

Comparison of skin test reactivity to histamine on back and forearm in young children

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Summary

Rationale: Skin responses to standardized positive and negative controls are important in the interpretation of a skin prick tests (SPT). However, this information in young children is lacking. We aimed to determine skin reactivity and compare the skin responses to these controls on the upper back and forearm in young children.

Methods: SPTs for histamine hydrochloride 1 mg/ml (positive control) and 50% glycerol-saline (negative control) were performed on the upper back and forearm of children aged 6-25 months who came to the well-child clinic at Songklanagarind Hospital. SPTs to common allergens (cow's milk, soybean, egg white and house dust mite) were also evaluated.

Results: A total of 133 children with a mean age of 12.4 months were enrolled in the study. Seventy-five children (56.4%) were male. The results from the upper back and the forearm of the histamine-induced mean wheal diameter \pm standard deviation (SD) were 4.74 ± 1.37 mm and 3.86 ± 1.82 mm ($p < 0.0001$). The mean flare responses to histamine on the upper back and the forearm were 18.47 ± 4.28 mm and 16.37 ± 5.50 mm ($p < 0.0001$). The SPT results from the negative control on the upper back and forearm also had significant differences among the sizes of the wheal (0.57 ± 1.17 vs. 0.34 ± 0.89 mm, $p = 0.007$) and flare (4.57 ± 3.04 mm vs. 3.34 ± 1.91 mm, $p < 0.0001$).

Conclusions: Our study showed regional differences in wheal and flare responses to standardized positive and negative controls in young children. The upper back is more reactive than the forearm and is the preferred SPT site in young-aged children. (*Asian Pac J Allergy Immunol* 2012;30:301-5)

Key words: skin prick test, skin reactivity, infants, young children

Introduction

A skin prick test (SPT) is recommended as the primary test for the diagnosis of IgE-mediated allergic diseases.^{1,2} A skin prick test can provide useful confirmatory evidence for a diagnosis of clinical sensitivity induced by aeroallergens, foods and drugs.¹ The diagnostic validity of skin prick tests has been confirmed not only in patients exposed to allergens under natural conditions but also in patients undergoing controlled organ challenge tests.³⁻⁸ SPT is also known for simplicity, rapidity of performance, low cost, and high sensitivity. Moreover, SPT is safe with only occasional systemic reactions being observed with non-commercial extracts. The overall rate of generalized reactions with fresh food was 0.52% in children⁹ and 0.26% in another study in children and adults.¹⁰ No fatalities have been reported in children.¹¹ These advantages explain the key position of SPT in allergy diagnosis.

Histamine hydrochloride and 50% glycerol-saline are widely used as standardized positive and negative controls in the interpretation of a SPT. The criteria for a positive reaction should always compare the size of the wheal induced by allergen extracts with that elicited by a histamine solution. A variation in histamine skin reactivity may influence the prevalence of a positive specific allergen skin test.¹² A variation in histamine reactivity, the site of skin testing and the age of the subjects may affect the skin testing results. Although a skin prick test can be performed in young children, infants and younger children (<2 years) tend to have smaller skin reactions than adults.^{13,14} Infants react predominantly with a large erythematous flare and a

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small wheal. In adults, it has been reported that the back is more reactive than the forearm.¹⁵ However, there is no data reporting the effect of the area of the body tested on the results of skin prick tests in infants and young children. Moreover, there is no report about the skin test reactivity among young Asian children. Therefore, we aimed to determine and compare the skin reactivity to standardized positive and negative controls on the upper back and the forearm in young children.

Methods

Study population

Healthy young children, aged 6 to 25 months, were enrolled during well-child visits at Songklanagarind Hospital. Exclusion criteria were subjects who had a history of dermatographism and those taking antihistamines within 2 weeks prior to the testing. All skin prick tests were conducted between June 2011 and September 2011. The protocol was approved by the Institutional Review Board of the Faculty of Medicine, Prince of Songkla University.

Skin prick testing

Skin prick tests were performed at the Pediatric Outpatient Department in Songklanagarind Hospital by the rotation method with the Duotip-Test device (Lincoln Diagnostics). Histamine hydrochloride (1 mg/ml) and 50% glycerol-saline were used as positive and negative controls. Skin responses to 3 common food allergens (cow's milk, soybean and egg white) and house dust mite (*Dermatophagoides pteronyssinus*) were also evaluated. All tests were performed on the upper back and the volar surface of the forearm by the same well-trained investigator. The results were recorded 15 minutes thereafter by an experienced investigator. For comparison of the size of reactions on the back and forearm, wheal and flare outlines were marked with a felt-tip pen and transferred with transparent tape to a permanent record. The longest and the orthogonal diameters were measured using INSIZE Digital Vernier Caliper[®] and the mean diameters were employed for analysis. All test solutions were obtained from ALK-Abelló, Port Washington, New York, USA.

