ORIGINAL ARTICLE

The Efficacy of Sublingual Immunotherapy with Traditional Coca's Extract as a Treatment of Respiratory Allergy

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ABSTRACT

Background: *Allergic manifestations affect adults and children worldwide and the symptoms interfere with daily activities of the patients.* ***Objective:*** *To evaluate the efficacy of Sublingual (SLIT) versus Subcutaneous (SCIT) Immunotherapies in treating respiratory allergy, and to compare the SLIT protocol applied in Egypt with that applied in France.* ***Methodology:*** *This study included 83 allergic patients (Egyptian and French). The diagnosis of respiratory allergy was performed clinically and laboratory. All Egyptian patients were subjected to skin prick test using different homemade Coca's extracted allergens. Total and specific serum IgE levels were detected by enzyme linked immunosorbent assay before and after 6 months of immunotherapy. Patients were divided into three groups: Group I included 28 Egyptian patients receiving SLIT, Group II included 30 Egyptian patients receiving SCIT and Group III included 25 French patients receiving SLIT.* ***Results:*** *After 6 months of immunotherapy, there was a significant decrease in total and specific IgE levels in Group I patients (P <0.05). In group II, specific IgE levels were significantly decreased (p <0.05), except for wool, cotton and Aspergillus fungi. Analysis of the symptoms of Egyptian patients before and after 6 months of treatment revealed that all symptoms were significantly improved in both groups (P <0.05), but SLIT was significantly superior to SCIT in improving nasal obstruction and discharge (P<0.05). Comparing protocols used in Egypt versus France, we found the disappearance of allergic symptoms in some patients; a significant decrease in the number of group II cases (P <0.001) was detected. No change in symptoms in French patients was detected.* ***Conclusion:*** *SLIT with Coca's extracted allergen showed good efficacy in the treatment of respiratory allergy.*

INTRODUCTION

Allergic manifestations affect adults and children worldwide and the symptoms interfere with daily activities as well as sleep. These are usually associated with fatigue, poor concentration and reduced productivity. Symptom-relieving medications such as intranasal corticosteroids and antihistamine drugs can treat symptoms but they have no impact on the allergic disease itself[1]. Subcutaneous (SCIT) and sublingual (SLIT) immunotherapies are the main types of allergen immunotherapy, and both are considered effective treatments for allergic rhinitis, conjunctivitis, rhino conjunctivitis and asthma[2-4]. They can modify the course of allergic disease and induce immune tolerance to specific allergens [1, 2, 5]. The clinical improvement can persist for many years after the discontinuation of a successful treatment course [3,6]. SCIT and SLIT share many characteristics but also differ in others; both are effective in the treatment of allergic rhino conjunctivitis and allergic asthma, both can prevent the development of asthma in patients with allergic rhinitis, both can prevent the development of new sensitivities in patients who are mono-sensitized, and both induce T_{reg} cells with immune deviation of the cytokine profile from Th2 to Th1. They differ in the severity and frequency of systemic reactions, defined doses whether effective or ineffective and effectiveness of multiple allergen extracts in each dose [6].

The decision to choose between SCIT or SLIT depends on several factors, including geographic location, cost, product availability, the ability of the patients to continuously attend the clinic, patient

characteristics, physician preference, patient's preference, and adherence to the treatment protocol [3, 5].

Subcutaneous immunotherapies induce adverse reactions that can be local or systemic. The severity of systemic reactions ranges from mild symptoms to life-threatening complications such as anaphylaxis and even death. Most systemic reactions (approximately 86%) occurred within 30 minutes after subcutaneous administration, while most delayed-onset systemic reactions were mild, but severe reactions may also occur. For this reason, the guidelines recommended that patients administered SCIT should be supervised in a medical facility and monitored for 30 minutes after the injection [5]. SLIT has a better safety profile than SCIT, and this advantage allows home administration. The common adverse effects reported with SLIT are local reactions such as oromucosal pruritic reaction and/or mild local edema, which may occur for a few days and subsequently resolve without any medical intervention and treatment is continued without further adverse effects. SLIT-induced systemic reactions are rare, and no fatalities related to SLIT have been reported [4, 7].

Many European countries have shifted to SLIT for its approved safety [5]. In Egypt, both SCIT and SLIT are approved but the data about SLIT efficiency are still deficient, and more investigations to shift to this line of treatment are needed. Egypt is still considered a developing country with a low socioeconomic level. Therefore, homemade extracts represent a favorable economic alternative through which immunotherapy can be continuously delivered to allergic patients [8].

