

Received: 2018.07.06
Accepted: 2018.09.15
Published: 2019.01.11

Efficacy of Sublingual Administration of *Dermatophagoides Farinae* Drops for Treatment of Pediatric Allergic Rhinitis Accompanied by Adenoid Hypertrophy and Improvement of Immune Function

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 **Wangbo Yu***
AB 2 **Lifang Mao***
BC 1 **Qingchun Pan**
BC 1 **Tao He**
AE 3 **Ming Yu**

1 Department of Otorhinolaryngology – Head and Neck Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, P.R. China
2 Department of Integrated Western and Chinese Colorectal and Anal Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, P.R. China
3 Department of Otorhinolaryngology – Head and Neck Surgery, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, P.R. China

* Both authors contributed equally to this work and should be considered as equal first coauthors

Corresponding Author: Ming Yu, e-mail: mingyu3937@163.com
Source of support: Departmental sources

Background: The aim of this study was to determine the efficacy of sublingual administration of *Dermatophagoides farinae* drops for the treatment of allergic rhinitis (AR) accompanied by adenoid hypertrophy and the effect on immune function in children.


Material/Methods: Eosinophil counts in peripheral blood before and after treatment were determined; serum levels of immunoglobulin E (IgE), total IgE (T-IgE), immunoglobulin G4 (IgG4), interleukin-2 (IL-2), and interleukin-6 (IL-6) before and after treatment were detected by enzyme-linked immunosorbent assay.

Results: The total effective rate in the study group was significantly higher than that in the control group ($P < 0.05$). In both the study and control groups, symptom scores, medication scores, eosinophil counts in the peripheral blood, and serum levels of IgE, T-IgE, and IL-6 were significantly lower than those before treatment ($P < 0.05$), while the serum levels of IgG4 and IL-2 were significantly higher than those before treatment ($P < 0.05$). After treatment, symptom scores, medication scores, eosinophil counts in the peripheral blood, and serum levels of IgE, T-IgE, and IL-6 in the study group were significantly lower than those in the control group ($P < 0.05$), while the serum levels of IgG4 and IL-2 were significantly higher in the study group than those in the control group ($P < 0.05$).

Conclusions: Sublingual administration of *D. farinae* drops improved the clinical symptoms of pediatric AR caused by *Dermatophagoides* mites and improved the immune functions in children.

MeSH Keywords: **Adenoids • *Dermatophagoides Farinae* • Rhinitis, Allergic, Seasonal**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/911982>

 3310

 2

 4

 29



Background

Allergic rhinitis (AR) is a common disease with immune dysfunction caused by intolerance to allergens in the external environment [1]. The principal clinical manifestations of AR include runny nose, nasal itching, and paroxysmal sneezing. In some patients, the aforementioned symptoms are accompanied by cough and itching of the eyes, which markedly affect the patients' quality of life [2]. At present, the pathogenesis of AR has not been elucidated and it is not considered a strictly genetic disease [3]. Most scholars believe that AR development is closely associated with changes in the surrounding environment, and the incidence of AR is increasing with improved standards of living and economic prosperity. The incidence of AR in developed Western countries is approximately 40%, with the percentage in children being slightly higher than that in adults [4].

The incidence of AR has been increasing in recent years. Changes in environmental factors are capable of regulating the immune system of the body, which can result in an allergic state [4]. With the improvement in living standards, there has been a greater emphasis living a clean life. A decrease in the probability of exposure to pathogenic microbes and extensive application of antibiotics in children are major factors influencing immune system disorders in children, and a decrease in infectious diseases will indirectly increase the incidence of allergic diseases [5]. AR not only affects the quality of life of patients, but also seriously endangers the physical and psychological health of the affected children when accompanied by a series of complications such as adenoid hypertrophy, asthma, and otitis media, which makes AR a global health problem [6]. Allergen-specific immunotherapy (SIT) enables changes in the natural immune system of AR patients to alter natural disease processing via the use of a small dose of the sensitized allergen, thereby inducing clinical tolerance and preventing disease development [7]. Several forms of SIT, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), are available [8]. SLIT is administered via the oral mucosa; it induces the generation of immune tolerance gradually in AR patients and is well tolerated [9,10]. *Dermatophagoides farinae* drops is an SIT that makes patients sensitive to mites, inducing specific immune tolerance and blocking antibodies, and reduces the allergic reaction, thereby treating AR [11].

