Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 1.7, Oct. 2024, Supplement Issue

Manuscript ID: ZUMJ-2112-2436 (R1) **Doi: 10.21608/ZUMJ.2022.111530.2436**

ORIGINAL ARTICLE

Sublingual immunotherapy's effectiveness in lowering Platelet Factor-4 levels in 7 to 11-year-old aged children having a clinical history of House Dust Allergen-induced allergic rhinitis.

Heba M. El-Naggar[1,*], Mohammed M. Romih[1], Eman M. El-Behedy[2], Ali A. Abdel-Hamed[1], Shereen A. Baioumy[2]

[1]Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt
[2]Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author*
Heba M. El-Naggar

E-mail:
HebaElNaggar2510@gmail.com

Submit Date 20-12-2021
Revise Date 09-02-2022
Accept Date 01-03-2022

ABSTRACT

Background: Allergic rhinitis (AR) is a chronic inflammatory illness of the upper respiratory tract that has a significant impact on children's quality of life and school learning performance. Platelet activation's role in allergic inflammation is gaining more attention. Sublingual immunotherapy (SLIT) for AR could alter the immune response to allergens rather than merely treating symptoms. Our work aimed to investigate the role of platelet activation after SLIT in AR Children. **Methods:** A controlled randomized clinical study had conducted out at the Pediatric department in collaboration with Zagazig University's Allergy and Immunology Unit, was performed on Thirty children aged 7-11 years old with House Dust Allergen (HDA) sensitive AR. All participants received HDA extract in the form of sublingual immunotherapy for 6 months and symptoms score was recorded monthly. Platelet Factor-4 (PF-4) levels were measured in all subjects before and after SLIT therapy using an Enzyme-Linked Immunosorbent Assay (ELISA). **Results:** Our findings revealed that nasal sneezing (80 %) was the most prevalent AR symptom, with odor (93.3 %) as the most prevalent triggering factor and 60 % having a family history of AR ~ 3.3 times the odds of having the disease than those born to healthy parents. There was a substantial statistical decrease in PF-4 expression six months after-SLIT treatment 1.784 ± 0.196 compared to pre-SLIT 2.281 ± 0.177, $P < 0.001$. A significant positive association ($P = 0.020$) was seen between the decrease in nasal discharge score and serum PF-4 concentrations after SLIT therapy. **Conclusions:** Our results endorse our assumption that following SLIT, platelet activity was significantly decreased. Hence SLIT may be regarded as a potentially viable safe option with high patient acceptability for the treatment of allergic rhinitis in children.

Keywords: Controlled randomized study; Allergic rhinitis; Platelet Factor-4; Sublingual immunotherapy.

INTRODUCTION

Allergic rhinitis (AR) is the most frequent atopic disease in children that is heavily correlated to asthma. It is an immunoglobulin E (IgE)-a based inflammatory condition of the nasal mucous membranes characterized by mucus hypersecretion, and eosinophilic cell infiltration, which is exacerbated by normally harmless environmental proteins, [1]. Typical symptoms include nasal congestion, anterior and/or posterior watery rhinorrhea, paroxysmal sneezing, and itching.

AR is the most common allergic illness and is currently regarded as a major medical issue, affecting up to 20% of children globally (one out of every five people), that might interfere with sleep and quality of life in AR children and impose a significant economic burden on public health school learning performance and academic achievement, [2] [3]. The prevalence of AR in Egyptian children aged 3 to 15 years was estimated to be 34.5 percent, according to Al Dhduh, [4]. This has been postulated that Egypt's geographical location and favorable climatic conditions, in combination with other factors, contribute to the prevalence of house dust allergies (HDA), [5].

AR is an IgE-mediated reaction to various allergens in the nasal mucosa causes. Atopic people produce allergen-specific IgE when they are exposed to an allergen such as house dust allergen (HDA). When the same allergen is breathed again, an IgE-antibody reaction occurs, causing the cell to become activated, and mast cells in the nasal tissues emit chemical mediators that cause allergic rhinitis symptoms [6].