The aim of this study was to evaluate the efficacy of SLIT versus SCIT in treating different types of respiratory allergies and to compare the SLIT protocol applied in Egypt with that applied in Limoges University, France.

METHODOLOGY

Study design

This is a randomized control study in which, 90 patients (decreased to 83 at the end of the study due to noncompliance with immunotherapy) attending Allergy Outpatient Clinics were included in the study after obtaining their consent. The study compared sublingual versus subcutaneous immunotherapy in Egyptian patients, then compared the results of homemade sublingual immunotherapy in Egyptians with the commercially approved immunotherapy in French patients. The study was conducted from August 2018 to December, 2020 and approved by Fayoum University, Faculty of Medicine Ethical Committee under the number D81.

Patient involvement

Inclusion criteria:

Patients attending Allergy Outpatient Clinics who gave their consent to be included in the study. Data were collected through a full detailed medical history, symptoms and medications were reported including present history of symptoms such as sneezing, rhinorrhea, and nasal obstruction, precipitating factors of allergy, family history of allergic diseases such as allergic rhinitis and bronchial asthma, number of allergic attacks per week, and past history of allergic rhinitis, conjunctivitis, bronchial asthma and atopic dermatitis.

Exclusion criteria:

Patients with active upper respiratory tract infection within one month before the study, patients with malignancies or autoimmune diseases, patients with any previous immunotherapy and chronic treatment with systemic corticosteroids or immunosuppressive drugs were excluded from the study. Allergic rhinitis (AR) patients with nasal polyps were also excluded. Any patient refuses to be included in the study was excluded. The included subjects were divided into three groups as follows: Group I included 28 Egyptian patients receiving sublingual immunotherapy, Group II included 30 Egyptian patients receiving subcutaneous immunotherapy and Group III included 25 French patients receiving sublingual immunotherapy in the allergy unit, chest department, Faculty of Medicine, Limoges University. Egyptian patients were randomly selected to be included in two different groups, as both subcutaneous and sublingual immunotherapy are approved in Egypt, while only sublingual immunotherapy is approved in France (Group III).

Laboratory tests for diagnosis and follow-up

Skin prick test:

All Egyptian patients were subjected to a skin prick test using different homemade Coca's extracted allergens. Extracts were prepared as an aqueous glycerinated solution as described previously using the weight/volume unit [9, 10]. The allergens tested were date palm pollens, house dust mites, tobacco, mixed fungi, cotton, wool and Rice straw. Reading and interpretations of the skin prick test were performed and interpreted as described previously [10, 11]. The skin prick test was not included in the diagnostic protocol in French patients.

Detection of serum levels of total and specific IgE:

Total serum IgE levels were measured before starting immunotherapy and 6 months later in all patients by enzyme linked immunosorbent assay (ELISA) (Padtan Elm, Iran) according to manufacture instruction. Specific serum IgE levels were detected in all patients before immunotherapy, while only Egyptian patients were investigated for specific IgE levels after 6 months of treatment as specific serum IgE is not included in the follow up protocols in Limoges Faculty of Medicine. The specific IgE levels were detected by ELISA technique according to manufacture instruction (R-Biopharm AG, An der neuen Bergstrabe, Germany)

Allergen immunotherapy:

Subcutaneous immunotherapy used with Egyptian patients:

Subcutaneous immunotherapy (SCIT) was divided into two phases: the build-up phase and the maintenance phase. During the build-up phase five increasing concentrations of the allergens were administered (1/10000 W/V twice a week for 10 doses, 1/1000 W/V twice a week for 6 doses, 1/500 W/V twice a week for 6 doses, 1/250 W/V twice a week for 6 doses, 1/125 W/V weekly) (total duration 17-18 weeks), followed by the maintenance phase (conc. 1/125 W/V) every week until the end of the treatment course [10, 11].

Sublingual immunotherapy (SLIT):

Sublingual immunotherapy dosage used with Egyptian patients:

All allergen extracts were prepared using 50% glycerin in 20 ml simple bottles with droppers. Extracts were administered in the morning as sublingual drops with an empty stomach, and the drops were kept under the tongue for two minutes and then swallowed. Sublingual immunotherapy was divided into 2 phases: the build-up phase and the maintenance phase. During the build-up phase, three increasing concentrations of the allergens were administered (1/200 W/V for 1 month, 1/100 W/V for 1 month and 1/50 W/V for 1 month), and the doses administered of each concentration were as follows: 3 drops daily for 10 days, followed by 5 drops daily for 10 days and then 7 drops daily for 10 days. The maintenance phase was conducted with a concentration of 1/50 W/V until the end of the treatment course as follows: 7 drops day after day for a month then 2 days a week for a month then one day a week until the end of maintenance phase [10, 11].

