

LETTER TO THE EDITOR

Tolerance of needleless subcutaneous immunotherapy in children

To the Editor,

Subcutaneous allergen immunotherapy (SCIT) is an effective treatment of respiratory allergy,¹ but injections in children may cause pain,² fear,³ and sometimes systemic adverse events.⁴⁻⁶ Needle-free injectors, who generate a "liquid needle" with a sufficient force to pass through the skin and enter the subcutaneous tissue, do not inject fluids directly into the vein. They have never been used for the delivery of SCIT. In this prospective, double-arm, randomized, patient-blinded, intra-individual multi-center clinical trial, we compared a needleless vs. a traditional administration of SCIT in children and adolescents with grass pollen or house dust mite (HDM) allergy. The study was approved by the local ethical committees and registered as an investigator-initiated clinical trial at

ClinicalTrials.gov under the number NCT02965612. The respective informed consent form was signed by children over 12 and by parents in all cases.

Children aged between 6 and 18 years with moderate-severe persistent rhinoconjunctivitis (ARIA) and/or level I-III allergic asthma (GINA criteria) were treated with a glutaraldehyde-polymerized depot allergenic extract (Allergovac Polymerized®, Bial Aristegui) for 6 months. Six 0.5 mL doses were administered in the triceps fat pad⁷ of blindfolded patients divided into two parts. Half was injected in one arm, and half was administered after 20 minutes in the other arm by a syringe or a reusable spring-powered, handheld Injex 30® device designed for insulin delivery. The sequence of needle/needleless arms was randomized using a Microsoft Excel table. Forty right/

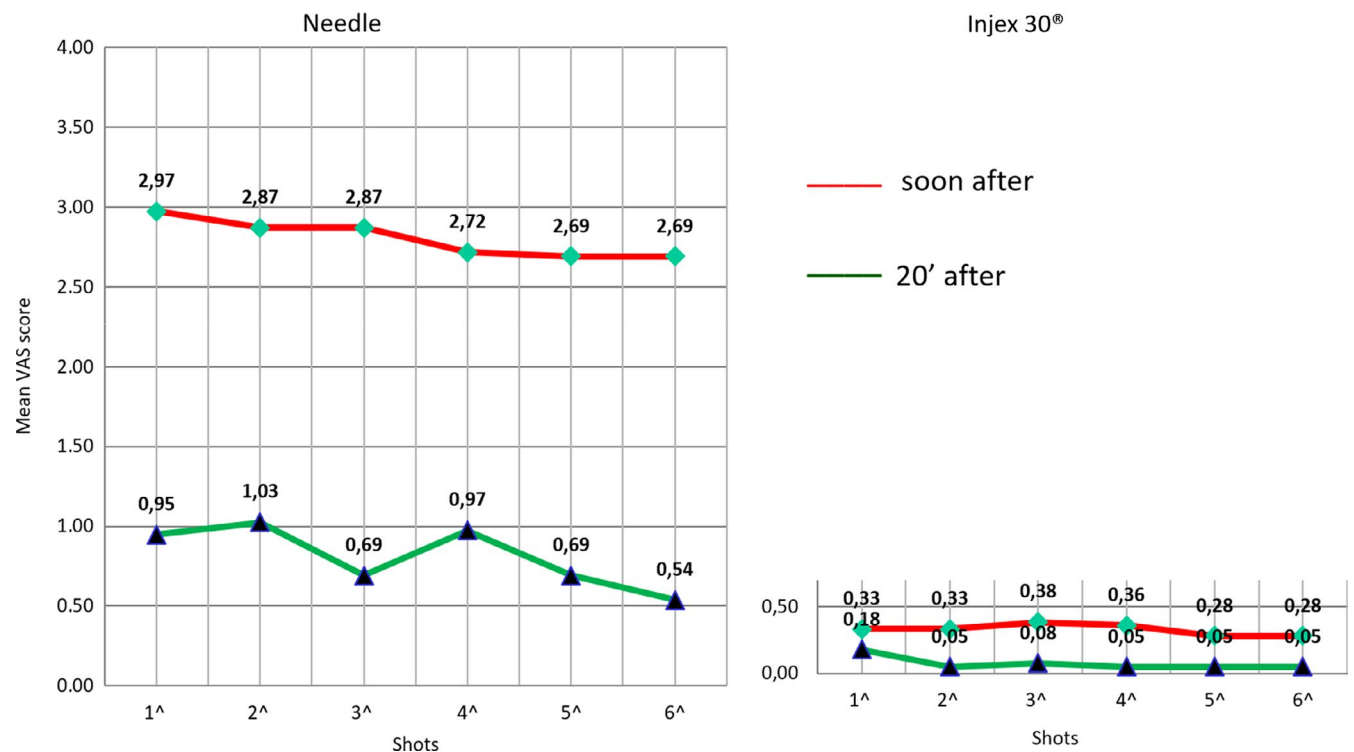


FIGURE 1 Mean VAS score of pain perception rate immediately (red line) and 20 minutes after (green line) the administration of the 6 doses

left sequences were generated, and each participant was assigned to its group by a person unrelated to the study.