Platelet factor 4 is a minor chemokine protein expressed by stimulated platelets. Its primary physiological role is to enhance blood clotting [7]. In additional activities beyond simply promoting blood coagulation, PF-4 expression is elevated and has a role in chronic inflammation (as in allergic rhinitis). Platelet-activating factor (PAF) is a phospholipid that is secreted by alveolar macrophages, endothelial cells, and granulocytes, particularly blood basophils, after IgE-mediated allergic airway reactions in response to stimuli. PAF inhalation causes bronchoconstriction and increases vascular permeability [8]. Platelets can be activated immediately by an allergen and are able of creating a wide range of physiologically active mediators that play an important role in IgE-mediated allergic responses [9]. Platelet Factor-4 (PF-4) is one of PAF, and it has chemotactic properties, making it a useful indicator of platelet activation and degranulation [10].

AR is treated in three ways: avoidance of allergens or environmental controls, medications, and allergen-specific immunotherapy (sublingual or allergy shots) [11]. Many common pharmacological medicines, however, have not been properly evaluated in the setting of House dust allergy, and many House dust-allergic patients obtain only poor to moderate symptom management.

The only treatment that tackles the underlying immunological response of IgE-mediated hypersensitivity is immunotherapy. Although Subcutaneous immunotherapy (SCIT) has been the gold standard, sublingual immunotherapy (SLIT) has emerged as a feasible replacement and gaining popularity, particularly among children since it is easy to administer and has not been associated with systemic or life-threatening side effects [12].

SLIT is anticipated to work similarly to SCIT, altering T-cell responses and circulating antibody expression levels, particularly

allergen-specific IgG4. Langerhans-like dendritic cells capture the allergen in the mouth cavity. They then mature and migrate to the proximal lymph nodes, where they produce blocking IgG antibodies and activate suppressor T cells [13].

The purpose of this study was to evaluate the effectiveness and safety of sublingual immunotherapyin lowering platelet factor-4 levels in 7 to 11 years old aged children having a clinical history of HDA-induced allergic rhinitis.

METHODS

This controlled randomized clinical study was conducted for 8 months from June 2020 to February 2021 in the Pediatric Department in collaboration with the Allergy and Immunology Unit (AIU) of the Medical Microbiology and Immunology Department at Zagazig University Hospitals, Zagazig City, Sharika Governorate, Egypt. The study included 30 children having a clinical history of HDA-induced allergic rhinitis for at least one year.

Before the start of the study, the suggested protocols were announced to all parents who agreed and whose children satisfied the inclusion requirements listed below. Obtaining a whole history, including (age, sex, and, weight).

A skin prick test (SPT): SPT was used to identify children who've been allergic to HDA. The AIU of Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University prepared a panel of typical inhalant allergens [Coca extracted: smoke, house dust, wool, cotton, maize, hay rice dust, and date palm pollen] for *SPT.*

Technique:

SPT was performed on the inner side of the forearm, according to the procedure reported earlier by Dreborg [14]. The skin was disinfected with 70% ethyl alcohol and left to dry. The forearm was coded with a marker pen corresponding to the tested allergens, which were at least 2 cm apart. A drop of each allergen solution, negative (Saline) and positive controls (histamine) was placed beside each mark, Figure (1). A small prick through the drop was made to the skin using a sterile prick lancet. After 15-20 minutes, each wheal and flare was outlined with a pen. An itchy, red, swollen skin with a wheel diameter of $\geq$ 3 mm was considered a positive reaction [14]. All our studied children had average wheals that were > 5 mm in diameter.

Full detailed allergy history: which includes the nature of the illness, age of onset, and what produces and relieves symptoms. symptoms at home and outside, previous and present treatment. Family history of allergic diseases. History of any drugs for allergic diseases. History of exposure to specific environmental triggers like smoking.

Inclusion criteria: Seven to Eleven years old aged children with a clinical history of allergic rhinitis for at least one year, both male and female, children with moderate to severe allergic rhinitis in which criteria for AR diagnosis are according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines Bousquet et al., [15], which interfere with daily activity or sleep or children with allergic rhinitis who failed medical treatment, desire an alternative to pharmacotherapy.

Exclusion criteria: Children with persistent lung and heart illnesses (such as asthma), medical complications (such as cystic fibrosis, epilepsy, and gastroesophageal reflux disease), or chronic drug use (such as immunosuppressives, antiepileptic, and nasal or oral corticosteroids), or children who had

an infection within one month of the first study visit, or patients who had previously received immunotherapy.

