

Sensitivity and specificity of different skin prick tests with latex extracts in pediatric patients with suspected natural rubber latex allergy – A cohort study

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Skin prick tests (SPT) with latex extracts are commonly used in the diagnostic approach of natural rubber latex (NRL) allergy. Non-ammoniated latex extracts are commonly utilized for this purpose. There is only one commercially available ammoniated latex extract for both diagnostic and therapeutic purposes. To our knowledge, no direct clinical comparisons have been made so far comparing sensitivity and specificity of different latex extracts in patients with clinically confirmed latex allergy. The objective of this study was to evaluate sensitivity and specificity of non-ammoniated or ammoniated SPT of latex extracts in children with a clinical history suggestive of NRL allergy. Forty-two subjects (age 4–15 yr), referred to our Allergy Clinic Center, with suspected clinical signs of NRL allergy were evaluated. Patients were selected according to the following inclusion criteria: pediatric patients of age above 4 yr with a suspected clinical history of urticaria, rhinoconjunctivitis and/or asthma due to sensitization to NRL. A definitive NRL allergy diagnosis was made on the identification of latex-specific IgE (> 0.7 kU/l), positive glove use test and a highly indicative clinical history. NRL allergy was confirmed in 26 (62%) subjects. SPT for latex were performed with three different SPT solutions containing non-ammoniated NRL extracts (product A: Lofarma SpA, Milan, Italy and product B: Stallergenes, Milan, Italy) or an ammoniated extract (product C: ALK-Abellò, Madrid, Spain). A positive result was considered as the appearance of a wheal with a diameter > 3 mm. In patients with confirmed NRL allergy, wheal mean (s.d.) diameters were 7.3 (2.1) with product C, and 5.7 (2.3) and 4.4 (1.8) with products B and A respectively ($p = 0.004$ C vs. B and A). Mean wheal diameters were significantly higher for product C in comparison with product B and A ($p < 0.04$). Sensitivity according to the different products tested was 65% (product A); 81% (product B) and 96% (product C) ($p = 0.0084$; C vs. A). No difference between the three products was observed regarding diagnostic specificity (94%, 88% and 94%, product A, B and C, respectively). Our study shows that diagnostic sensitivity of different latex extract for SPT could differ. In this particular clinical setting (i.e., children with NRL allergy) ammoniated latex extract shows a higher sensitivity in comparison with non-ammoniated products. This aspect should be considered in the diagnostic approach in subjects with suspected NRL allergy. In children with clinical confirmed latex allergy, sensitivity and

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specificity of different commercially available skin prick test could vary. Ammoniated latex extract has shown a higher sensibility in comparison with non-ammoniated products.

Immunoglobulin E (IgE)-mediated sensitization to natural rubber latex (NRL) is a potentially life-threatening, clinical issue (1, 2). NRL products can trigger urticaria, angioedema, bronchial asthma and anaphylaxis after exposure in sensitized subjects (3). The prevalence of allergy to NRL is common among healthcare professionals (4) but also in children undergoing multiple operations (5, 6). Clinical manifestations could range from mild urticaria to severe anaphylactic reactions (7). The diagnosis of latex allergy is based on the identification of individuals with latex-specific IgE and symptoms consistent with IgE-mediated reactions to latex containing products. Skin prick tests (SPT) with latex extracts are a commonly utilized method in the diagnostic approach of NRL (2). Reproducibility of the test depends on several factors, some of which are difficult to standardize (8). *In vivo* diagnostic for latex allergy has been reviewed by Turjanmaa (9). In general non-ammoniated latex extracts are utilized for diagnostic purpose (10). However, ammonia is commonly added to prevent coagulation of raw material therefore enhancing rubber structural qualities. This procedure could have an effect on the allergen composition of NRL. So far there is only one commercially available (at least in some countries) ammoniated latex extract for both diagnostic and therapeutic purposes (6, 11, 12). The use of ammoniated or non-ammoniated latex extracts for NRL allergy is still a matter of debate. Even if some authors have faced this problem evaluating the immunological properties of ammoniated and non-ammoniated latex extracts in children with NRL allergy (13), to our knowledge no direct clinical comparisons have been made so far comparing sensitivity of different latex extracts in patients with clinically confirmed latex allergy. Therefore, we performed a study in order to evaluate and compare sensitivity and specificity of three different latex skin prick tests in children with suspected NRL allergy.

Patients and methods

Patients selections and demographics

Forty-two subjects (24 male and 18 female, mean age 10 ± 4 yr, range 4–15 yr) referred to our Pediatric Allergy Clinic Center with suspected

clinical signs of allergy to NRL were evaluated, after parental written informed consent, in a cohort prospective study. Diagnostic evaluation included: detailed clinical history, assessment of serum IgE (Unicap RAST, Pharmacia, Peapack, USA) and unmasked glove use provocation test. A positive history for multiple surgery intervention was found in 16 of 42 patients (38%). Two of these children suffered from spina bifida. Four subjects were surgically treated due to congenital urinary tract malformations. An indicative history of allergy to fruit and/or vegetables was reported in 13 subjects (31%).