SLIT is a new method for treating AR in recent years and is considered to be the only way to change the natural course of AR. The mechanism underlying the efficacy of *D. farinae* drops in improving immune tolerance of AR patients remains unclear. Thus, this study further explored the clinical efficacy of this treatment and its impact on the body's immune function, aiming to provide a reference for the treatment of clinical AR patients with adenoid hypertrophy.

Material and Methods

General information

Clinical data of 102 cases of AR accompanied by adenoid hypertrophy in our hospital from March 2015 to February 2018 were retrospectively analyzed. In 52 of these cases, *D. farinae* drops were sublingually administered; these cases were considered as the study group. In another 50 cases, conventional anti-allergic drugs were administered; these cases were considered the control group. The study group included 33 male and 19 female patients aged 4 to 11 years, with the average patient age being 6.15 ± 0.83 years. The disease course was 4 months to 5 years in the study group, with the average disease course being 2.41 ± 1.34 years. The control group included 29 male and 21 female patients aged 4 to 12 years, with the average patient age being 6.34 ± 0.91 years, and the disease course was 6 months to 6 years, with the average disease course being 2.32 ± 1.19 years. The study was approved by the Ethics Committee of our hospital, and parents/guardians of all subjects were informed, agreed with the clinical research, and signed the informed consent.

Inclusion and exclusion criteria

The inclusion criteria were: compliance with the diagnostic criteria of AR as described in the Diagnosis and Treatment Principles and Recommendations for Allergic Rhinitis; only dust mite sensitivity (positive ++ or above ++) found in the skin prick test; no use of anti-allergic drugs within 2 weeks before the treatment; stable physical signs; good mental state and language ability; and availability of complete medical records. The exclusion criteria were: presence of drug therapy intolerance; acute respiratory infection, bronchial asthma, or tuberculosis; severe liver and kidney dysfunction; and connective tissue, endocrine, and metabolic diseases, and infectious diseases.

Treatment method

The patients in the control group were given 10 mg/d ebastine (Jiangsu Lianhuan Pharmaceutical Group CO., LTD, batch number: H20040119) orally and levocabastine (Shanghai Johnson Pharmaceutical Co., Ltd., batch number: 20160072) by nasal spray. The patients in the study group were given *D. farinae* drops (Zhejiang Wolwo Pharma Technologies Inc., batch number: S20060012) by sublingual administration. The detailed administration method was as follows: 1 drop of *D. farinae* drop 1 was dripped under the tongue of the patients; the patients were asked to swallow after 3 min. *D. farinae* drops 2 and 3 were given 2 and 3 weeks, respectively, after treatment for 7 consecutive days, once daily. The doses administered during the 7 days were 1 drop on the first day, 2 on the second day, 3 on the third day, 4 on the fourth day, 6 on the fifth day, 8 on the

sixth day, and 10 on the seventh day. Four weeks after treatment, *D. farinae* drop 4 was given once daily for consecutive treatment. The patients in both groups were treated consecutively for 15 months with 1 drop daily, and their physical condition was monitored throughout the treatment period. If necessary, oral loratadine tablets (Xi'an Yangsen Pharmaceutical Co., Ltd., batch number: H20070030) were administered and discontinued after symptom relief.

Observation index

Clinical efficacy was evaluated based on 4 aspects: sneezing, nasal itching, runny nose, and nasal congestion [12]. The severity of the symptoms was evaluated on a scale of 1 to 3, with 12 being the highest overall score possible for symptom severity. Improvement rates of $\geq 66\%$, 26–65%, and $\leq 25\%$ represented treatment excellence, effectiveness, and ineffectiveness, respectively. The improvement rate was determined using the following formula: (total score before treatment–total score after treatment/total score before treatment) $\times 100\%$. The total effective rate was determined as follows: (cases showing treatment excellence+cases showing treatment effectiveness)/total cases $\times 100\%$. The patients were given 5-mg loratadine tablets (Bayer Medicine [Shanghai] Co., Ltd., batch number: H10970410) weekly. One-time administration was scored as 1 point; the daily average medication scores of the study group and the control group were determined.