Following the exclusion of non-respondents parents or children based on the aforementioned exclusion criteria, all study participants provided signed informed consent from their parents, after which all children were referred for the following.

Sublingual Immunotherapy (SIT):

Coca's allergen-extracted antigens, which were used in SPT, were also used in SLIT and were administered as sublingual drops, which were held under the tongue for a few minutes before swallowing. On an empty stomach in the morning, the sublingual drops were administered. The schedule of treatment doses, according to the manufacturer's instructions, was not a fixed proposal and was adjusted for each patient by omitting a dose, repeating a previous dose, or reducing a dose based on clinical response or evidence of local or systemic reaction after the preceding dose. Medication adherence was assessed using a parent questionnaire as well as a drug weight measurement administered every other week. The nose symptoms were scored (zero to three) by the children with the help of their parents (sneezing, runny nose, itchy nose, blocked nose), as reported early by Chen et al., [16].

Assessment of platelet factor 4 levels (PF-4)

Blood sampling collection for platelet factor 4 analysis:

A blood sample was transferred to an Eppendorf tube at room temperature, allowed to clot, and centrifugated at 10000 x g for 15 minutes using (Heraeus Biofuge Primo, Thermo Scientific, Waltham, MA). Serum samples were collected and stored at -80 ° C until ELISA was used to determine serum levels of platelet factor 4.

Test principle and Assay procedure

Human PF-4 is an enzyme immunoassay technique that may be stated in 3 stages according to the protocol described earlier by Farhadi et al., [17]. According to the manufacturer's instructions, an enzyme-linked immunosorbent assay (ELISA) was applied to detect PF-4 levels using a commercial kit by sunred-biotechnology company, United Kingdom. Using an ELISA reader (Stat fax 303 plus), the optical density (OD) of each well was measured spectrophotometrically at 450 nm. The color intensity of the reaction mixture is proportional to the PF-4 concentration of the test specimens, standards, and controls. Each triplicate's mean OD was computed.

ETHICAL CONSIDERATION

The protocols for this study were carried out by the Helsinki Declaration and the approval was obtained from the Institutional Review Board (IRB) unit [IRB Number: ZU-IRB#5882#10-02-2020], and by the Research Ethical Committee in the Faculty of Medicine, Zagazig University.

STATISTICAL ANALYSIS

The information gathered during the history, laboratory examinations, basic clinical investigation, and result evaluations was coded and analyzed using Microsoft Excel software. Data was fed into the computer and analyzed using SPSS version 26 (Statistics Package Social Science, SPSS Inc., Chicago, IL), USA. Numbers and % were used to describe qualitative data, while range (minimum and maximum), mean, standard deviation (SD), and median were used to describe quantitative data. The Chi-square test (X2) was used to estimate qualitative variable difference and association, while ANOVA was used to compute differences between quantitative independent multiple groups. The

paired nonparametric t-test was used to calculate the P-value in each group ($P < 0.05$ was considered significant).

RESULTS

This was a controlled randomized clinical study, conducted at the Outpatient Clinic and pediatricdepartment in collaboration with AIU, Zagazig University Hospital, Zagazig City, Sharika Governorate, Egypt. Table (1), dedicated to the demographic data of 30 children (63.33 % females) who were enrolled and complete the study protocol, with mean ages of 9.97 ± 1.19 years old, and the mean disease duration of 2.683 ± 1.49 years. Table (1) also revealed that nasal sneezing (80 %), nasal discharge (60 %), nasal itching (53.3), respiratory dyspnea (23.3 %), Skin Eczema (6.7%), and eyelid Edema (6.7 %) were the most prevalent AR symptoms in our patients.

The findings of our investigation indicated that odor was the most common triggering factor in 28 (93.3 %) of the studied children, 60 % had a family history of AR and 3.3% had a previous operation. Moreover, regarding diurnal and seasonal variation in symptoms, we found that 19 (63.3%) among the studied cases with night and 4 (13.3%) with morning variation in symptoms, while 14 (46.7%) with winter variation in symptoms, Table (1).

As shown in Table (2), the mean blood PF-4 levels during and 6 months after SLIT therapy were considerably lower than those before SLIT with statical significant difference (1.784 ± 0.196 ng/ml versus 2.281 ± 0.177, respectively, $p \leq 0.001$).

