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Assessment of Efficacy of Sublingual Immunotherapy Compared to the Standard Treatment in Children with Bronchial Asthma in Zagazig University Hospitals

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ABSTRACT

Background: Sublingual allergy immunotherapy (AIT) has been proven in meta-analyses to reduce both symptoms and medication use in asthma. **Objective:** To assess safety and efficacy of sublingual immunotherapy as add on treatment for 6 months on asthmatic children.

Patients and Methods: In a randomized controlled study, we did this study at Department of Pediatrics at Zagazig University Hospitals, during the period from May 2019 to October 2019. It included 60 children who have mild to moderate persistent asthma symptoms according to (GINA guide lines 2015) confirmed with skin prick test for positive allergen sensitivity. Sixty asthmatic children were categorized in two groups (30 children, each): Group A: received only the standard treatment of asthma, Group B: received specific sublingual immunotherapy (SLIT) with the standard treatment of asthma.

Results: After receiving SLIT treatment, total IgE was significantly lower than before treatment with improvement in pulmonary functional parameters in SLIT group. The SLIT group showed significant increase in control of asthma after six months of treatment with SLIT. There was a significant decrease in using medications after receiving SLIT group.

Conclusion: Clinical evidence supports the use of SLIT for the treatment of asthma in children. Reduces allergic asthma symptoms and the need for medication.

Keywords: Sublingual Immunotherapy, Bronchial Asthma.

INTRODUCTION

Adults and children alike bear a significant socioeconomic burden due to asthma, a chronic and diverse illness. According to some estimates, by 2025 there could be as many as 400 million individuals worldwide living with bronchial asthma[(1)]. Even though there are a variety of tests available, diagnosing allergic illness can be difficult, especially in young children. Many allergic illnesses require skin testing as part of the diagnosis process. Although these tests are most commonly used for diagnosing inhalant allergies, there is a growing trend to utilise them for other types of allergies, including those to food, venom, occupational agents, and medications. There is still a strong reliance on skin prick tests (SPTs) and intradermal testing as the gold standard for diagnosing IgE-mediated (type I) allergies and bronchial asthma. They are extensively used in outpatient clinics because they are simple to administer, cheap, and provide results rapidly[(2)].

However, current pharmaceutical therapy options successfully manage clinical symptoms and the underlying inflammatory process but have little impact on the disease progression since they do not alter the dysregulated immune response[(1)].

In both allergic rhinitis and allergic asthma, allergy immunotherapy (AIT) has been demonstrated in meta-analyses to reduce symptoms and medication use when given sublingually (sublingual immunotherapy [SLIT]) or subcutaneously (subcutaneous immunotherapy [SCIT]), as an added bonus, it changes the immunologic abnormalities that lead to allergy sensitization, making the reaction to the administered allergen more similar to that seen in people who aren't allergic[(3)].

Therefore, for sensitised asthmatic patients in steps 3 and 4 who are not under control, House Dust Mite (HDM) SLIT is proposed in the most recent version of the Global Initiative on Asthma (GINA) recommendations, combined with a high degree of lung function preservation (Forced Expiratory volume in the First Second - FEV1 >70% of expected) and the presence of allergic rhinitis[(4)]. The efficacy, cost-effectiveness, and safety of AIT in asthma were recently demonstrated in a systematic review and meta-analysis by the European Academy of Allergy and Clinical Immunology (EAACI)[(5)].

Evidence-based practical instructions on how to properly employ AIT in asthma were also published by the European Academy of Allergy and Clinical Immunology (EAACI) in their latest guidelines on allergen immunotherapy for allergic asthma [(6)].

STUDY OBJECTIVES

This study's purposes are to assess safety as well as efficacy of sublingual immunotherapy as add on treatment for 6 months on asthmatic children, in addition to evaluate the prevalence of sensitization to common allergens using skin prick test. Also, it aims to detect the impact of sublingual immunotherapy on the improvement of pulmonary function, clinical symptoms, and decrease of medication usage.

