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Epinephrine-coated Syringe for SCIT Reduced Local Reactions: A Randomized, Double-Blind, Placebo-Controlled Trial

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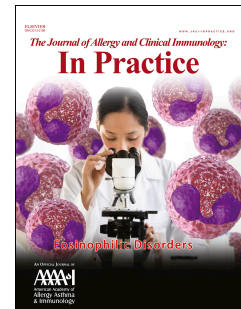
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A short running title: Epinephrine Coated Syringe for SCIT Reduced LR

Clinical Trial Registration No. NCT03963115

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Table: 1

Figures: 1

27 Clinical implications

28 A syringe coated with epinephrine for subcutaneous immunotherapy (SCIT) could
29 significantly reduce both immediate and late local reactions (LRs) compared to placebo in
30 patients who have frequent large LR's despite premedication with antihistamine with or
31 without leukotriene receptor antagonist.

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TO THE EDITOR:

Adverse reactions to subcutaneous immunotherapy (SCIT) were classified as local (LRs) and systemic reactions (SRs).¹ The timing of adverse reactions was categorized as immediate (occurring ≤ 30 minutes after injection) and late reaction (occurring >30 minutes after injection).² Large local reactions (LLRs) were defined as erythema and/or swelling (>25 mm) at the site of injection.³ Children had similar rates of LR compared to adult patients, but had lower rates of severe SRs.⁴

Several studies indicated that individual LR did not predict subsequent SR.⁵ However, patients with a greater frequency of LLRs were at increased risk for future SRs.^{3,6} The odds ratio of SRs increased from 7.08 to 22.54 when the LLR rate increased from 10% to 50%.³ Recognizing the significance of frequent LLRs is important for safer SCIT protocols. Many strategies to minimize LR were reported. Oral antihistamines, leukotriene receptor antagonist (LTRA), or anti-IgE could reduce LR during the built-up phase.⁷ To our knowledge, the effect of coating a syringe with epinephrine prior to drawing the allergen extract for SCIT in patients with frequent LLRs has never been explored.

Patients aged >6 years who were on a maintenance dose of SCIT and complained of having LLRs $\geq 20\%$ of injections during the previous 5 months despite premedication, were recruited. Patients' underlying diseases were asthma and/or allergic rhinitis with or without allergic conjunctivitis or atopic dermatitis. We excluded patients who experienced SRs $>$ grade 1 of the WAO SCIT systemic reaction grading system.⁸ Patients with uncontrolled asthma and other systemic diseases were also excluded. Patients with asthma had to be asymptomatic, and their FEV1 had to be $\geq 70\%$. Patients were allowed to use their previously premedication, such as antihistamine with or without LTRA, 60 minutes prior to SCIT.

This study was approved by the Institutional Review Board. Written informed consent was obtained from patients >18 years of age, or from parents of children ≤ 18 years of age. In

addition, assent was obtained from patients aged 7-18 years prior to enrollment. Interventions were performed during 2 SCIT visits that were scheduled 4 weeks apart (Figure E1). During the first visit, subjects were randomly assigned to receive either epinephrine or normal saline (NSS, placebo)-coated syringe for SCIT by simple randomization. The syringe(s) for the second visit was coated with the agent that was not used during the first visit. In patients who received 2 injection/visit, both injections were linked to the same intervention. The patients and SS, who drew and injected the allergen shots, were blinded to the assignment from the beginning to the end of the interventions. The 1-ml syringes were coated with 0.2 ml of either epinephrine (1 mg/ml, The Government Pharmaceutical Organization, Thailand) or NSS. The allergen extracts were prepared according to the standard guideline.² The allergen extracts were from ALK-Abello Pharm, Port Washington, NY, USA. Multiple allergen extracts were mixed under a sterile condition in the same bottle, except for cockroach and mold/fungi extracts that were prepared in a different bottle. Patients who received 2 injections per visit were given one injection in each arm. For the second visit, patients received the same allergens at the same concentration, dosage, and site of injection.

Patients were observed for immediate reactions after SCIT for 30 minutes at the Pediatric Allergy Clinic. Late reactions were recorded at 2, 4, and 6 hours at home. Patients/parents were trained to record LR and SRs prior to discharge. LLR was defined as the presence of erythema or swelling >25 mm at the injection site.¹ Sample size calculation was based on our pilot study, which revealed a median LR of 51.3 mm and 50% reduction after epinephrine-coated syringe was used. Comparisons of treatment arms were performed using Wilcoxon signed-rank test. A p -value of <0.05 was considered statistically significant.