To investigate the influence of platelet activation on the symptom, the relationship between symptom and all other variables with serum PF-4 levels pre and post-SLIT therapy was examined. We revealed that before SLIT treatment, there was a statistically non-significant relation between elevated PF-4 and symptoms as well as other variables; [Diurnal and seasonal variation in symptoms, trigger factors, and family history), $P > 0.05$], while odor (trigger factor) was statistically significantly related to elevated PF-4, $p = 0.0001$, Table (3). Whereas post-SLIT, nasal discharge improvement, and other precipitating factors were statistically significantly related to serum PF-4 concentration reduction ($P = 0.019$), as shown in Table (4).

Table 1: Children's demographic characteristics, baseline symptoms, diurnal change in symptoms, and triggering factors.

Item	Number	Percent
Age (Mean ± SD.years)	9.97 ± 1.19	
Sex *Male* *Female*	 11 19	 36.66 % 63.33 %
Mean Disease Duration (years ± SD.)	2.683 ± 1.49	
Baseline symptoms *Respiratory Dyspnea* *Nasal Sneezing* *Nasal Discharge* *Nasal Itching* *Skin Eczema* *Eye lids Edema* *Redness of conjunctives*	 7 24 18 16 2 2 1	 23.33 % 80 % 60 % 53.3 % 6.7 % 6.7 % 3.33 %

Item	Number	Percent
Diurnal variation in symptoms		
No	3	10 %
Morning	4	13.3 %
Night	19	63.3 %
Morning, night	2	6.7 %
All	2	6.7 %
Seasonal variation in symptoms		
NSV	10	33.3 %
W,S	2	6.7 %
IBS	2	6.7 %
Winter	14	46.7
All	2	6.7 %
Precipitating factors		
Odors	28	93.3 %
Infection	1	3.3 %
Change in weather	3	10 %
Others	4	13.3 %
History		
Family history	18	60 %
Previous operation	1	3.3

NSV = No seasonal variation *W,S* = Winter,Spring *IBS* = In between season
Otherprecipitating factors mean (Foods, bed mattress, and Emotions)

Table 2: The distribution of Platelet Factor-4 (PF-4, ng/ml) serum levels before and after Sublingual immunotherapy (SLIT) treatment in the tested populations (n = 30).

Serum PF.4 (ng/ml)	Before SLIT Treatment	Post SLIT Treatment	T	P
Mean ± SD.	2.281 ± 0.177	1.784 ± 0.196	10.307*	< 0.001*

Table 3: Relation between serum Platelet Factor-4 (PF.4, ng/ml) level and symptoms, Diurnal variation in symptoms, precipitating factors and family history, Before- Sublingual immunotherapy (SLIT) treatment (n = 30).

	Occurrence	Number	Serum PF.4 (ng/ml) level Before SLIT		
			Mean ± SD	T	P
Baseline symptoms					
Respiratory Dyspnea	No Yes	23 7	2.68± 0.2١ 2.62 ± 0.29	0.508	0.625
Nasal Sneezing	No Yes	6 24	2.45 ± 0.34 2.29 ± 0.22	1.069	0.314
Nasal Discharge	No Yes	12 18	2.29 ± 0.29 2.32 ± 0.18	0.319	0.753
Nasal Itching	No Yes	14 16	2.33 ± 0.201 2.27 ± 0.18	0.856	0.399
Skin Eczema	No Yes	28 2	2.32 ± 0.26 2.26 ± 0.02	1.173	0.250
Eye lids Edema	No Yes	28 2	2.32 ± 0.24 2.23 ± 0.35	0.357	0.778