The pain perception rate (PPR) was evaluated separately for the two arms, immediately and 20 minutes after the injection. Our questionnaire used a Wong-Baker scale for children aged 3-8 years and a visual analogue scale (VAS) afterward. Before the study, children underwent a seriation task to verify their ability to use the VAS; those who failed the test were excluded.

The clinician administering the SCIT was required to fill a procedural difficulty rate (PDR) questionnaire immediately after the administration of each dose, rating the difficulties on a VAS and describing them in a specific, free-writing sheet. We also evaluated the PPR 20' after every administration, the number and severity of allergenic adverse reactions to the treatment,⁸ and their effect on changes in treatment schedule.

Thirty-nine patients (28 males, 11 females; mean age: 11.99 ± 3.70 years) allergic to HDM ($n = 13$) or grass pollen ($n = 26$) received over a mean period of 246 ± 161 days 468 SCIT doses, 234 of which are needleless, for an average cumulative dose of 1000 TPU grass pollen (Phl p1/Phl p5 $1.46/1.49$ $\mu\text{g/mL}$) or HDM (Der p1/Der p2 $2.00/0.20$ $\mu\text{g/mL}$) allergen.

The mean PPR immediately after the administration was 16.82 ± 6.11 (needle) vs 1.97 ± 2.19 (needleless) (median 17 vs 2; $z = -5.448$ $P < .001$ $r = -0.62$; Figure 1). Twenty minutes after, the PPR was 4.87 ± 5.71 vs 0.46 ± 0.99 (median 2 vs 0; $z = -4.292$ $P < .001$; $r = -0.49$). The PPR soon after the administration did not vary over the six doses in the needle ($\chi^2 1.589$, $P = .903$) nor in the needleless ($\chi^2 1.572$ $P = .905$) arm (Figure 2). The same happened 20' after the administration (needle: $\chi^2 6.308$, $P = .277$; needleless: $\chi^2 7.537$, $P = .184$).

The operators reported the highest difficulty at the first (mean PDR 1.85 ± 1.00) and fourth (1.87 ± 0.65) needleless administration, with a reduction to a 1.41 ± 0.87 PDR at sixth administration. Friedman test ($\chi^2 16.661$, $P = .005$) indicated a significant difference

through the sequence. Post hoc tests, carried out by Bonferroni correction ($\alpha 0.0033$), showed significance only between the first and the sixth ($z = -3.012$ $P = .0030$ $r = -0.34$) and the fourth and the sixth administrations ($z = -2.924$ $P = .0030$ $r = -0.33$). The most reported problems were recoil of the device (15 cases), liquid loss (seven cases), and a self-perception of inability to exert the firm pressure necessary to ensure the adherence of the nozzle to the skin (five cases).

None of the children had systemic reactions to SCIT. Nine mild-to-moderate (grades I-II) reactions were recorded in five patients in the needle-treated arm and four in four patients in the needleless-treated arm (Table 1). None required SCIT cessation. A reduced maintenance dose was necessary in four cases of moderate reaction. Dust mite allergen, used in 32.5% of programs, was responsible for 30.8% of adverse reactions.

In this experience, the administration of SCIT by needleless device reduced the pain perception by 8.5-fold soon after the administration and by 10.5-fold after 20'. This remarkable difference, registered for both allergens, persisted over time and through the different administrations. The traditional administration determined a 2.97 ± 1.53 PPR, only slightly reduced after the 6th dose (2.69 ± 1.40). Thus, needleless administration causes less pain and may be more acceptable to children. The pain reported by our patients is determined by the lesion of the tissues determined by the metallic needle. These injuries involve the risk of direct penetration of allergenic material into the circulation, potential cause of systemic reactions. Our experience is too narrow to warrant safety from this point of view, but the accumulated experience indicates that the needleless techniques may reduce the risk of inadvertent i.v. administration.⁹