PATIENTS AND METHODS

Sixty children at Zagazig University Hospitals, Department of Pediatrics, Faculty of Medicine, in this nonrandomized controlled trial study were involved.

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Ethical consent:

Research Ethics Council at Zagazig University approved the study (ZU-IRB#8697) as long as all parents of participants provided informed consent forms. Ethics guidelines for human experimentation were adhered to by the World Medical Association's Helsinki Declaration.

Sixty asthmatic children were categorized into two groups (30 children, each): Group A: received only the standard treatment of asthma and Group B: received specific sublingual immunotherapy with the standard treatment of asthma.

Inclusion Criteria: As reported by GINA in defining asthma, 60 children aged 5 to 12 years old with recurrent symptoms of mild to moderate asthma were included in the study[7]. These children were confirmed with skin prick test for positive allergen sensitivity.

Exclusion criteria: Subjects were not considered for this study if they exhibited any of the following: Severe uncontrolled asthma. Co-existent autoimmune disease. Children with combined morbidity including skin lesions or lung diseases other than asthma. Children with any associated chronic disease such as cardiac, renal, hepatic or metabolic disease**.** Children below 5 years. Children on oral steroids (should be stopped 48 hours before skin test, 72 hours if dexamethasone), and children previously received allergen immunotherapy.

All studied groups underwent the following:

1. History taking: Full history was collected and protocols of treatment of asthma, as well as family history.

2. Clinical examination: General examinations, vital signs, in addition to anthropometric measures; weight, height, BMI (BMI= weight/height m^2) was computed from these data as weight in kilo grams divided by the square of height in meters (kg/m^2) and grouped by age and gender. Patients with BMI above 95^{th} percentile is defined as obese (BMI >30), patients with a BMI of 25-30 are considered overweight, but those with a BMI of 75-95 are considered obese, waist circumference, blood pressure measurement.

3. Chest X-ray (CXR): Posteroanterior CXR was done to all subjects.

4. Laboratory investigations: (1) Routine complete blood count, eosinophilia was considered if > 6% (Normal range 0-6%). (2) C-Reactive Protein. (3) Liver function tests. (4) Kidney function tests. (5) Skin Prick test. (6) Total IgE: Total serum IgE levels were measured using commercially available kits (RIDASCREEN Total IgE kit) from Clinilab. (7) Pulmonary function test: Asthmatic patients aged 5 and above underwent pulmonary function testing utilizing forced spirometry by D-97024 Hochberg, Germany, which is a programme that offers a rapid and reliable evaluation of the respiratory resistance based on a tidal breathing study; with assessment of Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (EFV1), PEF, FVC%, FCV1% and PEF%.

Sublingual allergen immunotherapy: The same allergens constituents used in the skin prick test, which were prepared in Allergy and Immunology unit of Microbiology Department, Faculty of Medicine in Zagazig University in concentration 1/10 V/W on glycerin coca solution 5%.

Schedule of administration: A course of 3 years administration was adopted as the following schedule:

Dose adjustment: Each patient's treatment regimen was customized based on their individual clinical responses, the duration of time between doses, the presence of seasonal allergen exposure, and the occurrence of local or systemic reactions following the preceding dose. We judged the ideal dose to be a patient-specific dose that produced a high clinical efficacy without significant side effects, and we acknowledged that for certain individuals, not reaching the recommended top maintenance dose was acceptable.

If patient missed dose:

Initiation phase: - If the break will be less than seven days, the routine shouldn't be altered. - If there is a delay of 7-15 days, reduce the dose by one drop for every five days. - If the interruption is >15 days, contact physician for reassessment either to restart from the starting dose or repeat the skin test.

Maintenance phase: - 2-4 weeks reinstituted with half of the dose last given. - 4 weeks, contact physician for reassessment either to restart from the starting dose or repeat the skin test.

