

Sublingual desensitization in children with congenital malformations and latex allergy

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The frequency of latex allergy in children requiring multiple surgery ranges from 16.7% to 65%. The aim of this study was to investigate the safety and efficacy of latex desensitization in a group of 10 patients with a history of multiple surgical procedures and clinically manifested allergy to latex. We selected 10 children (female–male ratio = 5:5), aged 4–16 yr (mean $\pm$ s.d.: 9 ± 4), with a history of multiple surgical procedures, adverse reactions to latex and positive skin test to latex and/or specific immunoglobulin E (IgE). Latex allergy diagnosis was confirmed by specific provocation tests (cutaneous, sublingual, mucous, conjunctival tests). Rush (4-day) sublingual desensitization was performed with increasing doses of latex extract (ALK Abellò) under patients' tongue until the highest dose of 500 μ g of latex. A maintenance therapy (10 drops of undiluted solution three times a week) was recommended. During the 2-yr follow-up mean values of specific IgG4 and IgE, eosinophilic cationic protein and total IgE did not show significant variations. Patients did not manifest any adverse effect during the rush phase and only two patients manifested mild local symptoms during the maintenance therapy. All the challenges showed a reduction in terms of percentage of positivity and mean scores. All the patients showed a reduction of the mean individual score ($p < 0.001$). Furthermore patients who needed dental examination or surgery underwent such procedures without the occurrence of symptoms. Our preliminary results show sublingual desensitization to latex can be an important therapeutic tool in the management of young allergic patients requiring multiple operations.

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Allergic reactions to latex products have been reported since 1970s and in the last decades they have become an important health problem (1).

Even though the general population may be involved as well, some groups at high risk to develop latex allergy have been identified, such as children with urogenital or neural malformations, patients undergoing multiple operations, healthcare and rubber industry workers, because of the high frequency of latex exposure (2–13). Particularly, the frequency of latex allergy in children requiring multiple surgery ranges from 16.7% to 65% (14, 15). Other risk factors for latex allergy are atopy, female sex, coexistence of bronchial asthma and chronic hand dermatitis.

Several latex allergens have been characterized; among them, Hev b1 (Rubber elongation factor), a 14-kDa protein involved in rubber biosynthesis, and Hev b3, a 22-kDa protein with unknown function, have been identified as the major allergens responsible of latex sensitization in spina bifida (SB) patients by direct contact with mucous membranes (16). Many authors report that, among patients with SB, 73–81% showed specific IgE against Hev v1 and 73–83% against Hev v3 (17, 18). Hev b 7, the 46-kDa patatin-like Hevea latex protein, is the third SB-associated latex allergen (19).

Clinical manifestations range from local reactions (edema, itching, erythema and papulae),

rhino-conjunctivitis, asthma, pharyngeal edema, to less frequent severe systemic reactions such as anaphylactic shock.

The aim of this study was to investigate the safety and efficacy of latex desensitization in a group of 10 patients with a history of multiple surgical procedures and clinically manifested allergy to latex.

Materials and methods

Patients

We selected 10 children (female–male ratio = 5:5), aged 4–16 yr (mean $\pm$ s.d.: 9 ± 4), with a history of multiple surgical procedures, adverse reactions to latex and positive skin test to latex and/or specific IgE at least of class 1.

Demographic data are shown in Table 1.

Three patients had meningomyelocele, two hydrocephalus, one cryptorchidism, one clubfoot, one diaphragmatic hernia, one patient had Proteus Syndrome (rare condition involving atypical growth of the bones, skin and head and a variety of other symptoms), one Ehlers-Danlos syndrome (soft and hyperextensible skin, subcutaneous nodules, clubbed feet and a mild degree of pigeon chest).

Patients (or their parents) were questioned about bronchial asthma, allergic diseases, chronic eczema, number of surgical procedures and adverse reactions after latex exposure and ingestion of cross reacting foods.

Patients were investigated by an accurate allergological evaluation.

Skin tests

Skin prick tests were performed with a standard latex extract (500 μ g/ml; ALK Abelló, Madrid, Spain) and a 1-cm² piece of surgical glove latex material (prick-by-prick method: a puncture device is pushed into the skin through a piece of surgical latex glove manufactured by Triflex Allegiance Health Care Co., McGaw Park, IL, USA). A panel of aeroallergens (olive, cypress, grass and ragweed pollen, house dust mite, parietaria j, cat and dog danders, Alternaria, Penicillium, Aspergillus) and food allergens according to anamnesis (chestnut, banana, kiwi and tomato) were also studied.