Statistical analysis

Statistical analysis was performed by using R software (version 2.14.0; The Comprehensive R Archive Network). Mean diameters of the wheal and flare reactions at the histamine, 50% glycerol-saline and allergen extract sites were calculated separately for the back and forearm and compared within the

same subject and also compared between the different age groups.

Results were analyzed by using Student's t-test and repeated measures ANOVA, with the within-subject factors body site (forearm and back). A result was statistically significant when the *p* value was less than 0.05.

Results

A total of 133 children (75 males and 58 females) with a mean age of 12.4 months were enrolled in this study. Participants were categorized by age groups and the number of allergen sensitizations (Table 1).

The mean wheal and flare sizes of the skin reactions to histamine and 50% glycerol-saline on the upper back and the forearm are presented in Table 2. The mean histamine wheal size on the upper back was significantly larger than those on the forearm (4.74 mm vs. 3.86 mm, *p* < 0.0001). For the flare response to histamine, there was a highly significant difference among the sizes on the upper back and the forearm (18.47 mm vs. 16.37 mm, *p* = 0.0001).

There were also regional differences in the skin reactivity to 50% glycerol-saline, with significantly larger wheals (*p* = 0.007) and flares (*p* < 0.0001) on the upper back compared with the forearm (Table 2). Two subjects (1.5%) had no wheal with histamine on the upper back and 16 subjects (12%) had no wheal response to the positive control on the forearm.

Table 1. Characteristics of the study population

Variable	N (%)
Total (N)	133 (100)
Gender	
Male	75 (56.4)
Female	58 (43.6)
Age (months), mean ± SD (range)	12.4 ± 5.1 (6-25)
Age (categories)	
6 - <12	75 (56.4)
12 - 25	58 (43.6)
Number of Allergen Sensitizations	
0	110 (82.7)
1	18 [*] (13.5)
2	2 [†] (1.5)
3	2 [‡] (1.5)
4	1 [§] (0.8)

^{*}Sensitization to cow's milk (6), egg white (2), soybean (4), house dust mite (6)

[†]Sensitization to cow's milk + house dust mite (1), egg white + house dust mite (1)

[‡]Sensitization to cow's milk + egg white + house dust mite (1), cow's milk + soybean + house dust mite (1)

[§]Sensitization to cow's milk + soybean + egg white + house dust mite



Table 2. Comparison of skin reactivity on the upper back and forearm

	Upper Back	Forearm	Mean Difference	95%CI*	P-value
Wheal diameter, mean \pm SD (mm.)					
Histamine (N = 133)	4.74 \pm 1.37	3.86 \pm 1.82	0.88	0.53-1.23	< 0.0001
50% Glycerol-saline (N = 133)	0.57 \pm 1.17	0.34 \pm 0.89	0.23	0.06-0.39	0.007
Flare diameter, mean \pm SD (mm.)					
Histamine (N = 133)	18.47 \pm 4.28	16.37 \pm 5.50	2.09	1.05-3.13	0.0001
50% Glycerol-saline (N = 133)	4.57 \pm 3.04	3.34 \pm 1.91	1.19	0.70-1.68	< 0.0001

*95% confidence interval of mean difference

Subgroup analyses were performed and it was found that wheal responses to histamine on the upper back were significantly larger than those on the forearm in males ($p = 0.0001$), females ($p = 0.002$), sensitized ($p = 0.03$) and non-sensitized participants ($p < 0.0001$), children aged 6 to less than 12 months ($p = 0.0002$) and 12 to 25 months ($p = 0.003$). No statistical differences between histamine-induced wheal responses were found in subjects with mono-sensitization and poly-sensitization.

Sensitized subjects seemed to have larger histamine wheal sizes than non-sensitized subjects but this did not reach statistical significance (Figure 1 and Table 3). There were no significant differences in skin responses between participants with poly-sensitization and mono-sensitization, males and females and between the age groups of 6 to less than 12 months and 12 to 25 months (Table 3). No adverse effects from skin prick tests were found in this study.

Discussion

In our study, we investigated the skin responses to standardized positive and negative controls in young children aged 6-25 months and demonstrated

that the skin of the upper back is more reactive than the forearm. These findings are similar to those of a previous report that examined the difference in skin reactivity on the back and forearm in 52 adults by Nelson HS et al.¹⁵ The mast cell numbers in the skin at these two different sites might influence the skin test results.

However, the mean histamine wheal diameters in our study were different from those reported by Menardo JL et al. who showed that the mean size of wheal induced by 1 mg/ml of histamine at the forearm in infants aged 6-12 months (N = 20) and 12-24 months (N = 17) were 1.67 \pm 0.69 mm and 2.23 \pm 1.14 mm.¹³ Moreover, Van Asperan PP et al performed skin prick tests to determine skin reactivity in 79 infants using histamine 1 mg/ml and found that the mean histamine wheal sizes in these infants were 1.8-2.5 mm.¹⁴ By contrast, our study showed a larger histamine-induced wheal diameter in young children. The skin prick testing technique, and the number and ethnic origin of subjects might have an effect on these differences.

