be made available.

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INTRODUCTION

Natural rubber latex (NRL) exposure can cause or exacerbate a number of IgE-mediated clinical diseases.¹ Populations at high risk for NRL exposure include health care workers, patients with spina bifida, patients who have undergone frequent catheterization, and people who work at latex product factories.² The percentage of latex allergy has been reported to be 3% to 12% in health care professionals, whereas it is approximately 1% in the general population. The high prevalence of latex sensitization and allergy in health care workers is attributed to widespread exposure to latex gloves. Exposure studies confirm that levels of airborne latex allergen in hospitals are determined largely by the intensity of glove use³ and are much higher when powdered surgical gloves are used. Induction of latex allergy commonly occurs after exposure of skin or mucous membranes to NRL or by inhalation mainly caused by glove starch powder.⁴

The typical allergic reaction to latex protein is characterized by pruritus, erythema, and edema.⁵ As severity and exposure to allergen increase, urticaria may also develop, initially restricted to the site of the latex contact, but it may

eventually become systemic. Airborne exposure may lead to nasal, ocular, and pulmonary symptoms. The severe forms of latex allergy are characterized by wheezing, stridor, sneezing, rhinorrhea, ocular itching, urticaria, hypotension, and anaphylaxis.⁶

Treatment of latex allergy has been limited to the preventive measure of avoiding latex-containing products and symptomatic medication.⁷ For health care workers, the use of nonpowdered and nonallergenic gloves, as well as replacement of all material likely to contain NRL in examination or operating rooms, is essential.

However, sometimes complete avoidance cannot be possible for some reasons, such as lack of nonlatex alternatives for some uses, lack of acceptability of nonlatex alternatives, or lack of access to them. Latex-specific immunotherapy has been proposed and evaluated by some researchers since 1999. In the first double-blind, placebo-controlled study with subcutaneous immunotherapy (SCIT) using latex extract, Leynadier et al⁸ showed that rhinitis, conjunctivitis, and cutaneous symptoms scores, but not asthma scores, were significantly lower in patients treated with latex SCIT. In a later SCIT study by Sastre et al,⁷ clinical efficacy was shown mainly on cutaneous symptoms, although a significant improvement in rhinitis and asthma symptoms was observed during therapy. In only 1 double-blind, placebo-controlled study with sublingual immunotherapy (SLIT), Nettis et al⁹ found that 12 months of SLIT improved the symptom scores and reduced the medication scores in their study participants. We conducted this double-blind, placebo-controlled study to

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determine the efficacy and safety of latex SLIT in health care workers.

METHODS

Patients

Thirty patients (28 health care workers) diagnosed as having latex allergy were enrolled in the study. The diagnosis of latex allergy was based on clinical history, a positive latex prick test result (ALK-Abello, Madrid, Spain), a positive latex glove provocation test response, and a latex specific IgE (sIgE) level of at least class 2 (Pharmacia, Uppsala, Sweden). All patients were advised to avoid latex exposure, given information about the prevention measures, and asked to return 2 months later. They were reevaluated at the end of 2 months. Sixteen patients had been able to provide prevention measures; most of them had changed their working places. Of these, 6 patients were free of symptoms, whereas 10 were still mildly symptomatic despite prevention. The remaining 14 patients did not avoid latex exposure completely and were equally symptomatic. In total, 24 patients were informed about the latex SLIT study and asked to participate. However, only half (12) of them gave approval and were randomized as active and placebo groups. Written informed consent forms were obtained from these 12 participants, and the Ethical Committee of Istanbul Faculty of Medicine approved the study.

Symptom Scores

Symptom scoring was performed for skin, nasal, respiratory, and systemic symptoms at baseline, 6 months, and 12 months of treatment (Table 1).

Glove Provocation Test

After wetting 1 forefinger, a fingertip of the latex glove was placed on it and kept on for 15 minutes. If any symptom did not arise, a whole latex glove was worn on the wet hand and kept on for 30 minutes. Symptoms were scored as 1 for local itching and redness, 2 for itching and redness accompanied by wheals, and 3 if any systemic reactions appeared. This test was performed at the baseline and the 6th and 12th months of therapy, and the same batch of NRL gloves was used. During the glove provocation tests, the same physician observed and scored the patients.

Immunotherapy Protocol

Treatment consisted of 5 concentrations of the latex extract. The placebo preparation was identical to the active treatment in terms of composition, appearance, prevention, taste, and color. A 4-day sublingual induction phase was followed by a 12-month maintenance phase consisting of 3 administrations per week. All dose increments were performed in the hospital at the supervision of a trained allergist, and for safety reasons, the last doses were followed by a period of observation of 1 hour each day. Maintenance doses were self-administered at home in accordance with detailed instructions. The drops were always held under the tongue for 3 minutes before being swallowed.