Prick tests were performed with a Morrow-Brown needle (ALK Abelló) on the volar surface of the forearm. Glycerin solution and histamine (10 mg/ml) were used as negative and positive controls. A positive response was defined as one producing a wheal greater than 3 mm in diameter at 20 min after application, without reaction to negative control.

Patch tests were performed to exclude a type IV delayed cell-mediated hypersensitivity to latex: their results were checked 72 h after the patch had been placed, assessing positivity according to the North American Contact Dermatitis Group criteria: negative reaction (0); macular erythema (?); erythema, infiltration, and possibly papules (1+); erythematous papules and/or vesicles (2+); and spreading blisters and/or crust with ulceration (3+) (20).

Table 1. Demographic data

Patient	Age (yr)	Sex	Congenital malformation	Surgical procedures	Atopy†	Bronchial asthma	Latex–fruit syndrome	Exposure	Symptoms
1	7	M	HC	4	Yes	No	Yes (tomato)	Balloons*	UAS, conjunctival hyperemia
2	16	F	MMC	6	Yes	Yes	Yes (chestnut, banana, kiwi)	Surgery	UAS, dyspnea
3	9	F	HC	2	No	No	No	Dental examination	RC, cough
4	10	M	Cryptorchidism	2	Yes	Yes	Yes (peach)	Balloons*	UAS
5	7	F	Proteus syndrome	10	No	No	No	Surgery	Generalized itching erythema
6	7	M	Ehlers-Danlos syndrome	2	No	No	Yes (chestnut, banana, kiwi)	Balloons*	RC, asthma
7	7	F	MMC	4	No	No	No	Balloons*	UAS
8	7	F	Congenital diaphragmatic hernia	5	No	No	No	Dental examination	UAS, asthma
9	4	M	MMC	7	No	No	No	Balloons*	UAS
10	16	M	Clubfoot	5	Yes	Yes	No	Balloons*	RC, UAS

HC, hydrocephalus; MMC, meningomyelocele; UAS, urticaria-angioedema syndrome; RC, rhinoconjunctivitis.

*Handling or inflating latex balloons.

†Atopy: personal history of atopic diseases (food and/or respiratory allergy).

Blood samples

Specific anti-Natural Rubber Latex (NRL) immunoglobulins IgE were measured by means of fluorescent enzyme immunoassay (UniCAP System; Pharmacia, Uppsala, Sweden).

Specific IgE to food and aeroallergens were also dosed in the serum during the first evaluation.

Samples with specific IgE concentration of ≥ 0.35 kU/l were regarded as positive.

Also serum total IgE, eosinophilic cationic protein (ECP) (UniCAP System; Pharmacia) and specific IgG4 (CAP-FEIA, Pharmacia) were measured. ECP < 20 $\mu\text{g/l}$ and total IgE < 200 kU/l were considered normal. Blood samples were collected before and after 5 days, 3, 6, 12, 24 months of treatment.

Challenge tests

Latex allergy diagnosis was confirmed by specific provocation tests. They were performed in day-hospital regimen. Antihistamines were withheld for 10 days before each challenge. Expiratory peak flow, pulse rate and blood pressure were monitored during each challenge. Patients remained under medical control for 2 h after each challenge. Tests were considered positive if one or more immediate-type symptoms occurred (erythema, local or generalized cutaneous itching, mucous itching, urticaria, angioedema, conjunctivitis, rhinitis, cough, dyspnea, asthma, etc.).

Challenges were performed before and after 1 yr of treatment.

- Cutaneous test: it was carried out asking the patients to wear a latex glove (Allegiance Triflex) until symptoms appeared. The maximum exposure time was 1 h. Before the challenge patients had to wash and perfectly dry hands. As a control they had to wear a synthetic (vinyl) glove on the opposite hand. Then the gloves were taken off and hands were washed again. A physician assessed possible clinical reactions. The test was considered positive if immediate-type symptoms occurred without reactions to the control glove. Patients with active hand dermatitis at the time of the challenge were excluded. Patches were applied on hand lesions to avoid abnormal latex entering through the skin.
- Mucous (oral) test: patients were asked to hold a latex-gloved test tube in their mouth for 1 h or until the occurrence of symptoms. A preliminary control test with a vinyl glove was

performed. Patients with oral lesions at the time of the challenge and with a positive control test were excluded.