-Sublingual immunotherapy used with French patients:

Staloral® (Stallergenes Greer, Australia) is used for immunotherapy and is a liquid solution with a dosage pump. Sublingual immunotherapy was divided into 2 phases; the build-up phase and the maintenance phase. During the build-up phase, the patient administered daily increasing doses of 1 to 10 presses of 10 IR/mL solutions from days 1 to 6 and 1 to 8 presses of 300 IR/mL solutions from day 7 to 11 (Table 1 supplementary file). During the maintenance dose, the patient took the allergen (8 presses of 300 IR/mL) once daily for one month then day after day until the end of maintenance phase.

Patient reassessment:

Patients were reassessed by symptoms, frequency of attacks, and total and specific IgE after 6 months of immunotherapy.

Statistical Analysis:

The collected data were summarized as the mean ± SD and range for quantitative data while frequency and percentage were used for qualitative data. Comparisons between the different study groups were carried out using the test of proportion (Z-test) to compare two proportions, and the Chi-square test and the Fisher exact test (FET) to compare more than two proportions as appropriate. Differences between two groups of nonparametric quantitative data were carried out using the Mann−Whitney test and the Wilcoxon signed rank test as appropriate. One-way analysis of variance (ANOVA; F) and the Kruskal−Wallis test were used to compare more than two groups regarding quantitative parametric and nonparametric data, respectively. The post hoc test using the Bonferroni method was used to detect differences in pairs.

Statistical significance was accepted at a p value <0.05 (S). A p value <0.001 was considered highly significant, while a p value <0.05 was considered significant. All statistical analyses were carried out in STATA/SE version 11.2 for Windows (STATA Corporation, College Station, Texas).

RESULTS

Demographic data of the studied groups

No significant differences were detected between the tested groups regarding age, sex, and family history of allergy (**Table 1)**.

Risk factors precipitating allergy in Egyptian patients

Overall, the most important precipitating factor of allergies was smoking (98.2%) followed by fumes (77.5%) (**Figure 1)**.

Total immunoglobulin E serum levels in the study groups before and after treatment

There was a significant decrease in total IgE levels in Egyptian patients receiving sublingual immunotherapy (p<0.001); on the other hand, there was no significant change in the levels in Egyptian patients receiving subcutaneous immunotherapy. Additionally, French patients (group III) had significantly higher levels of serum total IgE than Egyptian patients in both groups (p<0.05) (Table 2).

Table 1: Demographic data and family history of tested groups

Personal data		**Group I Egyptian patients receiving sublingual immunotherapy (no=28)**	**Group II Egyptian patients receiving subcutaneous immunotherapy (no=30)**	**Group III French patients receiving sublingual immunotherapy (no=25)**	**p value**
Age	Mean ±SD; (range)	25.03±17.52; (5-65)	29.17±9.64; (15-45)	20.48±10.75; (8-52)	0.051
Sex	Female no.(%) Male no. (%)	18 (64.29) 10 (35.71)	19 (63.33) 11 (36.67)	15 (60.0 10 (40.0)	0.99
Family history of allergy	Yes (%)	15 (53.57)	15 (50.0)	12 (48.0)	0.92