	Occurrence	Number	Serum PF.4 (ng/ml) level Before SLIT		
			Mean ± SD	T	P
Redness of conjunctives	No Yes	29 1	2.31 ± 0.25 2.40	----	------
Diurnal variation in symptoms					
No Morning Night Morning, night All		3 4 19 2 2	2.14 ± 0.25 2.35 ± 0.22 2.33 ± 0.26 2.21 ± 0.08 2.41 ± 0.39	0.5343	0.7117
Seasonal variation in symptoms					
NSV W,S IBS Winter All		10 2 2 14 2	2.28 ± 0.25 2.21 ± 0.08 2.28 ± 0.12 2.34 ± 0.27 2.41 ± 0.39	0.234	0.917
Trigger factors					
Odour	No Yes	2 28	2.61 ± 0.01 2.29 ± 0.24	6.97	0.0001***
Infection	No Yes	29 1	2.32 ± 0.25 2.14	-------	-------
Change in weather	No Yes	27 3	2.31 ± 0.25 2.32 ± 0.31	0.053	0.961
Other	No Yes	26 4	2.32 ± 0.26 2.28 ± 0.16	0.380	0.726
History					
Family history	No Yes	12 18	2.32 ± 0.24 2.41 ± 0.26	0.432	0.669
Previous operation	No Yes	29 1	2.32 ± 0.25 2.04	----------	----------

NSV = No seasonal variation *W, S* = Winter, Spring *IBS* = In between season

Table 4: Relation between serum Platelet Factor-4 (PF.4, ng/ml) level and symptoms, Diurnal variation in symptoms, precipitating factors, and family history, After- Sublingual immunotherapy (SLIT) treatment (n = 30).

	Occurrence	Number	Serum PF.4 (ng/ml) level After- SLIT		
			Mean ± SD	T	P
Baseline symptoms					
Respiratory Dyspnea	No Yes	23 7	1.83 ± 0.25 1.85 ± 0.32	0.151	0.882
Nasal Sneezing	No Yes	6 24	1.89 ± 0.29 1.83 ± 0.26	0.462	0.657
Nasal Discharge	No Yes	12 18	1.72 ± 0.25 1.94 ± 0.23	2.437*	0.023*
Nasal Itching	No Yes	14 16	1.79 ± 0.28 1.87 ± 0.24	0.834	0.411

	Occurrence	Number	Serum PF.4 (ng/ml) level After- SLIT		
			Mean ± SD	T	P
Skin Eczema	No Yes	28 2	1.85 ± 0.26 1.71 ± 0.15	1.197	0.388
Eye lids Edema	No Yes	28 2	1.86 ± 0.26 1.68 ± 0.27	0.913	0.513
Redness of conjunctives	No Yes	29 1	1.84 ± 0.26 1.76	-------	-------
Diurnal variation in symptoms					
No Morning Night Morning, night All		3 4 19 2 2	1.61 ± 0.14 1.83 ± 0.29 1.86 ± 0.27 1.87 ± 0.04 1.98 ± 0.29	0.746	0.570
Seasonal variation in symptoms					
NSV W,S IBS Winter All		10 2 2 14 2	1.81 ± 0.23 1.87 ± 0.04 1.69 ± 0.06 1.85 ± 0.31 1.98 ± 0.29	0.326	0.858
Trigger factors					
Odour	No Yes	2 28	2.07 ± 0.32 1.82 ± 0.25	1.081	0.463
Infection	No Yes	29 1	1.84 ± 0.26 1.71	-------	-------
Change in weather	No Yes	27 3	1.83 ± 0.26 1.89 ± 0.26	0.379	0.734
Other	No Yes	26 4	1.86 ± 0.27 1.67 ± 0.04	3.356*	0.002*
History					
Family history Previous operation	No Yes No Yes	12 18 29 1	1.83 ± 0.26 1.84 ± 0.27 1.84 ± 0.26 1.84	0.101 ----------	0.919 ---------

NSV = No seasonal variation *W,S* = Winter ,Spring *IBS* = In between season

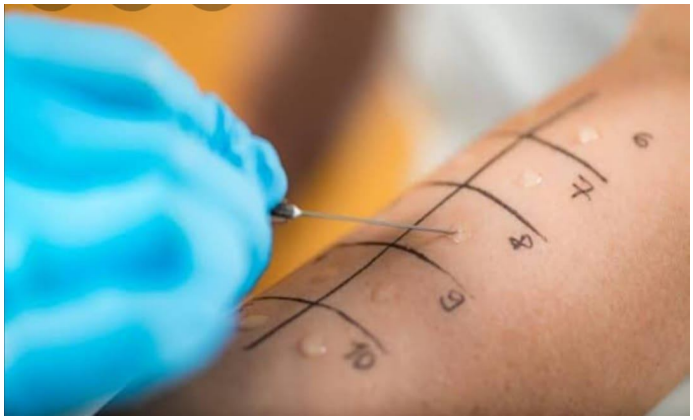

Figure 1: Skin Pike Test (SPT)

DISCUSSION

Allergic rhinitis is a prevalent illness that, despite adequate treatment with antihistamines and topical nasal corticosteroids, can considerably impact the quality of life [18].