Patient's assessment: A diary card was used to keep track of each patient's symptoms, reactions to rescue medications, and any other noteworthy events. During the baseline period and for three weeks prior to each visit, patients were asked to make a daily diary of their symptoms and the rescue medications they used. Asthma symptoms during the night and during the day were rated on a four-point scale. The diary card was used to record the patient's response to treatment pre-treatment, 3-months, and 6-months[8].

Childhood asthma control test: We administered the Asthma Control Test Child's Score to kids aged 4-11 years old. At age 19, a child's asthma symptoms may not be under control. Possible very poor asthma control, per 12[8].

Statistical analysis:

In order to analyze the data acquired, Statistical Package of Social Sciences (SPSS) version 20 was used to execute it on a computer. In order to convey the

findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t-test (t) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X^2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Table (**1**) shows that when comparing the groups based on age, weight, height, gender, and place of residence, researchers found no statistically significant differences.

Table (1): Demographics of the studied groups

Variable	Experimental group (n=30)		Control group (n=30)		t test	P value
Age: (years) Mean ± SD Median (Range)	7.46 ± 1.70 5 – 12		7.63 ± 1.62 5 - 12		-0.279	0.781 (NS)
Weight: Mean ± SD Median (Range)	27.7 ± 6.77 20 - 59		28.4 ± 5.15 20 - 40		-0.431	0.668 (NS)
Height: Mean ± SD Median (Range)	123.1 ± 10.7 103 - 145		124.9 ± 8.30 110 - 140		-0.724	0.472 (NS)
	No.	**%**	**No.**	**%**	**χ^2**	**P**
Gender: Male Female	 14 16	 46.7 53.3	 16 14	 46.7 53.3	0.267	0.606 (NS)
Residence: Urban: Rural:	 15 15	 50 50	 14 16	 46.7 53.3	0.067	0.796 (NS)

The severity of asthma was not significantly different between the groups. It was noticed that moderate persistent asthma was lower among the control group when compared to the experimental one (63.3% versus 66.7% respectively) **(Figure 1)**.