SD: Standard Deviation

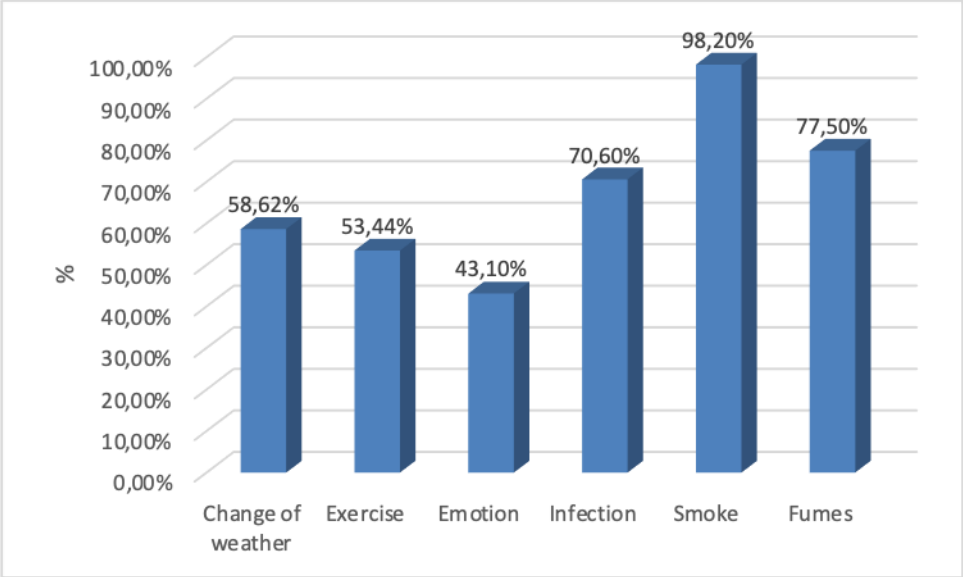

Fig. 1: Precipitating factors for allergic rhinitis in Egyptian patients.

Table 2: Comparisons of total IgE before and after treatment between the study groups

Total IgE	**Mean ± SD; (range)**			**p1**	**p2**	**p3**	**p4**
	Group I Egyptian patients receiving sublingual immunotherapy (no=28)	**Group II Egyptian patients receiving subcutaneous immunotherapy (no=30)**	**Group III French patients receiving sublingual immunotherapy (no=25)**				
Before immunotherapy	**298.02±171.97; (65-628.4)**	**164.52±145.53; (8.5-509.8)**	**721.33±990.67; (13-3475)**	**0.002***	0.64	**0.008***	**0.003***
After immunotherapy	**83.74±79.67; (22-320)**	**113.78±83.99; (8-260.8)**	**NA**	0.14	-	-	-
p	**0.000****	0.11	-				

SD: Standard Deviation, (HS): Significant p-value, ****:** Highly Significant p-value, p1: p value between Group I vs. Group II, p2: p value between Group I and Group III, p3: p value between Group II and Group III, p4: p value between Group I, Group II and. Group III, NA: non-applicable.

By analysing data according to different allergic manifestations (conjunctivitis, asthma and allergic rhinitis) before immunotherapy, a significant higher total IgE levels in French patients than Egyptian patients was detected. Uunexpectedly, we detected significant differences as regard total IgE serum levels in Egyptian patients with different allergic manifestations between group I and II (Table 3).

Specific immunoglobulin E serum levels (IU/ml) in the study group

In group I (Egyptian receiving SLIT), a significant decrease in specific IgE serum levels against all tested allergens after treatment was observed ($p < 0.01$) (Figure 2), while in group II (Egyptian receiving SCIT), specific IgE serum levels to different allergens were significantly decreased ($p < 0.05$), except for wool, cotton, and Aspergillus fungi (Figure3).

As the protocol used for diagnosis and treatment in French patients investigates only specific IgE serum levels before treatment, the data acquired are presented in Table 4.

Table 3: Total immunoglobulin E levels (IU/ml) in patients with and without different allergic manifestations before treatment in the study groups.

Clinical manifestation	Total IgE						p1	p2	p3	p4
	Group I Egyptian patients receiving sublingual immunotherapy (no=28)		Group II Egyptian patients receiving subcutaneous immunotherapy (no=30)		Group III French patients receiving sublingual immunotherapy (no=25)					
	No.	Mean ±SD; (range)	No.	Mean ±SD; (range	No.	Mean ±SD; (range				
Conjunctivitis	15	289.27±164.92; (90-601)	21	166.4±146.17; (24.7-509.8)	15	826.8±1165.59; (13-3475)	**0.018***	0.60	0.06	**0.04***
Asthma	23	313.46±183.78; (65-628.4)	22	147.58±115.34; (17.5-426.7)	8	1340.12±1318.2; (106-3475)	**0.002***	**0.009***	**0.001***	**0.000****
Allergic rhinitis	26	285.94±170.57; (65-628.4)	28	156.2±147.07; (8.5-509.8)	23	770.27±1019; (13-3475)	**0.002***	0.40	**0.004***	**0.001***

SD: Standard Deviation, (HS): Significant p-value, ****:** Highly Significant p-value, p1: p value between Group I vs. Group II, p2: p value between Group I and Group III, p3: p value between Group II and Group III, p4: p value between Group I, Group II and. Group III