Our study did not find a significant difference in the mean histamine wheal size between males and females which is consistent with a report from Van

Table 3. Comparison of histamine-wheal sizes on the upper back and forearm, by age, gender and allergen sensitization

	Histamine wheal size (mm), mean \pm SD					
	Upper back	95%CI*	P value	Forearm	95%CI*	P value
Age (months)						
6-<12 (N=75)	4.65 \pm 1.35	-0.68 - 0.27	0.40	3.70 \pm 1.82	-0.10 - 0.26	0.25
12-25 (N=58)	4.86 \pm 1.41			4.07 \pm 1.82		
Gender						
Male (N=75)	4.69 \pm 1.39	-0.35 - 0.60	0.61	3.93 \pm 1.61	-0.80 - 0.46	0.60
Female (N=58)	4.81 \pm 1.36			3.76 \pm 2.07		
Allergen sensitization						
Yes (N=23)	5.22 \pm 1.53	-0.03 - 1.20	0.06	4.30 \pm 1.17	-0.29 - 1.36	0.20
No (N=110)	4.64 \pm 1.32			3.77 \pm 1.92		
Number of allergen sensitization						
Polysensitization (N=5)	5.37 \pm 0.94	-1.83 - 1.46	0.81	4.64 \pm 1.33	-1.67 - 0.82	0.48
Monosensitization (N= 18)	5.18 \pm 1.68			4.21 \pm 1.15		

*95% confidence interval of mean difference



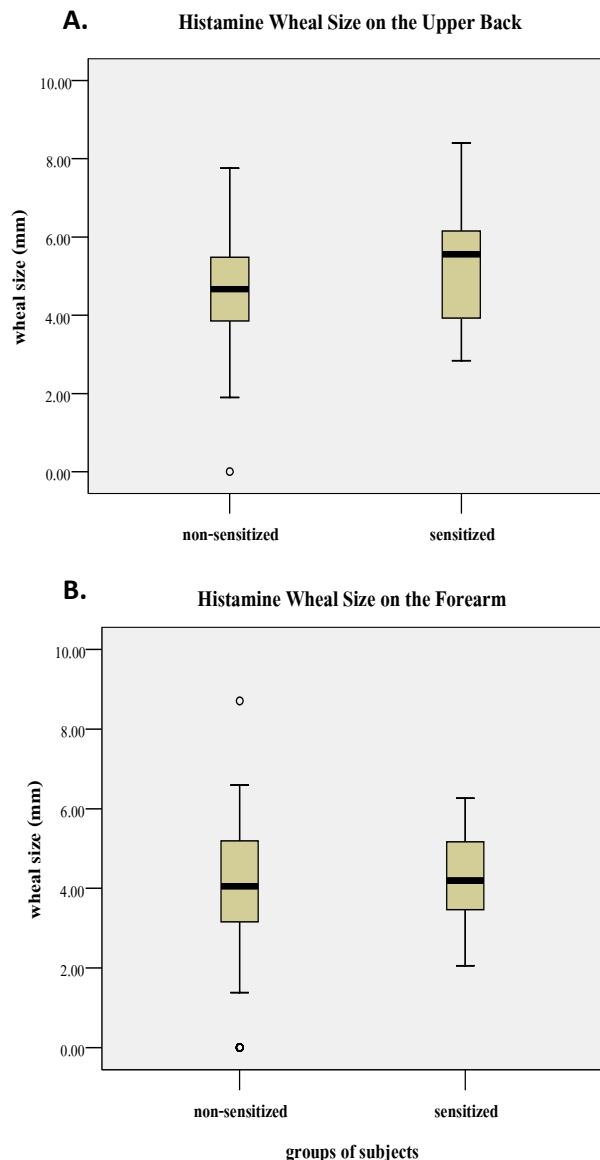


Figure 1. Distribution of skin reactions to histamine A. on the upper back and B. forearm among non-atopic (subjects without allergen sensitization) and atopic (subjects with allergen sensitization) groups.

Gysel et al.¹⁶ In contrast with previous studies¹⁶⁻¹⁸ in which skin tests were performed in children and adults, our study found no statistically significant difference in histamine skin reactivity among subjects with or without allergen sensitization. However, our study group included only a small number of subjects who had allergen sensitization.

In conclusion, we demonstrated that skin prick tests can be performed in young children as young as 6 months of age and the upper back provides more skin reactivity to histamine which results in larger wheal and flare sizes than the forearm.

Because of this variation and the limited skin surface area on the forearm of very young children in performing SPTs, the upper back is the preferred test area, especially during infancy.

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