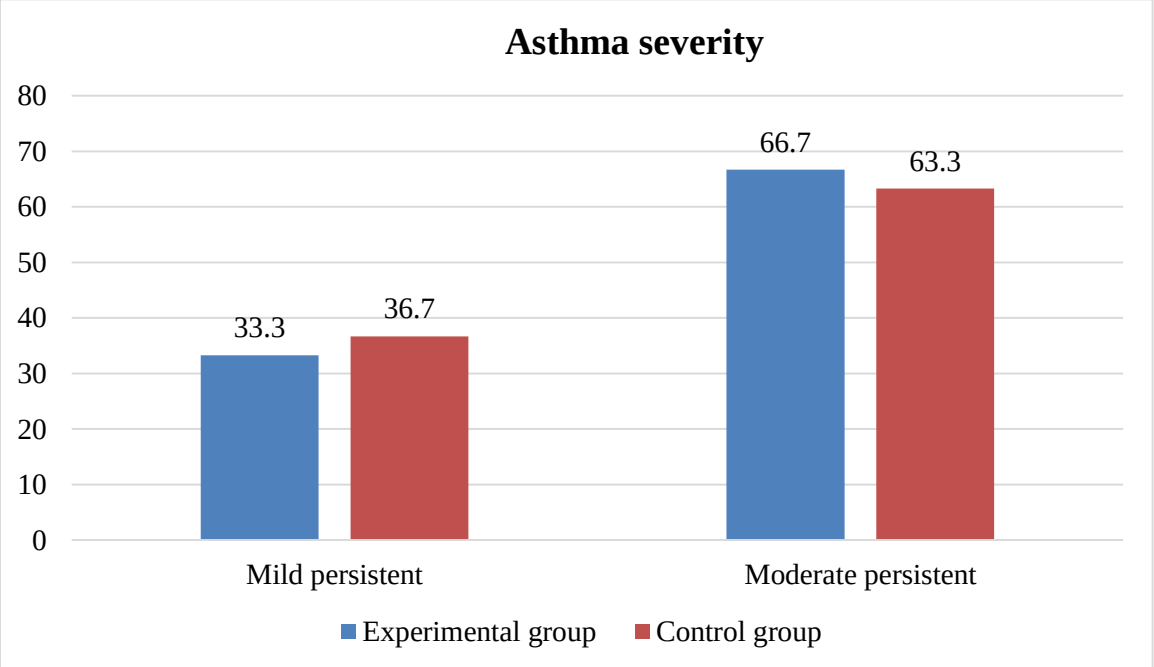

Figure (1): Severity of asthma among the studied groups

Table (**2**) shows that no statistically significant difference in pretreatment IgE levels was seen between the groups. IgE level was found to be significantly lower after receiving sub-lingual immunotherapy when compared to its level before receiving it (391.4 versus 423.7 respectively).

Table (2): Comparison of IgE before and after six months among the studied groups:

Variable	Experimental group (n=30)	Control Group (n=30)	MW Test	P value
IgE: (before)				
Mean ± SD	423.7 ± 95.1	324.7 ± 71.4	-0.155	0.877
Median	200	110.6		(NS)
Range	13.4 - 2868	54.4 - 1600		
IgE: (after)				
Mean ± SD	391.4 ± 81.4	---	---	---
Median	157.5			
Range	18.9 - 3301			
p-value: #	**0.001 (S)**	---		

Table (**3**) shows that there was no statistically significant change in FEV1 or FEV1 percent between the control and treatment groups. However, FEV1 was significantly higher among the experimental group when compared to control one after receiving treatment (97.6 versus 82.8 respectively). Also, there was significant difference in each group separately among before and after receiving treatment (p=0.02). And, FEV1% was found to be significantly higher after treatment than before it in the experimental group (103.3 versus 95.2 respectively).

Table (3): Comparison of FEV1 before, after 3 months and after six months among the studied groups:

Variable	Experimental group (n=30)	Control group (n=30)	t-test	P value
FEV1: (before)				
Mean ± SD	87.3 ± 11.4	83.7 ± 8.89	1.340	0.185
Range	51.6 – 112.3	66.6 – 105.3		(NS)
FEV1: (after 3)				
Mean ± SD	89.3 ± 9.25	83.7 ± 8.89	**2.337**	**0.02**
Range	55 – 103	66.6 – 105.3		**(S)**
FEV1: (after 6)				
Mean ± SD	97.6 ± 8.73	82.8 ± 10	**6.135**	**<0.001**
Range	75.5 – 113	49.1 – 105.4		**(HS)**
p-value: #	**<0.001 (S)**	0.497 (NS)		
FEV1*%: (before)				
Mean ± SD	95.2 ± 12.6	97.2 ± 13.2		0.541
Range	61.5 – 115.3	63.5 – 117.9	-0.614	(NS)
FEV1*%: (after3 m)				
Mean ± SD	101.4 ± 6.34	97.1 ± 13.1		0.110
Range	88 – 112.3	65.5 – 117.9	1.622	(NS)
FEV1*%: (after 6 m)				
Mean ± SD	103.3 ± 12.2	97.2 ± 12.1		0.058
Range	47.8 – 120	64.7 – 116.9	1.934	(NS)
p-value: #	**<0.001 (HS)**	0.856 (NS)		

***FEV1:** Forced Expiratory Volume in the First Second

Table (**4**) shows that after 3 and 6 months of therapy, the experimental group had considerably greater FVC than the control group. FVC significantly increased after treatment when compared to before it (98.3 versus 94.3) in experimental group, however the difference was non-significant in control group.