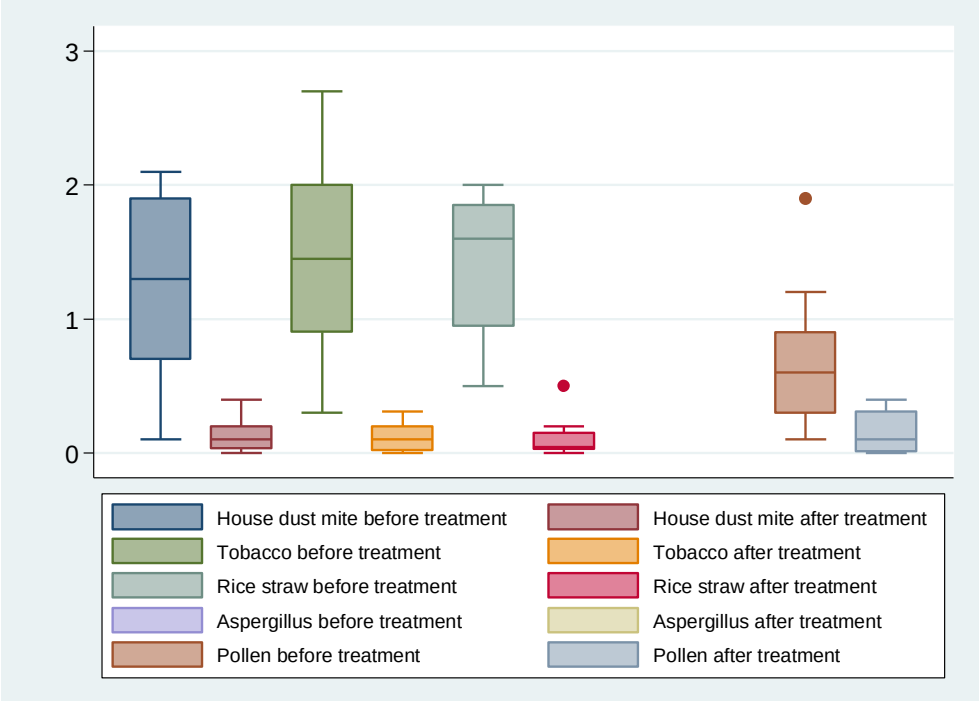

Fig. 2: Specific IgE to different allergens before and after treatment in Egyptian patients who received sublingual immunotherapy

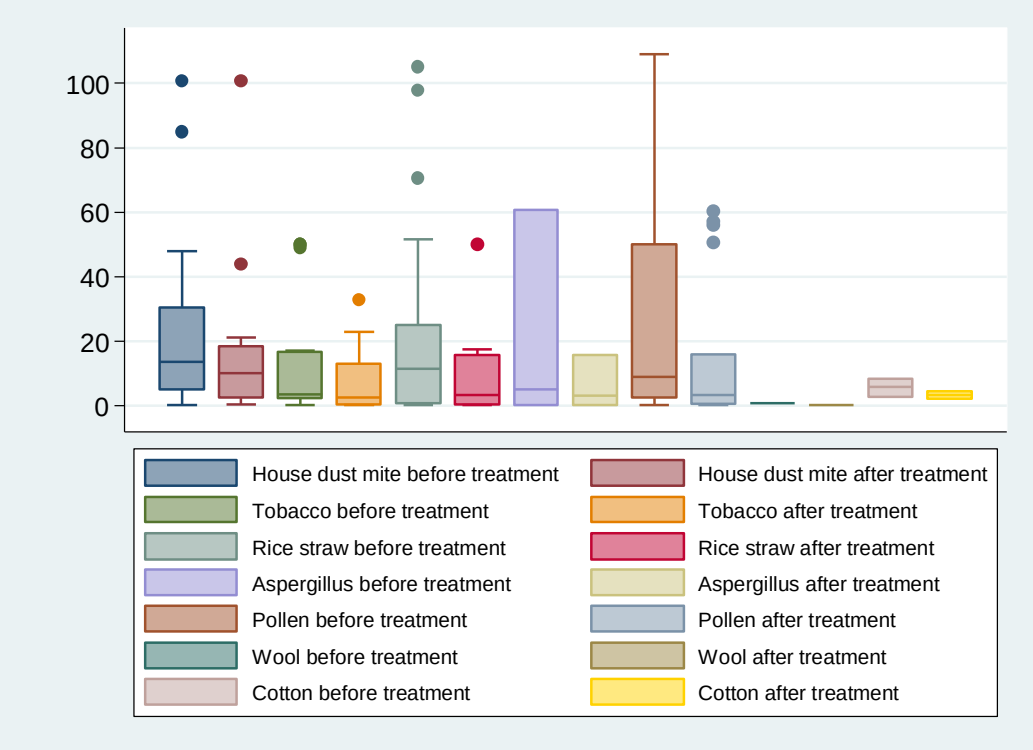

Fig. 3: Specific IgE to different allergens before and after treatment in Egyptian patients who received subcutaneous immunotherapy

Table 4: Specific IgE (Mites) in the studied French allergic rhinitis patients.