The PDR decrease through doses indicates that the operator gradually becomes familiar with the tool and its difficulties. With minimal training, these difficulties can be easily overcome. To further minimize them, the devices of the future will contain pressure

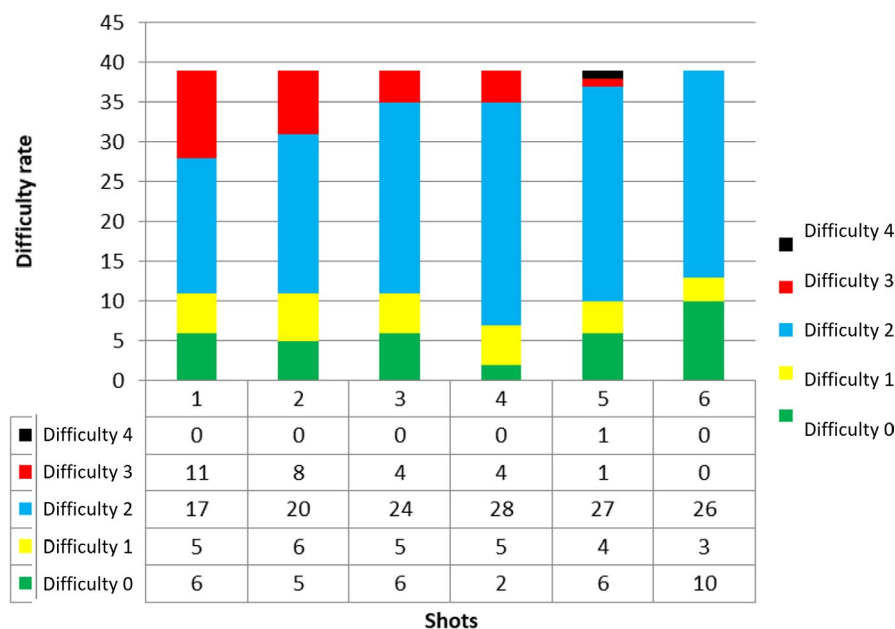


FIGURE 2 Mean difficulty rate across shots using Injex 30®

TABLE 1 Adverse reactions and severity in eleven children

Children	Allergen Used	Symptom	Severity	Time to adverse event (min)
Needleless administration				
1	Grass	Localized urticaria	1	<10
2	Grass	Localized urticaria	1	<10
3	Grass	Gastrointestinal (abdominal cramps)	2	10-20
4	Mites	Rhinitis	1	<10
Traditional administration				
5	Grass	Localized urticaria	1	10-20
		Localized urticaria	1	>20
6	Mites	Lower respiratory (asthma)	2	10-20
7	Mites	Angioedema	1	10-20
8	Mites	Localized urticaria	1	<10
9	Grass	Gastrointestinal (abdominal cramps)	2	
10	Grass		1	<10
	Grass	Angioedema	1	<10
11	Grass	Localized urticaria	1	<10
		Localized urticaria		

gauges able to assist the operator in the execution of perfectly correct needle-free injections.¹⁰

This study has several limitations. The patient, but not the operator, was blinded; the blinding was to sight, but not hearing. As Injex produces a shot, we cannot exclude that, especially after the first injections, some patients did identify the needleless procedure. The sample size, calculated on the perception of pain and operational difficulties, does not allow us to assert with certainty that the side effects of the inoculum site are lower in one of the two arms. However, as a direct penetration of allergenic material into a vein is the cause of the most fearful SCIT reactions and the needleless techniques reduce this risk, we assume that their safety can be high.

The dose administrable by Injex is limited to 0.3 mL, and the TPU administered for both grass and HDM in this study was quite low. The cumulative dose we administered by this way would not be sufficient to an efficient AIT in a reasonable time. While in our case this has been corrected by the double administration, the application of Injex in a clinical phase would entail the design of specifically designed devices with an ampoule capable of 1 mL of solution.

Despite all these limitations, our experience suggests that needle-free technology is a possible alternative for SCIT. It may become of particular interest with aqueous SCIT. Specific devices must be developed that take into account the viscosity, the volume, the speed of injection necessary, and the side effects obtainable with different allergen preparations. However, the benefits of pain, speed, and reduction of side effects could become decisive in the therapeutic orientation of children with respiratory allergies.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of Mario Mancini PhD to the manuscript.

CONFLICT OF INTEREST

No author stated any conflict of interest.

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Editor: Marina Atanaskovic-Markovic

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