Table (4): Comparison of FVC before, after 3 months and after six months among the studied groups:

Variable	Experimental group (n=30)	Control group (n=30)	t-test	P value
FVC*: (before)				
Mean ± SD	94.3 ± 15.2	88.1 ± 10.1	1.861	0.069
Range	65.5 - 124	66 – 99.1		(NS)
FVC*: (after 3)				
Mean ± SD	94.1 ± 8.74	86.1 ± 8	**3.685**	**0.001**
Range	70.8 - 110	66 – 99.1		**(S)**
FVC*: (after 6)				
Mean ± SD	98.3 ± 8.25	85.9 ± 9	**5.558**	**<0.001**
Range	80.4 – 122.3	65.3 – 105.5		**(HS)**
p-value: #	**0.03 (S)**	0.868 (NS)		

***FVC:** Forced Vital Capacity

This table (**5**) shows that in pretreatment asthma tests, there was no statistically significant difference between the groups. However, the difference between them was significant after therapy. Controlled asthma test significantly increased after treatment than before it (83.3% versus 3.3%).

Table (5): Asthma control test before, after 3 months and after 6 months among the studied groups:

Variable	Experimental Group (n=30)		Control group (n=30)		χ^2	P
	No.	%	No.	%		
Asthma test before:						
Uncontrolled:	8	26.7	15	50		
Partial control:	21	70	15	50	4.130	0.127
Controlled:	1	3.3	0	0		(NS)
Asthma test after 3:						
Uncontrolled:	2	6.7	18	60		
Partial control:	19	63.3	12	40	**23.28**	**<0.001**
Controlled:	9	30	0	0		**(HS)**
Asthma test after 6:						
Uncontrolled:	0	0	10	33.3		
Partial control:	5	16.7	19	63.3	**40.32**	**<0.001**
Controlled:	25	83.3	1	3.3		**(HS)**
P-value:	**<0.001 (HS)**		0.083 (NS)			

This table (**6**) shows that medication use before, after, and between 3 and 6 months showed highly significant differences between the groups tested. Used medication significantly decreased after receiving therapy in the experimental group.

Table (6): Medication used before and after 6 months among the studied groups:

Variable	Experimental Group (n=30)		Control group (n=30)		χ^2	P
	No.	%	No.	%		
Medication before treatment:						
No:	17	56.7	12	40		
ICs:	24	80	20	66.7	6.771	0.0795
LK antagonist:	5	16.7	13	43.3		(NS)
LABA+ICs:	0	0	2	6.7		
Medication after 3 months:						
No:	15	50	0	0		
ICs:	13	43.3	19	63.3	**26.35**	**<0.001**
LK antagonist:	3	10	15	50		**(HS)**
LABA+ICs:	2	6.7	7	23.3		
Medication after 6 months:						
No:	12	40	0	0		
ICs:	7	23.3	29	96.7		
LK antagonist:	0	0	19	63.3	**43.18**	**<0.001**
LABA+ICs:	13	43.3	7	23.3		**(HS)**
P-value:	**<0.001 (HS)**		0.213 (NS)			

ICs: Inhaled corticosteroid

Majority of the experimental group didn't experience any side effects and only one patient develops a side effect in the form of vomiting **(Figure 2)**.