- Sublingual test: patients had to maintain one drop of latex solution under the tongue for 3 min and then spit, increasing the concentration (from the smallest of 500×10^{-8} $\mu\text{g/ml}$ to the largest of 500 $\mu\text{g/ml}$) every 20 min (Table 2). The threshold dose was defined as the smallest allergen concentration able to induce the appearance of symptoms. A preliminary control test with placebo (physiologic saline) was performed. Patients with oral lesions at the time of the challenge and with a positive control test were excluded.
- Conjunctival test: it was performed instilling one drop of latex solution, into the inferior fornix of alternate eyes every 20 min, starting with the smallest concentration of 500×10^{-8} $\mu\text{g/ml}$ to the largest of 50 $\mu\text{g/ml}$ (Table 2). The latter was considered as the largest threshold dose, because the larger (500 $\mu\text{g/ml}$) was able to cause the appearance of symptoms also in the controls, perhaps for a non-specific irritant action (21). A negative control test was performed with physiologic saline.

Symptom scores

Ocular (tearing, itching, edema, conjunctival edema), respiratory (rhinorrhea, nasal itching, nasal blockage, sneezing, wheezing, cough, dyspnea, laryngospasm) and muco-cutaneous symptoms (generalized pruritus, erythematous-papular rash, urticaria-angioedema (UAS), oral and pharyngeal itching) were recorded during challenges and scored on a 4-point scale: 0 (absent), 1 (mild), 2 (moderate), 3 (severe).

Drug scores

If patients experienced a FEV1 decrease 20% or more from baseline level, they were treated with inhaled bronchodilator and corticoid. If symp-

Table 2. Protocol for sublingual and conjunctival tests

Sublingual ($\mu\text{g/ml}$)	Conjunctival ($\mu\text{g/ml}$)
500×10^{-8}	500×10^{-8}
500×10^{-7}	500×10^{-7}
500×10^{-6}	500×10^{-6}
500×10^{-5}	500×10^{-5}
500×10^{-4}	500×10^{-4}
500×10^{-3}	500×10^{-3}
5	5
50	50
500	—

toms occurred patients were administered antihistamines and corticoids. On the basis of drug consumption during challenges and within 2 h after they have finished, for each patient, a score was recorded on a 5-point scale: 0 (no drugs), 1 (nasal/ocular steroid), 2 (inhaled bronchodilator and corticoid, oral antihistamine), 3 (intramuscular antihistamines, intramuscular and/or intravenous corticoids), 4 (subcutaneous epinephrine).

Mean total score

This is the mean value of the total score (symptom + drug score), recorded for each of the four challenges.

Mean individual score

This is the mean value of the total score (symptom + drug score), recorded for each patient.

Clinical protocol

Rush (4-day) sublingual desensitization was performed with increasing doses of latex extract (ALK Abellò) under patients' tongue for 3 min every 20 min, starting with a drop of latex solution (500 µg/ml) diluted 1:10¹⁸. After 3 min latex solution was swallowed. On the 4th day the protocol was completed with 1 ml of undiluted solution (500 µg of latex) in one administration (Table 3).

The protocol was performed in accordance with good clinical practice after being approved by our hospital's ethic Review Board. Parents gave their fully informed written consent.

Patients were hospitalized during such procedures and resuscitative equipment and personnel were available. Antihistamines were withheld for 10 days before the rush phase. Expiratory peak flow, pulse rate and blood pressure were monitored.

Maintenance phase

A maintenance therapy (10 drops of undiluted solution three times a week) was recommended.

Table 3. Protocol of desensitization

	First	Second	Third	Fourth
Dilution	From 10 ⁻¹⁸ to 10 ⁻¹⁰	From 10 ⁻⁹ to 10 ⁻¹	Pure solution (500 µg/ml)	
Dose	1 drop of each solution		1, 2, 3, 4, 5, 10 drops	1 ml
Total daily amount (µg of NRL)	28 × 10 ⁻¹⁰	2.8	500	500

Furthermore patients wore latex gloves for 30 min daily.