Allergen	Mean ± SD; (range)
Mites (D. pteronyssinus) (no.=21)	19.33±34.33; (0.1-105)
Mites (D. farina) (no.=21)	18.59±30.94; (0.1-101)
Grass specific IgE (no.=20)	37.08±42.92; (1.6-127)

The effect of immunotherapy on allergic manifestations after treatment in the study groups.

The frequency of allergic attacks/week was significantly decreased in groups I (from 4.37±2.75 to 1.78±1.05, P= 0.000) and II (from 5.4±4.09 to 2.73±1.48, P= 0.000) after treatment.

Analysis of the symptoms of Egyptian patients before and after treatment revealed that all symptoms were significantly improved in both groups of Egyptian patients (P <0.05), but it seems that the sublingual protocol is significantly superior to the subcutaneous protocol in improving nasal obstruction and discharge (P<0.05) (Table 5).

To evaluate the efficiency of both immunotherapy protocols and homemade immunotherapy Coca's extract used in Egypt, we compared the decrease in the number of patients suffering from allergic manifestations in Egyptian patients (groups I and II) with French patients (group III) during the 6-month duration of immunotherapy.

Our results revealed no change in the number of French patients suffering from conjunctivitis, asthma and allergic rhinitis, while there was a significant decrease in the number of those receiving subcutaneous immunotherapy (group II) (P <0.001). Additionally, Egyptian patients receiving sublingual immunotherapy (group I) showed a nonsignificant decreased number (Table 6).

No serious adverse effects were reported during the study period (such as laryngeal or oropharyngeal edema and anaphylactic shock).

Table 5: Allergic symptoms/week before and after treatment among the studied Egyptian patients

	Symptoms		Mean ± SD; (range)n		P value
			Group I Egyptian patients receiving sublingual immunotherapy (no=28)	**Group II Egyptian patients receiving subcutaneous immunotherapy (no=30)**	
Eye symptoms	Lacrimation	Before treatment	1.57±1.13; (1-4)7	1.5±0.53; (1-2)10	0.57
		After treatment	0.71±1.11; (0-3)	0.4±0.7; (0-2)	0.56
	P value		**0.01***	**0.004***	
	Eye congestion	Before treatment	1.77±1.23; (1-5)13	1.75±0.68; (1-3)16	0.50
		After treatment	0.61±1.12; (0-4)	0.62±0.72; (0-2)	0.55
	P value		**0.001***	**0.000 ****	
Nasal symptoms	Sinusitis	Before treatment	2.5±0.89; (1-4)16	2 ±0.95; (1-4)12	0.14
		After treatment	1.19±0.75; (0-3)	1.33±1.23; (0-4)	0.98
	P value		**0.000****	**0.009***	
	Itching	Before treatment	1.54±0.82; (1-3)11	1.61±0.87; (1-3)13	0.87
		After treatment	0.36±0.67; (0-2)	0.77±0.93; (0-3)	0.21
	P value		**0.002***	**0.006***	
	Obstruction	Before treatment	3.05±0.82; (2-5)20	3.16±0.83; (2-4)19	0.58
		After treatment	1.4±0.68; (1-3)	2±1; (1-4)	**0.04***
	P value		**0.000****	**0.000****	
	Discharge	Before treatment	3.24±0.94; (2-5)21	3.38±1.07; (1-5)21	0.56
		After treatment	1.52±0.81; (1-4)	2.33±1.32; (1-5)	**0.03***
	P value		**0.000****	**0.000****	
	Sneezing	Before treatment	3±0.97; (1-4)16	3.33±0.77; (2-4)18	0.32
		After treatment	1.69±1.14; (0-4)	1.89±1.18; (1-4)	0.68
	P value		**0.000****	**0.000****	
Respiratory symptoms	Expectoration	Before treatment	2.78±1.11; (1-5)18	3.37±0.76; (2-5)19	0.08
		After treatment	1.39±0.92; (0-3)	1.89±0.99;(1-4)	0.17
	P value		**0.000****	**0.000****	
	Wheezes	Before treatment	1.57±0.79; (1-3)7	1.67±0.65; (1-3)12	0.67
		After treatment	0.86±0.69; (0-2)	0.83±0.83; (0-2)	0.89
	P value		**0.02***	**0.003***	
	Cough	Before treatment	3±0.79; (2-4)20	3.1±0.79; (2-4)20	0.69
		After treatment	1.4±0.75; (0-3)	1.8±0.95; (1-4)	0.19
	P value		**0.000****	**0.000****	
	Dyspnoea	Before treatment	1.2±0.45; (1-2)5	1.77±1.01; (1-4)13	0.26
		After treatment	0.4±0.55; (0-1)	0.61±0.51; (0-1)	0.42
	P value		**0.04***	**0.002***	

SD: Standard Deviation, *****: significant difference (P <0.05), ******: Highly Significant difference (P<0.001)

Table 6: Number of patients expressing allergic manifestations before and after treatment in the study groups.

