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Fear of repeated injections in children < 4 years of age receiving subcutaneous allergy immunotherapy

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Introduction

Sensitization to aeroallergens within the first three years of life strongly predicts persisting or relapsing asthma [1, 2]. Subcutaneous allergy immunotherapy has been shown to be effective in treating asthma and allergic rhinoconjunctivitis in children and adults [3, 4] and can possibly prevent new onset of atopic asthma [5]. Allergic desensitization early in life before chronic airway inflammation is established may be effective in reducing childhood asthma. However, the official guidelines [6] recommend not starting subcutaneous immunotherapy until the age of 5 years. One of the reasons is the unknown safety profile, including the psychological effect of repeated needle injections at young age. The fear and distress experienced by children < 4 years of age receiving allergy injections has not been systematically studied to date. We therefore performed a prospective analysis of distress in children <4 years of age receiving repeated subcutaneous immunotherapy injections.

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Methods

Subjects

A prospective cohort of 18 children at a pediatric asthma center in Bronx, New York, who were part of an ongoing clinical trial to evaluate the efficacy of subcutaneous immunotherapy in reducing asthma morbidity (clinicaltrial.gov identifier NCT01028560) were considered for this analysis. The clinical trial is a randomized, non-placebo controlled, phase I/II clinical trial. Only children receiving immunotherapy were included in this analysis. All parents of participating children had provided written consent and the study was approved by our local IRB.

Immunotherapy

The number and type of allergen extracts used for immunotherapy was individually determined by skin prick testing (ComforTen[®], Hollister-Stier) and allergen specific serum IgE testing (Immulite 2000, Siemens) to 8 common aeroallergens (tree pollen mix, northern grass mix, giant and short ragweed mix, Dermatophagoides pteronyssinus/farinae, mouse epithelia, cat hair, dog epithelia, American and German cockroach mix) and prepared according to guidelines [6]. The extracts from multiple vials were drawn into one syringe if the total volume did not exceed 0.5 ml. If the total volume exceeded 0.5 ml, 2 injections were given, if the total volume exceeded 1 ml, 3 injections were given. Subcutaneous immunotherapy was given at weekly intervals during the step-up phase and biweekly during the maintenance phase using cumulative monthly extract doses as recommended [6] for a total of three years. Injections were given in a friendly, consistent environment and mostly provided by one pediatric nurse who has had many years of experience giving allergy injections to children.

The syringe and needle were not hidden from the view of the child. The use of pain modulating devices (lidocaine 2.5%/prilocaine 2.5% cream to be applied at least 20 minutes prior to the injections or shot blocker[®]) was offered to all participants. Children were being rewarded after each injection visit by getting a sticker or small toy.

Measurement of fear

At each visit, after the injection and usually before leaving the nurse's injection room, the personnel providing the injection asked the accompanying parent or guardian how much fear they thought their child experienced on a scale from 0–10, zero being no fear, and 10 being the worst fear imaginable in the child. The injection personnel would then also provide their fear score of the child using the same scale. The injection nurse was not blinded to the fear score given by the parent. The agreement (intraclass correlation) between the injection personnel's and the parent's fear score was 97% (95% CI: 92%–99%). We therefore considered an average combined fear score of parent and injection personnel (parent fear score + injection personnel fear score/2) as the "fear score" variable.

Statistical methods

Descriptive statistics of fear scores and average follow-up time were analyzed. The concordance between parents and injection personnel over time was examined by

constructing a summary area -under the curve and evaluating it using intraclass correlation coefficient. The time to a combined fear score of zero from the start of the study, and the time to two consecutive weeks of zero fear was computed using the Kaplan-Meier method. A Cox regression model with time independent and time-dependent covariates was used to investigate the effects of gaps in visits, the number of injections, adverse reactions, change in injection personnel and hospitalization. The child was considered to have missed an injection visit if > 1.5 weeks had elapsed between 2 visits. Adverse reactions were defined as any local or immediate-type systemic reaction after the injection. All analysis was performed using SAS 9.2 version.

Results

Subject's demographic and clinical characteristics

All 18 children receiving immunotherapy had significant asthma and allergy morbidities and the majority of children had experienced previous asthma related hospitalizations (table 1). Sixty-seven percent of children were of Hispanic and 28% were African-American background and all were Medicaid recipients, indicating a low socioeconomic status. At the time of this analysis, the median (range) follow-up was 81.5 (15, 165) weeks. Fifty-six percent of children had reached the immunotherapy maintenance dose. Depending on the number of antigens used, children received a maximum of three injections at a single time point (table 1).

Fear scores

During the majority of visits, children had no fear (score 0) or mild fear (score 0.5–2). The individual fear scores plotted against time are represented in figure 1.