Diagnosis of NRL allergy and SPT procedures

Gold standard for diagnosis of NRL allergy was based on the identification of latex-specific IgE (>0.7 kU/l), positive glove use test and positive clinical history. The glove use test was carried out asking the patients to wear a latex glove (Touchy Glove, Montechimica, Vicenza, Italy). Allergen content of the glove, according to the manufacturer, was considered to be moderate (i.e., >10 and <100 AU/ml). Glove use test was considered positive if immediate-type symptoms occurred (rhinitis, conjunctivitis, urticaria and or asthma). The skin prick test for latex was performed with three different commercially available skin prick test solutions containing natural NRL extracts (product A: Lofarma SpA, Milan, Italy and product B: Stallergenes, Milan, Italy) or an ammoniated NRL extract (product C: ALK-Abellò, Madrid, Spain). Each patient was skin-prick tested in triplicate on the volar side of the forearm with the three extract. Positive (histamine hydrochloride 10 mg/ml) and negative (saline solution) controls were also included in each test. SPT were performed according to international guidelines and manufacturer's instructions. A positive result was considered as the appearance of a wheal with a diameter >3 mm over that produced by the saline control at 15 min. Erythema diameters were also assessed.

Sensitivity and specificity evaluation of SPT

Diagnostic sensitivity [true positive fraction: true positive/(true positive + false negative)] and diagnostic specificity [true negative fraction: true negative/(true negative + false positive)] were

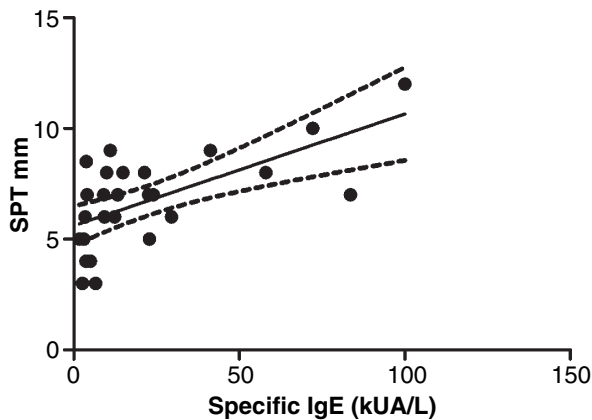


Fig. 1. Linear regression between serum IgE levels and SPT (product C) wheal diameters. ($R = 0.41$; $p = 0.0005$).

calculated for each SPT using the 'gold standard' (positive clinical history plus positive glove use test plus IgE) as reference.

Statistical methods

Mann–Whitney test, Fisher exact test and linear regression test were used to compare the variables analyzed between the three groups. Study protocol was approved by the local IRB (Institutional Review Board of Anna Meyer Children Hospital).

Results

Confirmation of NRL allergy (the 'gold standard': suggestive clinical history, positive glove rubbing provocation test and serum IgE > 0.7 kU/l) was made in 26 of 42 patients (62%). In 16 patients the clinical suspicion of NRL was not confirmed by diagnostic tests. Table 1 shows wheal mean diameters, according to the different products tested in the 26 patients with confirmed NRL allergy. The mean wheal and erythema diameters were significantly higher for product C in comparison with products B and A ($p < 0.04$; Mann–Whitney test). Table 2 reports sensitivity and specificity of the different SPT in comparison

Table 1. Wheal mean diameters after SPT with different products in 26 children with confirmed NRL allergy

Product	Wheal diameter, mm, mean (s.d.)
A (Lofarma)	4.4 (1.8)
B (Stallergenes)	5.7 (2.3)
C (ALK-Abellò)	7.3 (2.1)*¶
H (histamine)	5.1 (1.5)

* $p = 0.04$ C vs. B.

¶ $p = 0.0001$ C vs. A; Mann–Whitney test.

Table 2. Sensitivity and specificity of the three SPT products in 46 subjects with suspected NRL allergy

Product	Sensitivity % (95% CI)	Specificity % (95% CI)
A (Lofarma)	65% (47%–83%)	94% (88%–100%)
B (Stallergenes)	80% (65%–95%)	88% (80%–96%)
C (ALK-Abellò)	96% (88%–100%)‡	94% (88%–100%)

Gold standard reference: positive clinical history, positive glove use provocation test and serum IgE > 0.7 kU/l.

‡ $p = 0.0084$ C vs. A; Fisher exact test.

with the 'gold standard' evaluated in the 42 subjects. Sensitivity was significantly higher with product C in comparison with product A ($p = 0.0084$; Fisher exact test). A borderline significant difference in sensitivity was found in comparison with product B ($p = 0.08$). We found a significant correlation ($R = 0.41$; $p = 0.002$) (Figure) between wheal diameter and specific IgE for product C but not for product B and A ($p = 0.17$ and $p = 0.3$, respectively). Specificity was 94%, 88% and 94% for product A, B and C, respectively (NS).

Discussion

Natural rubber latex allergy is an increasing and important health problem (2). An early and accurate diagnosis is important for a correct therapeutic approach. Diagnosis of latex allergy is made by the history and immunological testing (10). The SPT is considered the most reliable method of NRL allergy diagnosis (9). Latex is commonly treated with 0.7% (high ammoniated latex) or 0.2% of ammonia (low ammoniated latex). The use of crude latex extracts both from non-ammoniated or ammoniated latex has been proposed for the preparation of reference product, but there is no general consensus on which is the most reliable extract (13). Hamilton and Adkinson (14) found an equivalent diagnostic sensitivity and specificity for skin reagents of ammoniated or non-ammoniated latex extracts. However, this study was performed in an adult population with both skin and respiratory symptoms. Furthermore, SPT were performed with progressive titration scheme. In addition, 64% of patients with NRL allergy were positive for other allergens. Our study was conducted exclusively in a pediatric population. SPT were performed according to the manufacturers' specifications at the recommended concentration. The results of our study show that diagnostic sensitivity of different latex extracts for SPT could differ. In this particular clinical setting (i.e., children with NRL allergy), ammoniated latex extract shows a

higher sensibility in comparison with non-ammoniated products. No differences were found regarding specificity. These aspects should be considered in the diagnostic approach in subjects with suspected NRL allergy.

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