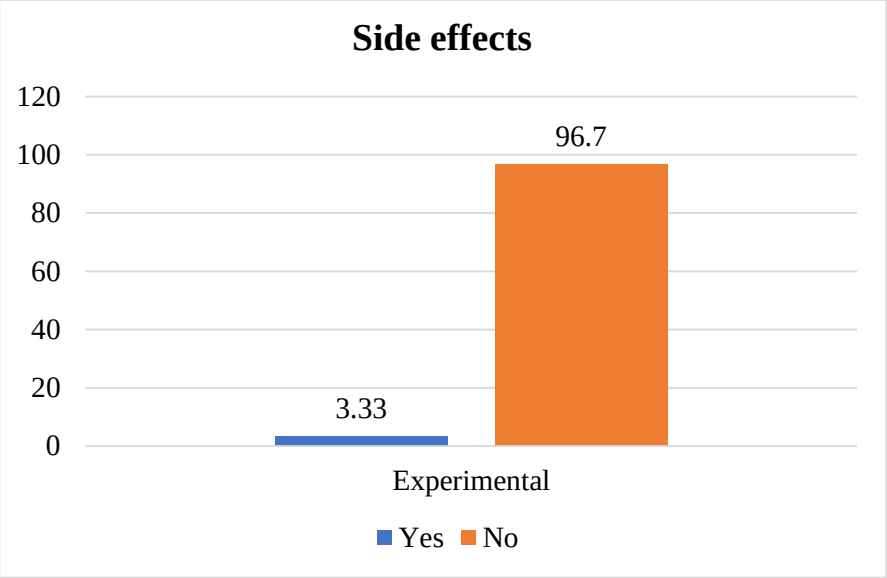

Figure (2): Frequency of side effects among the studied group

Table (**7**) shows that in the experimental group, there was no statistically significant difference between those with mild and moderate chronic asthma in terms of the number of positive pollens.

Table (7): Poly sensitization among the studied groups:

Variable	Mild persistent (n=10)		Moderate persistent (n=20)		χ^2	P
	No.	%	No.	%		
Experimental group:						
Less than 3 positive allergens	1	10	2	10		1.00
Equal to or more than 3 positive allergens:	9	90	18	90	0.00	(NS)
Variable	**Mild persistent (n=0)**		**Moderate persistent (n=30)**		**χ^2**	**P**
	No.	**%**	**No.**	**%**		
Control group:						
Less than 3 positive allergens	0	0	3	10		
Equal to or more than 3 positive allergens:	0	0	27	90	**NA**	**NA**

Table (**8**) shows that after three and six months, the experimental group had significantly fewer exacerbations than the control group. Also, among the experimental group the exacerbations were found to be reduced significantly after 6 months compared to after 3 months of treatment (6.7% versus 33.3% respectively).

Table (8): Exacerbations before, after 3 months and after 6 months among the studied groups:

Variable	Experimental Group (n=30)		Control group (n=30)		χ^2	P
	No	%	No	%		
exacerbation before treatment:						
No:	16	53.3	16	53.5	0.00	1.00
Yes:	14	46.7	14	46.7		(NS)
Exacerbation 3 months after:						
No:	20	66.7	10	33.3	**6.667**	**0.01**
Yes:	10	33.3	20	66.7		**(S)**
Exacerbation 6 months after:						
No:	28	93.3	10	33.3	**23.25**	**<0.001**
Yes:	2	6.7	20	66.7		**(HS)**
P-value:	**<0.001 (HS)**		**0.03 (S)**			

DISCUSSION

Airway remodelling can cause asthma to persist into adulthood, making it one of the most frequent chronic inflammatory illnesses in children. Asthma already affects an estimated 300 million people around the world, and it's expected that number will rise by another 100 million by 2025 [9].

This study was aimed to assess the efficacy and safety of sublingual immunotherapy as add on treatment for 6 months on asthmatic children, in addition to evaluate the prevalence of sensitization to common allergens using skin prick test. In addition, it aimed to detect the impact of SLIT on the improvement of pulmonary function, clinical symptoms and decrease of medication usage.

Overall, the results in the current study regarding demographic data showed that no significant differences were reported between the studied groups regarding age, weight, height, gender and residence. Similar results were reported by **Atta *et al.*** [10] and **Saporta** [8]. Regarding age, it was ranged between 5 to 12 years old in both groups. The similar range was detected by **Atta *et al.*** [10], while, by **Senna *et al.*** [11] was 5 to 16 years.

Regarding residence, nearly equal ratio was detected between patient from urban and rural areas in the current study. Evidence from several European, Canadian, and Australian researches suggest that children who are exposed to agricultural environments are less likely to develop asthma and atopy. **Hossny and colleagues** [12] found that urbanites, next those living in the suburbs, and finally those living in rural locations were the most likely to suffer from an allergy condition.