Statistical analysis

Student's *t*-test was used to evaluate score differences before and after the treatment. Two-tailed *p* < 0.05 were considered statistically significant.

Results

Primary evaluation

All the patients met the inclusion criteria: they had positive prick tests to latex extract (mean diameter: 9 mm) and latex glove (mean diameter: 10 mm), and serum specific IgE > 0.35 kU/l (mean: 39.5 kU/l). One patient had also positive patch test to latex. For details see Table 4.

The mean basal value of specific IgG4 was 2.8 µg/l.

Mean values of total IgE and ECP were 564 kU/l and 35 µg/l, respectively.

Six patients had total IgE > 200 kU/l and five patients had ECP > 20 µg/l.

Four patients suffered from respiratory allergy: patient 1 was allergic to cat dander, house dust mite, moulds (conjunctivitis), patient 2 to parietaria, house dust mite, olive pollen (bronchial asthma), patient 4 to grass pollen (conjunctivitis), and patient 8 to house dust mite (bronchial asthma).

Table 4. First evaluation

Patient	Latex specific IgE (kU/l)	Latex skin tests	Total IgE (kU/l)	ECP (µg/l)
1	1.25	Positive	156	16.7
2	>100	Positive	1215	16.7
3	74.2	Positive	573	47.3
4	11.9	Positive	632	10.9
5	21.9	Positive*	13.8	13.3
6	38.8	Positive	87.5	15
7	36.1	Positive	325	37.7
8	>100	Positive	2095	96.2
9	1.61	Positive	8.6	59.5
10	7.69	Positive	535	42.9

IgE, immunoglobulin E; ECP, eosinophilic cationic protein.

*Positive prick and patch tests to latex.

Four patients suffered from latex fruit syndrome. Patient 1 reported dyspeptic symptoms after ingestion of tomato (positive skin test and specific IgE <0.35 kU/l). Patient 2 manifested UAS after ingestion of banana and kiwi (both positive skin tests; specific IgE 3.57 and 0.43 kU/l, respectively) and erythema, asthma and fever after eating chestnut (positive skin test and specific IgE 2.20 kU/l). Patient 4 had a history of UAS after ingestion of peach (positive skin test and specific IgE <0.35 kU/l). Patient 6 reported rhinoconjunctivitis (RC) after ingestion of banana and kiwi (both positive skin tests; specific IgE 0.45 and <0.35 kU/l, respectively) and asthma after eating chestnut (positive skin test and specific IgE <0.35 kU/l).

Cutaneous challenge test was performed in all patients, of which seven resulted positive: after 10–45 (mean 38) min they presented cutaneous itching, urticaria, rhino-conjunctivitis (mean total score: 1.7).

Mucous (oral) test was performed in all patients, of which three resulted positive: after 20–48 (mean: 37) min they presented cutaneous and oral itching, cough, rhinitis (mean total score: 0.5).

Sublingual test was performed in all patients, of which three resulted positive: they presented oral itching, conjunctival erythema, cough, dyspnea and rhinitis (mean total score: 0.6). Two patients reacted to the pure solution (500 µg/ml), the third to the concentration of 500×10^{-8} µg/ml.

Conjunctival test was performed in eight patients because one patient had active conjunctivitis and one patient reacted to the control test. All the patients resulted positive: they presented conjunctival erythema, rhinitis, facial itching (mean total score: 2); four patients reacted to 500×10^{-1} µg/ml, two patients to 500×10^{-2} µg/ml, two patients to 500×10^{-8} µg/ml.

All patients underwent desensitization.

Skin and serum tests

After the desensitization, prick test to latex extract (mean diameter: 8 mm) and latex glove (mean diameter: 9 mm) did not show significant decrease. The mean value of latex-specific IgE had an increase after 4 days (41 kU/l, not statistically significant) and a further increase after 3 months (57 kU/l, $p = 0.03$), remaining higher than initial levels after 1 and 2 yr (56 and 64 kU/l, respectively, not significant). Mean values of specific IgG4 (4.9 µg/l), ECP (29 µg/l) and total IgE (772 kU/l) did not show significant variations after 2 yr.

Challenge tests

After the desensitization the cutaneous challenge test became negative in four of seven patients who were positive at the first evaluation and showed a significant reduction of mean total score and an increase of the onset time (mean: 56 min) (see Table 5 and Fig. 1).