Fourteen children (78%) had fear at their first injection visit (score >0) with an average fear score of 2.9, SD +/-2.0. Four children (22%) started with a fear score of “0” – however two of these children that started with a score of “0” expressed fear at their subsequent visit, possibly explained by a “priming effect” during the experience at their first visit. We then analyzed how many children reached a score of “0” in two subsequent visits during the course of the study, regardless of their starting score. Fifteen children (83%) achieved score zero during the course of the study. The Kaplan Meier-estimates showed that about 33%, 50%, 67% and 89% of children lost fear (achieved score 0 at two consecutive visits) for the first time during weeks 2, 9, 21 and 64, respectively (Figure 2.). Of the three remaining children (17%) that did not lose fear during the course of the study, two had dropped out. One of these children dropped out because the parents had conflicting work schedules and were unable to bring the child to the injection visits on a regular base and the other child dropped out for unknown reasons. All of these 3 children had not yet reached the maintenance phase and had missed a substantial amount of visits (12/24 weeks, 10/26 weeks and 13/26 weeks).

Predictors of increased fear score

Several factors were considered to possibly increase fear in children, including time intervals between injections, hospitalizations, increased number of injections at one visit,

change of personal giving the injection and age. Of all those possible predictors, only an increased interval between 2 injection visits was likely to increase fear. When defining “loss of fear” as time to first two consecutive zero score visits, children that missed their weekly scheduled injection visits were 7.9 times more likely to having fear at the subsequent injection visits in comparison with children not missing visits (HR for no fear 0.13, 95% CI: 0.02, 1.02, p-value=0.05). This relationship was not statistically apparent when “loss of fear” was defined as first time achieving score zero regardless of the score at the subsequent visit. Consequently, the larger the intervals between 2 injection visits, the more time it took and the more visits were required to decrease fear (Figure 3). In contrast, hospitalizations during the treatment course, number of injections, change of injection personal and age did not alter the risk of fear.

In addition, we analyzed if experiencing an adverse event (local or systemic allergic reactions) increase the risk of fear at the subsequent injection visit. Local reactions occurred at 25 visits in 13 children (72%) and were all mild; systemic reactions were experienced by 6 children (33%) at a total of 33 visits and consisted mostly of mild, readily reversible immediate reactions or non-immediate reactions. None of the reactions required treatment with epinephrine and none of the reactions prompted the parent to withdraw from the study. Experience of adverse events did not predict increase of fear at the subsequent visit.

Discussion

We describe the results of a preliminary, prospective analysis of fear scores in young children receiving subcutaneous allergy immunotherapy. All but 1 active study participants lost their fear of injections over time. Fifty percent of children achieved a fear score of 0, assigned by parent and injection personnel, by their 3rd injection visit. Increased fear was associated with an increased time interval between injection visit but not with preceding hospitalizations, number of injections, change of injection personal or the experience of local or immediate type systemic reactions at preceding visits.

To date, subcutaneous immunotherapy is the most established route of efficient allergen vaccination. Even though needleless routes (i.e. sublingual) of vaccine administration are under investigation, experience in children is limited and not yet established for important indoor allergens in inner city populations, such as cockroach and mouse antigens [7]. At the same time, early intervention with allergen vaccination may be effective in preventing allergy and asthma morbidity in atopic children with recurrent wheeze [1, 2, 8, 9]. Therefore it is important to establish the safety profile of subcutaneous allergy injection in young children, which includes the concern of distress and fear the children experience with needle injections.

Our preliminary results indicate that moderate (score 4.5–6) to high fear scores (score >6) were experienced during only 6.4% of all analyzed injection visits. To interpret this number correctly one has to keep in mind that most of our children have not yet completed the 3-year course of immunotherapy. As children typically lose fear over time and then go on without fear this number may decrease once all children have completed their 3-year course of immunotherapy. Children with high number of missed visits were more likely to retain

fear. However, we cannot exclude a reverse causation: The persistence or intensity of their children's fear may have caused the parents not to bring their child to their regular scheduled injection visits.

While we did not find that hospitalizations during the course of the study, number of injections, change of injection personnel, adverse events or age influenced the fear of injections in children, caution needs to be observed in interpreting the results because of the small sample size. A future analysis with a greater number of children and injection visits may reveal more robust results.