The mean weight of children in the current study was 27.7 Kg and 28.4 Kg in experimental and control groups, respectively. **Atta *et al.*** [10] reported that the mean weight was 21.69 kg in group 1 (SLIT), with no significant difference between the studied groups.

The high IgE levels within children in the current study might be conducted to many causes. First, all subjects in the current study were using inhaled corticosteroid (ICS). Like IgA and IgG4, AIT causes an early increase in IgE during the up-dosing phase, which fades away throughout the maintenance phase[1].

Regarding functional pulmonary parameters after 6 months of treatment. FEV1, FEV1% and FVC were significantly improved after 6 months of SLIT (97.6 ± 8.73, 103.3 ± 12.2 and 98.3 ± 8.25, respectively). FEV1 was significantly improved in experimental group when compared to the group with standard treatment only after treatment (97.6 ± 8.73 and 82.8 ± 10, respectively), with high significant improvement in SLIT group than control one (87.3 and 97.6, before and after treatment respectively, P <0.001). Similar results were reported by **Stelmach *et al.*** [13] and **Lin *et al.*** [14]. In contrary, **Rodrigo and Neffen** [15] reported that the improvement in FEV1 had not been detected after SLIT.

The FEV1% was significantly improved in SLIT group only after the treatment (95.2 and 103.3, before and after treatment respectively, P <0.001). The FVC was significantly improved among SLIT group than the other group after treatment (98.3 ± 8.25 and 85.9 ± 9, respectively, P <0.001), with significant increase in SLIT group after the treatment (94.5 and 98.3, before and after treatment respectively, P= 0.002). It has been shown that SLIT had produced objective improvements in lung function tests in asthmatic subjects [16].

In the current study, all children were poly-sensitized to 3 or more allergens, with no significant correlation in both groups. In accordance, **Atta *et al.*** [10] showed that no significant correlation between severity of asthma and the multiplicity of allergen positivity. In a large cross-sectional multi-centres study in China, more than 90% of patients were sensitized to two or more allergens [17].

Nelson [3] a study found that patients who were sensitised to more than one allergen responded equally well to AIT with a single allergen compared to those who were mono sensitised. That may be the reason why children in the current study showed clinical improvement after SLIT within the first six months.

In the current study, the SLIT group showed significant increase in control of asthma after six months of SLIT treatment (P <0.001), while in group with standard asthma treatment non-significant difference was observed (P= 0.083). Similar results were reported [10].

Regarding using asthma medications in the current study, there was a significant decrease in using medications after receiving SLIT group (P <0.005), with a high significant difference between the studied groups group (P <0.001. Similar results were reported [5]. SLIT decreases use of both long-term control and quick relief medication and improves quality of life.

Regarding adverse events in the current study, only one case (3.33%) in SLIT group showed adverse effect; in form of mild vomiting and oropharyngeal irritation during the induction phase. In accordance, low adverse event was reported in Egypt (4.34%) by **Atta *et al.*** [10]. The incidence of adverse events in the SLIT groups vary widely from study to study, from as low as 5% [18].

Overall, both the severity of allergic asthma attacks and the amount of medicine needed to control them are reduced with SLIT. More than that, it alters the immunologic flaws that set the stage for allergy sensitivity. Clinically, this restoration of immunological balance shows itself in a decreased risk of asthma development and in sustained clinical improvement that can last for years after treatment has been stopped[3].

CONCLUSION

SLIT showed clinical efficacy in asthmatic children population. It has been shown to reduce the

symptoms and medication requirements for allergic asthma. These findings suggest that SLIT has obvious role in asthma management; by combining clinical outcomes and respiratory function.

Conflict of interest: The authors declare no conflict of interest.

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Authors' contribution: Authors contributed equally in the study.

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