Table 1. Scoring of the Symptoms

Symptoms	Score
Skin symptoms	
Pruritus, erythema, and mild eczema of the hands	1
Pruritus, erythema throughout the body	2
Systemic urticarial lesions and angioedema	3
Rhinitis symptoms	
Mild rhinorrhea, nasal itching, or sneezing (no impairment of daily activities, work, or sleep)	1
Moderate rhinorrhea, sneezing, nasal itching, or conjunctivitis (1 of the following: abnormal sleep or impairment of work or troublesome symptoms)	2
Severe nasal and conjunctival symptoms (2 of the following: abnormal sleep, impairment of work, and/or troublesome symptoms)	3
Asthma symptoms	
Nocturnal symptoms more than twice a month, symptoms more than once a week but less than once a day	1
Nocturnal symptoms more than once a week, exacerbations affecting activity and sleep, and daily symptoms	2
Frequent nocturnal asthma symptoms, frequent exacerbations, and daily symptoms	3
Systemic symptoms	
Rhinitis and accompanying systemic urticaria	1
Rhinitis with asthma and urticaria	2
Systemic urticaria with hypotension or syncope	3
Sum of the scores	0-12

Statistical Analyses

The Wilcoxon signed rank test and the Mann-Whitney test were used to compare the mean symptom and provocation scores of active and placebo groups, as well as baseline, 6-month, and 12-month scores within each group.

RESULTS

The demographic characteristics, clinical findings, and allergic test results of the 12 patients are presented in Table 2. Eight patients were randomized to the active treatment group and 4 to the placebo group.

Safety

During the dose induction phase, 2 patients (from the active group) displayed serious systemic reactions and dropped out of the trial. One patient after the second dose of the second day (5 µg) and 1 patient after the second dose of the third day (1,000 µg) experienced acute flushing, itching, rhinitis, conjunctivitis, wheezing, dyspnea, chest tightness, and hypotension, and both were treated with adrenaline injections. Another patient experienced dyspnea at the time of the second dose on the second day and required treatment with short-acting β_2 -agonist inhalation. This patient also quit the study. The remaining 9 patients continued with the study protocol without any adverse events.

Table 2. Demographic Features, Clinical Findings, and Allergic Test Results of the Patients^a

Variables	Active group (n = 8)	Placebo group (n = 4)
Sex, No. M/F	1/8	1/4
Age, mean (SD) [range], y	28.7 (2.7) [26-32]	28.6 (1.9) [27-31]
Duration of disease, mean (SD), y	3.1 (2.6)	3.6 (2.3)
Occupation, No.		
Physician	1	1
Nurse	7	3
Clinical features, No.		
Cutaneous reaction	4	3
Angioedema	2	0
Rhinitis	4	3
Asthma	2	2
Conjunctivitis	5	4
Systemic reactions	3	2
Latex fruit syndrome	3	1
Latex skin prick test results, mean (SD, mm)	12.6 (4.7)	13.4 (4.4)
Latex specific IgE test results, mean (SD, kU/L)	29.6 (36.02)	12.3 (4.5)

^a All the findings were statistically insignificant.

Latex sIgE Subgroups

Serum samples of 2 latex immunotherapy-related anaphylaxis patients and 2 patients from the remaining active group were analyzed for the latex sIgE subgroups (ImmunoCAP; Phadia, Uppsala, Sweden). Of the anaphylactic patients, one patient (patient 2) displayed mainly Hev b 5 and lesser Hev b 6.01 and Hev b 6.02, whereas the other (patient 1) had only Hev b 6.01 and Hev b 6.02 sIgE. The sIgE test results of both patients to sweet chestnut were negative. Patient 3, who had a history of anaphylaxis with fruits, such as plum, peach, and strawberry, and tolerated a full period of latex immunotherapy, displayed the highest latex sIgE levels.

Efficacy

The comparison of mean symptom and provocation scores of the active and placebo groups at baseline and the 6th and 12th months is provided in Table 3. The mean values of rhinitis, asthma, cutaneous, and systemic symptom scores, as well as

total symptom scores, in the active group obtained at baseline were significantly reduced at the 12th month of treatment ($P = .01$, $P = .04$, $P < .001$, $P = .04$, and $P = .04$, respectively). The symptom scores were not different between the initial and final evaluations in the placebo group.

The difference of the provocation scores at baseline and the 12th month of the treatment was significant in the active group ($P = .04$), whereas this difference was not significant in the placebo group. The symptom and provocation scores at the 12th month were significantly lower in the active group than the placebo group ($P = .01$ for rhinitis, $P = .04$ for asthma, $P = .03$ for cutaneous symptoms, $P = .04$ for systemic symptoms, $P = .035$ for total symptoms, and $P = .01$ for provocation scores).

DISCUSSION

Although the number of participants in this study was rather low, our results suggest that latex SLIT was more effective than placebo in treating the symptoms of latex allergic health care workers. After the termination of the study at the 12th month, 4 patients from the active group continued with the treatment voluntarily for 2 years more. These patients were able to continue with their work without experiencing any great difficulty.