Our study is limited by the indirect method with which we measured fear. The score assigned by the parent or the injection personnel may not always reflect the real amount of fear and distress the child experiences. However, even validated and complex methods of measuring distress include this subjective measure as an important tool to quantify procedural distress in children [10]. One of the reasons is that the expression of fear varies widely among children (e.g. one child may cry and fight, while another may stay exceptionally still as an expression of fear). Even physical changes that may correlate with fear, such as heart or respiration, or perspiration rate would be undistinguishable from other effects in our study, as many times children ran around the waiting areas or hallways while waiting to receive their injections. Hence we concluded that the most reliable reflection of fear are the scores given by the parent or primary care giver as parents know their own child's reaction best as well as the score given by the injection nurse who had many years of experience giving immunotherapy to children of all ages. We cannot exclude that the fear score assigned by the injection nurse was biased by the fear score given by the parent as we had no mechanism of blinding in place. However, since the interclass coefficient between parent's and personnel fear scores was very high, this bias may be skewing the scoring towards the parent's estimates of fear but may not otherwise confound the results. In addition, an unavoidable bias may have been created by the fact that parents became friendly with the clinic personnel over time, prompting them to give lower fear scores to "please" the personnel; however even if such bias may have occurred, it is very unlikely that this would have caused a large discrepancy between the unbiased and the biased rating score and hence compromise the major conclusion of our analysis.

In this study, we tried to apply all reasonably available factors that may help overcoming fear of injections in children, i.e. pain modulating devices, small rewards and the provision of a friendly, consistent environment. This reflects what is available in most allergy immunotherapy clinics, which helps in applying our results to most practice settings.

This study provides important insights into the fear response of young children receiving allergy vaccination through subcutaneous immunotherapy. Our results indicate that fear of injections resolve in most children receiving subcutaneous immunotherapy over time, and do not seem to be a significant problem in most young children receiving subcutaneous allergy immunotherapy. Concern about excess fear should therefore not be a consideration in deciding on whether to give immunotherapy to young children.

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Figure 1.
Individual fear scores over time

Figure 2. Probability of fear over time when “loss of fear” was defined as achieving score “0” for the first time (Kaplan Meier analysis)

Figure 3.

Number of missed visits plotted against time at which children first lost their fear from the injection (score 0, filled circles). For the three children that did not achieve score 0 at the time of analysis (x) the time of their last visit at time of analysis is plotted against number of missing visits.

Table 1

Subject characteristics (n=18)	N (%)
Age at study entry in months (mean, SD)	37 (9)
Gender Male	16 (89%)
Race	
Hispanic	12 (67%)
African-American	5 (28%)
Other	1 (6%)
Eczema ever	16 (89%)
Eczema at present	11 (59%)
Number of wheezing episodes since birth	
0–2	3 (18%)
3–5	2 (12%)
6–15	6 (35%)
>15	6 (35%)
Number of ER visits for asthma since birth	
0	1 (6%)
1–2	6 (33%)
3–5	4 (22%)
6–10	4 (22%)
>10	3 (17%)
Number of hospitalizations for asthma since birth	
0	8 (44%)
1–2	8 (44%)
3 or more	2 (11%)
Weeks in study (median, range)	81.5 (15, 165)
Number of visits (median, range)	49 (12, 88)
Participants that reached maintenance dose	10 (56%)
Week when maintenance dose was reached (mean, SD)	57 (19)
Visit when maintenance dose was reached (mean, SD)	39 (3)
Use of pain modulating devices (% of visits)	
Local anesthetic cream	282 (36%)
Shotblocker®	105 (13%)
Not documented	48 (6%)
None	319 (41%)

Subject characteristics (n=18)	N (%)
Number of different allergen extracts used for immunotherapy (mean, SD)	4.2 (2.0)
Number of injections at each visit (n of children, at % of visits)	
1 injection throughout all visits	6 children
1 or 2 injections	10 children (1 injection at 83% of visits and 2 injections at 17% of visits)
1, 2 or 3 injections	2 children (1 injection at 65% of visits, 2 injections at 26% of visits, 3 injections at 9% of visits)
Consistency of personnel giving injections	
Number of visits (%) injections given by same nurse	736 (94%)
Number of visits (%) injections given by other personnel	44 (6%)
Adverse reactions to immunotherapy (in number (%) of children at number (%) of visits) *	
<u>Local reactions (mild)</u>	9 children (50%), 11/788 (1.4%) visits
<u>Systemic reactions</u>	5 children (28%), 28/788 (3.6%) visits
Immediate grade 1	3 children (17%), at 7/788 (1%) visits
Immediate grade 2	3 children (17%), at 8/788 (1%) visits
Non-immediate	4 children (22%), at 13 (1.6%) visits
Total (systemic and local)	13 children (72%), at 39/788 (4.9%) visits

* There was no difference in age between children having systemic reactions versus others (34.2 months, SD 6.7 versus 37.7 months, SD 9.7, p=0.47) or among children having local reactions versus others (37.0 months, SD 9.8 versus 36.4, SD 8.5, p=0.90)