Seventeen patients who received a total of 31 injections were recruited. The baseline characteristics are demonstrated in Table 1. All patients took the same premedication prior to the injection and completed both interventions in 2 visits without drop out. Epinephrine-

coated syringe significantly reduced LRs compared to placebo at all time-points (Figure 1A). The reduction of LR size by epinephrine-coated syringe compared to placebo at 30 minutes, 2, 4 and 6 hours were 100%, 61%, 55% and 39.8%, respectively. The maximum LR while patients received epinephrine-coated syringe was significantly smaller than placebo by 30% (Figure 1B). The number needed to treat to reduce the incidence of LLR was 3.88. We found that epinephrine-coated syringe could significantly reduce LRs by >25% in 20/31 injections (64.5%), and could reduce LRs by >50% in 11/31 injections (35.5%). The median size of initial skin prick test (SPT) to *Dermatophagoides pteronyssinus* was significantly larger in patients whose LR reduction was $\geq 25\%$ than LR reduction $< 25\%$ (11.5 vs 4 mm). Similarly, the median size of initial SPT to *Dermatophagoides farinae* was significantly larger in patients whose LR reduction was $\geq 25\%$ than LR reduction $< 25\%$ (12.5 vs 3 mm). There was no SR in both interventions. Three patients (5 injections) had transient burning sensation at the site of injection while they received SCIT with epinephrine-coated syringe, but not with placebo. The symptom resolved spontaneously after completion of the injection without further treatment.

The patients that we recruited for this study reported a high rate of LLRs and 76% of them had asthma which may increase risk of SRs. Therefore, an effort to decrease the incidence of LLRs was justified. To our knowledge, this is the first study to demonstrate the benefit of epinephrine-coated syringe in SCIT for reducing LRs. There might be a concern that epinephrine could delay the onset of SR, and even increase the risk of SR.⁷ Nevertheless, no SR was observed in any patients. The proposed mechanism of epinephrine to reduce LR is probably the vasoconstrictive effect that might decrease the absorption rate of the allergen.

107 In conclusion, our results demonstrated that syringes coated with epinephrine reduced
108 the size of immediate and late LRs associated with SCIT compared to placebo. A larger
109 study may be needed to explore the effect of this intervention on SR.

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FIGURE LEGEND

Figure 1. The effect of normal saline (NSS) or epinephrine coated syringe on local reaction (LR) of subcutaneous immunotherapy (SCIT). A, box plot of LR's sizes at different time points while patients received NSS or epinephrine coated syringe for SCIT. B, comparisons of maximum LR's sizes at any time points while patients received NSS or epinephrine coated syringe for SCIT.

156 **Table 1.** Baseline patient demographic and clinical characteristics

Characteristics	N=17, n (%)
Gender	
Male	7 (41.2%)
Age (years)	
Median (range: min-max)	17.3 (11-39)
< 18 years	12 (70.5%)
≥ 18 years	5 (29.5%)
Body mass index (BMI) (kg/m²)	
Median (range: min-max)	23.5 (16-41.6)
BMI ≤ 25	11 (64.7%)
BMI > 25	6 (35.3%)
Age started immunotherapy (years)	
Median (range: min-max)	12 (6-35)
Duration of immunotherapy (months)	
Median (range: min-max)	55 (13-123)
Frequency of large local reactions (%)	
Median (range: min-max)	80 (40-100)
Atopic diseases, n (%)	
Asthma	6 (35.3%)
Asthma and allergic rhinitis	5 (29.4%)
Asthma and allergic rhinitis and atopic dermatitis	2 (11.8%)

Allergic rhinitis	1 (5.9%)
Allergic rhinitis and allergic conjunctivitis	2 (11.8%)
Allergic rhinitis and atopic dermatitis	1 (5.9%)
Premedication	
2 nd -generation antihistamine	7 (41.2%)
2 nd -generation antihistamine plus montelukast	10 (58.8%)
Number of injection	
1	3 (17.6%)
2	14 (82.4%)
Allergen for immunotherapy	
Mite	16 (94.1%)
Cockroach	15 (88.2%)
Bermuda	11 (64.7%)
Johnson	10 (58.8%)
Cat	8 (47.1%)
Dog	7 (41.2%)
Acacia	7 (41.2%)
Careless weed	5 (29.4%)
Alternaria	2 (11.8%)
Aspergillus	2 (11.8%)
Cladosporium	1 (5.9%)
Number of allergens for immunotherapy	

1 allergen	0 (0.0%)
2 allergens	2 (11.8%)
3 allergens	2 (11.8%)
4 allergens	4 (23.5%)
5 allergens	2 (11.8%)
≥6 allergens	7 (41.2%)

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FIGURE LEGEND

Figure E1. Flow diagram of the study. The patients were allocated to receive the different sequence of normal saline or epinephrine coated syringe in the 1st and 2nd visits. All patients completed both interventions.