Improvement		**Group I Egyptian patients receiving sublingual immunotherapy (no=28)**		**Group II Egyptian patients receiving subcutaneous immunotherapy (no=30)**		**Group III French patients receiving sublingual immunotherapy (no=25)**	
		No.	**%**	**No.**	**%**	**No.**	**%**
Conjunctivitis	Before treatment	15/15	100.0	21/21	100.0	15/15	100.0
	After treatment	14/15	93.33	17/21	80.95	15/15	100.0
P value		0.317		**0.046***		1	
Asthma	Before treatment	23/23	100.0	22/22	100.0	8/8	100.0
	After treatment	20/23	86.96	18/22	81.82	8/8	100.0
P value		0.083		**0.046***		1	
Allergic rhinitis	Before treatment	26/26	100.0	24/24	100.0	23/23	100.0
	After treatment	24/26	92.31	17/24	70.83	23/23	100.0
P value		0.157		**0.008***		1	

*****: significant difference (P<0.05)

DISCUSSION

Subcutaneous immunotherapy is reported as an effective treatment option for allergies, but it requires multiple injections and frequent clinic visits, which increases the economic burden on healthcare facilities, and it is inconvenient for patients as well as their caregivers. In contrast, SLIT can be taken at home except for the first dose, which should be administered under medical supervision in the allergy unit or clinic [1]. SLIT is also reported to be safer than SCIT [4, 5]. Previous studies as well as patient surveys reported that patients have a very strong preference for SLIT over SCIT, as they can be easily administered at home with a well-known safety profile. For these reasons, it was considered a favourable treatment option in children receiving allergen immunotherapy [1, 12, 13].

The present study showed that smoking was the most important precipitating risk factor for AR, as 98.2% of allergic patients were smokers. This disagreed with Hisinger-Mölkänen et al. [14], who reported that the prevalence of allergic rhinitis was the same among nonsmokers (27.1%) compared to smokers (26.6%), with a total number of 3488 individuals. Our results revealed that 70.6% of Egyptian AR patients suffered from infection as a precipitating factor. Our results agreed with Refaat et al.[15], who isolated nasal *S. aureus* from 80% of allergic patients versus 25% of healthy individuals ($p<0.01$). Edwards et al.[16] reported that viral respiratory tract infections are associated with asthma precipitation in early life and asthma exacerbations in older children and adults.

Regarding total IgE levels in the present study, our work revealed a significant decrease in total IgE levels in Egyptian patients receiving SLIT after 6 months of treatment; on the other hand, there was no significant change in the levels in Egyptian patients receiving SCIT. French patients (group III) had significantly higher levels of serum total IgE than Egyptian patients in both groups before starting immunotherapy ($p<0.05$). In agreement with the current results, Sayed et al.[17] conducted a prospective comparative study on 100 patients suffering from IgE-mediated allergic conjunctivitis and reported a significant reduction in total serum IgE levels in all patients following immunotherapy when compared to baseline ($p =0.00$), with no significant differences between SLIT and SCIT methods. Measuring total IgE serum levels could be a relatively crude method for detecting allergic disorders, although normal serum levels of total IgE will not exclude allergic disease [18]. The significant difference in total IgE serum levels between Egyptian and French patients may be explained by differences in the environmental conditions, degree and frequency of allergen exposure or the different degrees of sensitization to an allergen. Additionally, a low amount of IgE in the blood may be explained by a scenario proposed in which IgE binds to nearby allergy cells after its production, bypassing the need to travel through the blood in any substantial numbers. There may be no high level of IgE to a particular allergen in the blood, but it could be present in high amounts on nasal allergy cells causing severe nasal allergy symptoms in the presence of that allergen [19].

When analysing our data according to different allergic manifestations (conjunctivitis, asthma, and allergic rhinitis) before immunotherapy, we detected significantly higher total IgE levels in French patients than in Egyptian patients. Unexpectedly, we detected significant differences in total IgE serum levels in Egyptian patients with different allergic manifestations between those receiving SLIT and SCIT. As we randomly selected the patients in each group, we decided to analyse the results before and after immunotherapy in each group to focus on the degree of improvement.