Platelet activation can occur both systemically and locally at the site of allergic inflammation, the percentage of platelet-derived mediators (such as PF.4, Thromboglobulin, and chemokines) that bound IgE in atopic allergic was much greater in their plasma than in normal donors, and such platelets may be immediately triggered by contact with the appropriate allergen.

Effective allergen-specific immunotherapy (AIT) results in the development of long-term clinical tolerance to allergens, leading to a reduction in symptoms and medication needs in allergic rhinitis, but its usage is limited due to the risk of severe systemic responses. As a result, there has been a lot of interest in alternate ways for noninjectable delivering allergy immunotherapy, notably the sublingual route (SLIT) [19]. The goal of this study was to evaluate the efficacy of SLIT, for reductions in symptoms and PF-4 levels in children with allergic rhinitis

The current study is one of the earliest trials to demonstrate in-vivo changes in platelet activity in AR children during SLIT. Thirty children were enrolled in the current investigation, with a mean age of 9.97 ± 1.19 years old and a mean illness duration of 2.683 ± 1.49 years, that lower than that reported earlier by Chen et al.. [16], and Bahçeciler et al., [20], 10.1 ± 3.66 and, 11.7 ± 3.3 years old, respectively. Our results revealed that nasal sneezing (80 %) was the most common symptom, while redness of conjunctive was the lowest prevalent symptom (3.3 %) among studied cases. This is consistent with the findings of Bartle [21], who reported that the most common symptoms were sneezing, itchiness, and a blocked or runny nose, but in contrast to our study, Roberts et al., [22], who reported that rhinorrhea (was the most common symptoms among their studied population.

Regarding diurnal and seasonal variation in symptoms, our results showed that 63.3 % of the cases studied had night variation in symptoms, which is more common than seasonal, ~ 46.7 % of children had winter fluctuation in symptoms. Contrary to our findings, Alsowaidi et al., [23], reported that 26% of the investigated patients had symptoms reported in the spring, while Soo-Youn et al., [24], found that seasonal AR ~64.2% was more common than perennial AR 35.8 %. Moreover, about 55.5 % of AR symptoms lasted< four days per week which were more common than symptoms lasting longer (~ 44.5 %). The majority of AR patients ~ 71.9 % experienced symptoms that lasted less than one month., and the majority of such participants (68.8 %) claimed to have disrupted their studies, employment, or sleep.

In our investigation, we found that odor was the triggering factor in 93.3 % of the studied cases. Li et al., [25], observed an elevated risk of allergy disorders among persons exposed to cigarettes, which is in line accordance with our findings. The odor may contribute to sensitivity to both perennial indoor allergens and certain outdoor allergens. In contrast to our findings, Soo-Youn et al., [24], found that smoking status, alcohol use, mean sleep time, higher-level stress exposure, and stress per se all elevated the risk of AR.

Furthermore, children with a family history of AR had ~ 3.3 times the odds of having the

disease than those born to healthy parents, which agrees with early studies reported by Alsowaidi et al., [23] and Baumann et al., [26], they concluded that the highest risk factor for AR in the general is the family history, i.e., genetic factor. Additionally, it is consistent with several epidemiological studies reported that the most repeated areas were found on chromosomes 2, 3, 4, and 9.

Surprisingly, in pre-SLIT therapy, the mean serum PF-4 was found to be significantly higher than post-treatment. Many studies supported our current findings, revealing that the mean PF-4 serum in children with AR was significantly greater than in healthy children. Knauer et al., [27] reported substantial increases in PF-4 levels in pollen-induced allergy patients after bronchial stimulation with ragweed extract. Also, in a study by Kasperska-Zajac et al., [28], they demonstrated that plasma PF4 levels in patients during the off-pollen season were much lower than during the pollen season and did not vary significantly from healthy people.