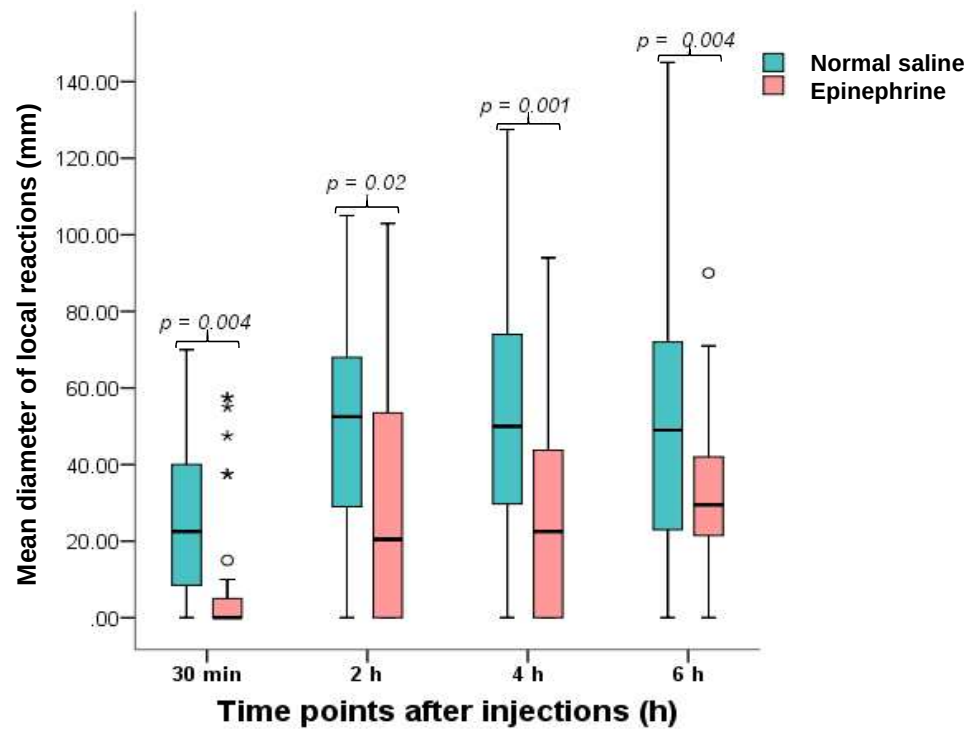
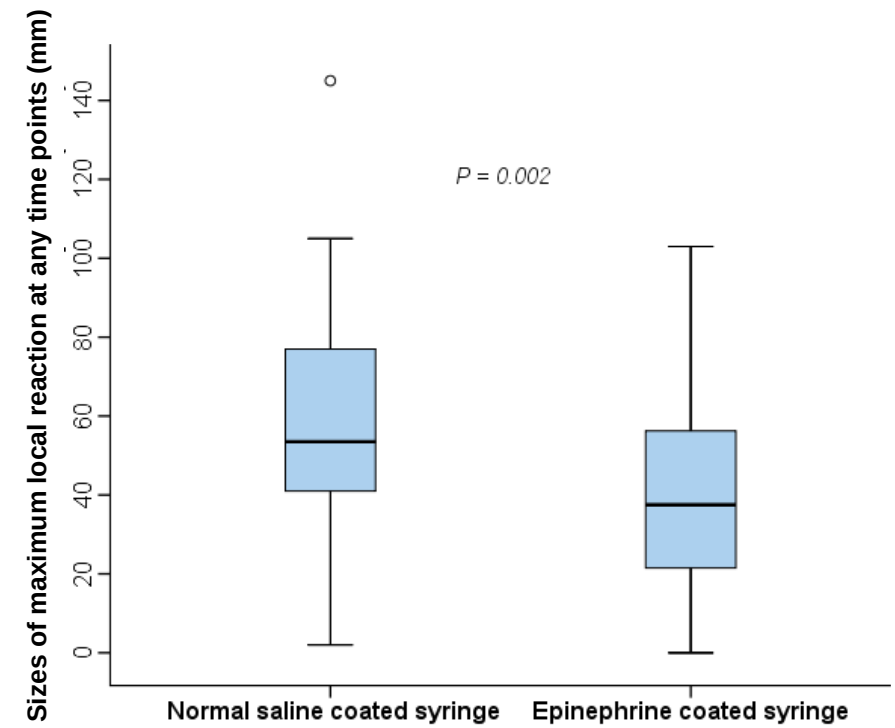
A**B**

Figure 1.