When investigating the specific IgE levels in the study groups, we detected a significant decrease in specific IgE serum levels against all tested allergens in group I after treatment ($p <0.01$). Additionally, in group II, specific IgE serum levels to different allergens were significantly decreased ($p <0.05$), except for wool, cotton and fungi. These results may favour SLIT over SCIT in addition to its safety. These results are in agreement with Gomez et al.[20], who studied patients with rhino conjunctivitis and bronchial asthma who underwent SLIT for 1-2 years and found that serum-specific IgE was significantly decreased at the end of the treatment period. On the other hand, Atta et al.[10] reported no difference in the mean levels of specific IgE between pretreatment levels and 6 months after SLIT and SCIT treatments of respiratory allergic patients. However, Moreno et al.[21] reported a significant elevation in serum-specific IgE levels in allergic asthma patients after one year of SCIT. Aasbjerg et al.[22] reported that SLIT tablets induced an initial 3-fold increase in specific IgE compared with SCIT after 3 months of treatment. One possible explanation for high IgE levels is exposure to relatively high doses of allergens during the initiation phase of immunotherapy; another explanation is the different treatment protocols applied.

In our work, analysis of symptoms of Egyptian patients as performed before and after treatment revealed that all symptoms (lacrimation, eye congestion, sinusitis, nasal itching, nasal obstruction, nasal discharge, sneezing expectoration, wheezes, cough and dyspnoea) were significantly improved in both groups of Egyptian patients ($p <0.05$), but it seems that the sublingual protocol is significantly superior to the subcutaneous protocol in improving nasal obstruction and discharge ($p<0.05$). Additionally, the frequency of

allergic attacks/week was significantly decreased in both groups of Egyptian patients ($p<0.001$), and the frequency of allergic attacks/week was significantly lower in patients receiving SLIT than in those receiving SCIT after 6 months of immunotherapy ($p<0.05$). The present results are consistent with Atta et al.[10], who detected a highly significant reduction in the mean symptoms and mean medication scores after 6 months in both groups of patients (SLIT and SCIT). Previous studies have reported that SCIT and SLIT can provide significant symptom relief, reduce the need for medications in AR patients and improve the quality of life of patients [23- 26].

Comparisons between the efficacies of SCIT versus SLIT in the literature are controversial. Chelladurai et al.[27] showed few differences in treatment effectiveness when comparing SCIT with SLIT; they provide low-grade evidence to support SCIT over SLIT in the reduction of asthma symptoms and moderate-grade evidence in the reduction of allergic rhino conjunctivitis. A meta-analysis by Nelson et al.[28] reported that SCIT was superior to SLIT, which is slightly different from our results.

To evaluate the efficiency of both immunotherapy protocols and homemade immunotherapy Coca's extract used in Egypt, we compared the decrease in the number of patients suffering from allergic manifestations in Egyptian patients (groups I and II) with French patients (group III) during the 6-month duration of immunotherapy. Although it is a crude method for evaluation, this is the only parameter we have to compare, as the French SLIT protocol did not include the investigation of post-treatment total and specific IgE serum levels for follow-up. Our results revealed no change in the number of French patients suffering from allergic manifestations, while there was a significant decrease in the number of those receiving SCIT (group II) ($p <0.001$). Additionally, Egyptian patients receiving SLIT (group I) decreased in number, although non-significantly. It seems that the SCIT protocol has more rapid action than SLIT. Similarly, the SLIT protocol and product have more rapid action than those used in France, although non-significant. The international guidelines recommended that both routes of administration (SLIT and SCIT) should be continued for a minimum of 3 years [29], which can explain the unchanged number of French patients due to the short duration of treatment.

In general, although both SCIT and SLIT are effective, on the grounds of safety and tolerability, SLIT is preferable to SCIT. SCIT could be associated with anaphylaxis and necessitate close supervision. While SLIT has few systemic side effects, anaphylaxis is extremely rare, and SLIT can be safely self-administered [30].

CONCLUSIONS

In conclusion, SLIT with Coca's extracted allergen could be used in low economic countries, especially those not covered with medical insurance. During preparation, sterility tests should be applied all the times with strict infection control measures. Standardization of the allergen in the coca solution should be performed when possible.

Declarations

Ethics approval and consent to participate

The study was approved by Fayoum University, Faculty of Medicine Ethical Committee under the number **D81**. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects. All authors have read and agreed the manuscript.

Competing interests

The authors declare that they have no competing interests.

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