There were no associations between serum PF-4 and symptoms, family history, diurnal, and seasonal variation in symptoms before SLIT treatment, while there was a positive correlation among studied cases between odor, the most trigger factor, and elevation of serum PF-4 pre-SLIT treatment. On the other hand, the improvement in nasal discharge score after SLIT was positively associated with a decrease in serum PF-4 concentration, which is consistent with earlier studies reported by Kasperska-Zajac et al., [28] who suggested that PF-4 and Beta-thromboglobulin (BTG) levels were not significantly different between patients and healthy subjects after immunotherapy.

Additionally, consistent with our findings, Guo et al., [29], showed that Intragroup analysis demonstrated a significant improvement in the active treatment group for individual nasal symptom score and Total Nasal Symptom Score (TNSS) ($p < 0.05$), although no improvement was observed in the placebo group of congestion, sneezing, and itching ($p > 0.05$).

CONCLUSIONS

Our finding endorses our assumption that suppressing platelet activation (PF-4) in the systemic circulation is an important mechanism during SLIT. By partly inhibiting platelet activation, SLIT may help to reduce symptoms. From the viewpoint of improving the patient's quality of life, we propose measuring platelet factor-4 levels in the blood before and after sublingual immunotherapy. However, one of our study's limitations is the small number of patients and the absence of a controlled placebo group. To further understand the role of PF-4 in SLIT, more study with bigger sample sizes is needed. Furthermore, large-scale follow-up studies in a large number of patients are required to confirm the PF-4 response between SLIT-responsive groups. To evaluate the local effect of platelet activation in the AR and SLIT processes, the change in PF-4 in nasal mucosa or nasal lavage before and after SLIT should be investigated in the future.

CONFLICT OF INTEREST

The authors did not report any conflict of interest in competing for financial or personal relations.

REFERENCES

1. **Saad K, Abdelmoghny A, Aboul-Khair MD, Abdel-Raheem YF, Gad EF, Hammour AE, et al.** Vitamin D status in Egyptian children with allergic rhinitis. EarNose Throat J2020; 99 (8): 508-12.

2. **Saad K, Zahran AM, Elsayh KI, Abdelmoghny A, Aboul-Khair**. Variation of regulatory T lymphocytes in the peripheral blood of children with allergic rhinitis. Arch Immunol Ther Exp (Warsz). 2018; 66 (4): 307-13.

3. **Zahran AM, Saad K, Elsayh KI, Abdelmoghny A, Aboul-Khair, Sobhy A, et al**. Myeloid-Derived suppressor cells and costimulatory molecules in children with allergic rhinitis. Ann Otol Rhinol Laryngol. 2019; 128 (2): 128-34.

4. **Al Dhduh MA, Sabri NA, Fouda EM**. Prevalence and severity of allergic diseases among Egyptian pediatric in different Egyptian areas." Int J Pharm Sci Res. 2015; 2: 107.

5. **Hassan AA, Hagrass SA.** Prevalence of bronchial asthma in primary school children. Am J Med Sci. 2017; 7 (2): 67–3.

6. **De Shazo, RD, and Kemp SF.** Pathogenesis of allergic rhinitis (rhinosinusitis)." Up To Date. Updated 15 (2019).

7. **Fox JM, Kausar F, Day A, Osborne M, Hussain K, Mueller A, et al.** CXCL4/Platelet Factor 4 is an agonist of CCR1 and drives human monocyte migration. Scientific reports. 2018; 8 (1): 1-15.

8. **Beer JH, Wüthrich B, von Felten A.** Allergen exposure in acute asthma causes the release of platelet-activating factor (PAF) as demonstrated by the desensitization of platelets to PAF. Int Arch Allergy Immunol.1995; 106 (3): 291-6.

9. **Topal E, Celiksoy MH, Demir F, Bag HG, Sancak, R.** Is the change in platelet parameters in children with allergic rhinitis an indicator of allergic inflammation. Med Sci. 2018; 7" 178-81.

10. **Akgedik R, Yağız Y**. Is Decreased Mean Platelet Volume in Allergic Airway Diseases Associated With Extent of the Inflammation Area? Am J Med Sci. 2017; 354 (1): 33-8.

11. **Klimek L, Bachert C, Pfaar O, Becker S, Bieber T, Brehler R, et al.** ARIA guideline 2019: treatment of allergic rhinitis in the German health system. Allergol Select. 2019; 3 (1): 22-50.