The only comparable study to ours in terms of the use of a sublingual route and double-blind, placebo-controlled method is published by Nettis et al.⁹ In their study group of 35 patients with NRL allergy consisting of different professions (only 11 health care workers), they showed that SLIT reduced the symptoms significantly. No serious reactions except mouth itching and burning and lip swelling were observed in that study as contrary to the findings of our study. The most important difference between our study and that of Nettis et al is the occurrence of anaphylactic events. The probable reason for this difference may be that our study group consisted of only health care workers whose NRL exposure is higher than other professional settings. Previously, using subcutaneous latex extract, Leynadier et al performed a placebo-controlled study in health care workers and demonstrated a significant improvement of rhinitis, conjunctivitis, and cutaneous symptoms of these patients.⁸ However, they draw attention to the risk of systemic reactions, especially during the maintenance phase. Similarly, Sastre et al⁷

Table 3. Comparison of the Mean Symptom and Provocation Scores of the Active and Placebo Groups at Baseline, 6 Months, and 12 Months

	Baseline visit		6-Month Visit		12-Month Visit	
	Active group (n = 5)	Placebo group (n = 4)	Active group (n = 5)	Placebo group (n = 4)	Active group (n = 5)	Placebo group (n = 4)
Mean (SD) rhinitis symptom scores	2.25 (0.9)	1.67 (0.6)	1.5 (0.6)	1.67 (0.6)	0.75 (0.5)	1.75 (0.6)
Mean (SD) asthma symptom scores	1.75 (0.7)	2.5 (0.7)	1.33 (1.5)	2.5 (0.7)	0.9 (0.4)	2.0 (0.4)
Mean (SD) cutaneous symptom scores	2.5 (0.5)	2.5 (0.6)	1.9 (0.8)	2.25 (0.5)	0.9 (0.6)	2.25 (0.9)
Mean (SD) systemic symptom scores	2.2 (0.8)	2.0 (1.0)	1.8 (0.8)	2.0 (1.7)	0.9 (0.9)	2.2 (0.6)
Mean (SD) total symptoms scores	9.6 (1.67)	8.5 (1.91)	6.2 (2.5)	8.75 (1.82)	4.8 (1.82)	7.5 (1.6)
Mean (SD) provocation scores	2.4 (0.5)	2.25 (0.5)	1.4 (1.1)	2.5 (0.5)	1.2 (0.7)	2.5 (0.5)

reported that SCIT with latex has a higher rate of systemic reactions. Our findings also suggested that latex SLIT is similar to latex SCIT in terms of adverse effects.

All 3 systemic reactions occurred at the dose induction phase (2 at the second and 1 at the third day) of the study. Therefore, extension of the dose enhancement period might be useful in the prevention of serious reactions. Contrarily, Nucera et al¹⁰ recently reported that they performed rush protocols of 2 or 3 days safely for dose induction instead of the 4-day period suggested by the manufacturer. Although they proposed that rush induction was a safe method for latex SLIT, they indicated that 7 adverse events occurred among the patients following the 2-day protocol. In our opinion, this matter needs an elucidated statement.

Considering the features of 2 patients who quit the study because of experiencing anaphylaxis at the dose induction period, we observed that both patients had a history of anaphylactic events to chestnut. It is known that almost half of latex-sensitized patients display an associated fruit allergy, most commonly to avocado, banana, and kiwi, but also to other species, including nuts. Hev b 6.02, a 4.7-kDa N-terminal fragment of prohevein (Hev b 6.01) belonging to the group of class I chitinases, which is the major allergen of health care workers sensitized to latex, has been identified as cross-reacting allergens in avocado, chestnut, banana, and sweet pepper.^{2,11} Sastre et al¹² reported a significant negative correlation between the maximum tolerated dose and sIgE to Hev b 6.01 at baseline, so the levels of sIgE to Hev b 6.01 might predict the maximum tolerated dose of allergen during immunotherapy. However, moderate levels of Hev b 6.01 and Hev b 6.02 were detected in the serum samples of our 2 patients who had experienced latex immunotherapy-induced anaphylaxis, whereas Hev b 5 was at the class IV level in 1 of those patients (patient 2). Interestingly, the results of sIgE tests to sweet chestnut were negative in those 2 patients despite anaphylaxis history with chestnut. On the other hand, another patient (patient 3, latex immunotherapy tolerant) had the highest level of latex sIgE (>100 kU/L) and a high level of Hev b 5. Latex sIgE test results were negative in the fourth patient. According to the findings of our limited patients, it is not possible to determine the probable reason of anaphylactic response to latex immunotherapy. Similarly, to predict the risk of systemic reactions before the latex immunotherapy does not seem likely at present.

In conclusion, latex SLIT can be used as an effective treatment for latex allergic patients having difficulties in applying adequate avoidance measures. However, the risk of systemic reactions should be kept in mind, and sufficient

precaution measures must be made available. In the future, developing hypoallergenic preparations of the major latex allergens might reduce the risk of latex immunotherapy. Novel developments, such as recombinant hypoallergenic preparations and T-cell epitope-based peptides, are promising.¹³

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