Sublingual and mucous tests turned negative in all patients and in all patients but one, respectively.

Conjunctival test became negative in 50% of patients and showed an important decrease of mean total score. Furthermore all the patients with positive test except one patient reacted to a larger threshold dose. All the patients showed a reduction of the mean individual score ($p < 0.001$).

Side effects

Patients did not manifest any adverse effect during the rush phase and finally tolerated 1 ml of pure latex solution. During the maintenance therapy only two patients manifested symptoms (one patient had oral itching and another patient had light local angioedema) some minutes after the sublingual administration of latex, spontaneously remitted. No patients discontinued the treatment for the occurrence of adverse events.

Efficacy

During the maintenance phase patients wore latex gloves for 30 min daily. After the treatment three patients underwent dental examination and

Table 5. Provocation tests: reduction of mean scores after the desensitization

Challenge	Before the treatment	After the treatment	p-value
Cutaneous	1.7	0.5	0.03
Mucous	0.5	0.2	NS
Sublingual	0.6	0	NS
Conjunctival	2	0.6	0.03

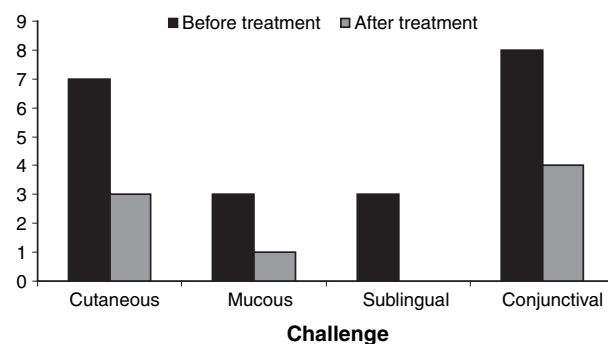


Fig. 1. Rate of positive reactions during challenge tests.

two patients surgery in a non-latex-safe area: in all these cases allergic adverse reaction did not occur. Furthermore one patient received the hepatitis B vaccination through the commercially available latex-containing vial.

Discussion

The clinical efficacy and safety of sublingual desensitization has been largely demonstrated in patients, both children and adults, with respiratory allergy (22–24).

Some reports in the Literature deal with specific immunotherapy by subcutaneous (25) and percutaneous route (26) in patients with latex allergy: protocols were used only in adult patients and the subcutaneous had also a high rate of adverse events.

In a previous study we performed a sublingual desensitizing treatment in 12 latex allergic patients: two of them were children (21). During the 3-month follow-up period all the patients did not show adverse events and developed clinical tolerance to latex. To confirm the safety and effectiveness of sublingual immunotherapy to latex also in young patients, we used the same protocol in 10 children with congenital malformation and latex allergy. They were followed up for 2 yr.

The protocol resulted effective: in fact all the patients presented a decrease of reactivity to latex showed by a statistically significant reduction of the mean individual score ($p < 0.001$) recorded during challenges. Cutaneous, mucous and sublingual challenges became negative in a high percentage of patients and showed a decrease of mean total scores. Conjunctival test became negative in 50%, but also positive tests showed a significant reduction of scores ($p = 0.03$) and an increase in threshold dilutions.

In addition, there were no relevant side effects, neither local nor systemic and the compliance of the patients and their parents was excellent: after 2 yr no patient interrupted the treatment.

Furthermore patients who needed dental examination or surgery underwent such procedures without the occurrence of symptoms.

Despite the excellent clinical outcome, the mechanism of action is still unknown: in fact our patients did not show significant variation of serum parameters and an immunological modulation underlying treatment efficacy was not found.

Some preventive measures have been recommended (unpowdered latex or synthetic gloves) to protect health care workers and patients from latex sensitization or allergic reactions. Particularly, primary prophylaxis has been shown to be

effective in reducing the prevalence of latex sensitization in SB patients, but it is difficult to apply, especially in hospital not experienced in the treatment of SB patients (27). Furthermore, anaphylaxis to latex may be a risk of an unintentional latex exposure out of the hospital setting (60% of our patients reacted while inflating latex balloons), where a complete latex avoidance is hardly feasible.

Even though further studies on a larger group of patients, with double-blinded, placebo-controlled protocols are needed, our preliminary results show sublingual desensitization to latex can be an important therapeutic tool in the management of young allergic patients requiring multiple operations.

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