12. **Passalacqua G, Bagnasco D, Canonica GW**. 30 years of sublingual immunotherapy. Allergy. 2020; 75 (5): 1107-20.

13. **Singh AB.** Allergy and Allergen Immunotherapy: New Mechanisms and Strategies. CRC Press. Book, 2017

14. **Dreborg S.** Skin Testing in Allergen Standardization and Research. Immunol Allergy Clin North Am. 2001;21:329–354.

15. **Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, Bindslev-Jensen C**. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2019; 143 (3): 864 – 879.

16. **Chen Y, Zhou L, Yang Y.** Effect of sublingual immunotherapy on platelet activity in children with allergic rhinitis. Braz J Otorhinolaryngol. 2017; 83 (2): 190-4.

17. **Farhadi R, Rafiei A, Hamdamian S, Zamani H, Yazdani, J.** Pentraxin 3 in neonates with and without diagnosis of pulmonary hypertension. Clinical biochemistry. 2017; 50 (4-5): 223-227.

18. **Wilson DR, Torres Lima M, Durham SR.** "Sublingual immunotherapy for allergic rhinitis: systematic review and meta‐analysis." Allergy 60.1. 2005; 4-12.

19. **Elliott J, Kelly SE, Johnston A, Skidmore B, Gomes T, Wells GA.** Allergen immunotherapy for the treatment of allergic rhinitis and/or asthma: an umbrella review. CMAJ open. 2017; 5 (2): E373.

20. **Bahçeciler NN, Işik U, Barlan IB, Başaran MM.** Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001; 32(1): 49-55.

21. **Bartle J.** Patient education in the effective management of hay fever. Nursing standard. Royal College of Nursing (Great Britain): 1987. 2016; 30 (43): 48-53.

22. **Roberts G, Xatzipsalti M, Borrego LM, Custovic**

A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the E uropean A cademy of Allergy and C linical I mmunology. Allergy. 2013; 68 (9): 1102-16.

23. **Alsowaidi S, Abdulle A, Shehab A, Zuberbier T, Bernsen R, et al.** Allergic rhinitis: prevalence and possible risk factors in a Gulf Arab population. Allergy. 2010; 65 (2): 208-12.

24. **Soo-Youn A, Choi HG, Kim SW, Park B, Lee JS, Jang JH, et al.** Analysis of various risk factors predisposing subjects to allergic rhinitis. Asian Pac J Allergy Immunol. 2015; 88 (2):33-42.

25. **Li, C. W., Zhong, J. T., Lin ZB, Lin ZB, Peng H, Lu HG, et al.** Epidemiological characterization and risk factors of allergic rhinitis in the general population in Guangzhou City in China. PLoS One. 2014; 9 (12): e114950.

26. **Baumann LM, Romero KM, Robinson CL, Hansel NN, Gilman RH, Hamilton RG, et al.** Prevalence and risk factors for allergic rhinitis in two resource-limited settings in Peru with disparate degrees of urbanization. Clin Exp Allergy. 2015; 45 (1): 192-9.

27. **Knauer KA, Lichtenstein LM, Adkinson Jr NF., Fish JE.** Platelet activation during antigen-induced airway reactions in asthmatic subjects. N Engl J Med. 1981; 304 (23): 1404-7.

28. **Kasperska-Zajac A, Brzoza Z, Rogala B.** Seasonal changes in platelet activity in pollen-induced seasonal allergic rhinitis and asthma. J Asthma. 2008; 45(6): 485-7.

29. **Guo Y, Li Y, Wang D, Liu Q, Liu Z, Hu L. A** randomized, double-blind, placebo controlled trial of sublingual immunotherapy with house-dust mite extract for allergic rhinitis. Am J Rhinol Allergy. 2017; 31 (4): 42-7.

Citation:

El-Naggar, H., Romih, M., El-Behedy, E. M., Abdel-Hamed, A. A., Baioumy, S. A. Sublingual immunotherapy's effectiveness in lowering Platelet Factor-4 levels in 7 to 11 years old aged children having a clinical history of House Dust Allergen induced allergic rhinitis.. *Zagazig University Medical Journal*, 2022; (4198-4209): -. doi: 10.21608/zumj.2022.111530.2436