Index determination

Peripheral blood samples from the subjects were obtained while fasting. Eosinophil count in the peripheral blood was determined using an AU5800 automatic biochemical analyzer (Backman Kurt Trade (China) Co., Ltd.). The enzyme-linked immunosorbent assay (ELISA) [13] was performed to detect serum levels of IgE, T-IgE, and IgG4 (kits from Shanghai Future Industrial Co., Ltd.) and of IL-2 and IL-6 (kits from Shanghai Fusheng Industry Co., Ltd.) according to the instructions provided by the manufacturers. The kits were removed from the refrigerator 30 min in advance to be equilibrated at 25°C with the test samples and the sample hole, standard hole, and blank hole being set up. No enzyme-labeled reagents and samples were added to the blank well, and 100- μ l test samples or standard substances were added to each of the other wells. After mixing, the film on the enzyme-labeled plate was covered to incubate for 2 h at 37°C. Then, the solution in each well was discarded, and the well was dried. Thereafter, 100 μ l of working liquid A was added to each well with the film covered to incubate for 1 h at 37°C. The liquid in each well was discarded, and the well was dried. An automatic plate washer (Xi'an Heng Ke Trade Co., Ltd) was used to wash the plate 3 times. Thereafter, 100 μ l of working liquid B was added to each well with the film covered to incubate for 1 h at 37°C. The liquid in each well was

then discarded and the well was dried. The plates were washed 3 times thereafter. A substrate solution (90 μ l) was added to each well with the film covered. The color was developed at room temperature away from light for 20 min. Then, 50 μ l of termination solution was added to each well before using the ELISA analyzer (Shanghai LNB Instrument Co., Ltd) to determine the OD values of each well at a wavelength of 450 nm.

Statistical analysis

Statistical analysis was performed using SPSS20.0 (Beijing Net Digital Times Science Technology Co., Ltd.). Data are expressed as mean \pm standard deviation ($\bar{x}\pm$ SD). The measurement data between groups were compared using the *t* test, and the scores were compared between the groups with the chi-square test. $P<0.05$ indicated statistical significance.

Results

Baseline data of the study and control groups

There was no significant difference between the study group and the control group in the general clinical baseline data, including sex, age, disease course, body weight, hemoglobin (Hb), red blood cell (RBC) count, platelet (PLT) count, and direct bilirubin (DBil), and total bilirubin (TBil) levels ($P>0.05$; Table 1).

Symptom and medication scores before and after treatment in the study and control groups

In the study group, the symptom and medication scores before the treatment were 7.76 ± 2.56 and 1.53 ± 0.36 , respectively; the corresponding post-treatment scores were 1.71 ± 0.82 and 0.37 ± 0.21 , respectively. The symptom and medication scores before treatment in the control group were 7.67 ± 2.13 and 1.48 ± 0.29 , respectively; the corresponding post-treatment scores were 2.18 ± 1.07 and 0.92 ± 0.26 , respectively. Intergroup differences in the symptom and medication scores before treatment were not significant ($P>0.05$). The post-treatment symptom scores in the study and control groups were significantly lower than those before the treatment ($t=15.940$, $P<0.001$; $t=16.290$, $P<0.001$, respectively). Further, the post-treatment symptom scores in the study group were significantly lower than those in the control group ($t=2.496$, $P=0.014$). The post-treatment medication scores in the study and control groups were significantly lower than those before the treatment ($t=19.780$, $P<0.001$; $t=10.170$, $P<0.001$, respectively). Further, the post-treatment medication scores in the study group were significantly lower than those in the control group ($t=11.770$, $P<0.001$; Figure 1A, 1B).

Table 1. Baseline data for the study and control groups [n (%)] ($\chi \pm SD$).

Category	Research group (n=52)	Control group (n=50)	t/ χ^2	P
Gender			0.319	0.686
Male	33 (63.46)	29 (58.00)		
Female	19 (36.54)	21 (42.00)		
Age	6.15 \pm 0.83	6.34 \pm 0.91	1.102	0.272
Course of disease (years)	2.41 \pm 1.34	2.32 \pm 1.19	0.358	0.721
Weight (kg)	15.13 \pm 6.38	15.27 \pm 7.12	0.104	0.916
Hb (gg/L)	132.98 \pm 9.16	131.57 \pm 9.58	0.759	0.449
RBC ($\times 10^{12}$ /L)	4.51 \pm 0.62	4.59 \pm 0.67	0.626	0.532
PLT ($\times 10^9$ /L)	154.74 \pm 24.63	158.28 \pm 27.28	0.688	0.492
DBil (μ mol/L)	4.15 \pm 1.02	4.27 \pm 1.22	0.539	0.590
TBil (μ mol/L)	10.24 \pm 2.67	11.07 \pm 2.35	1.664	0.099

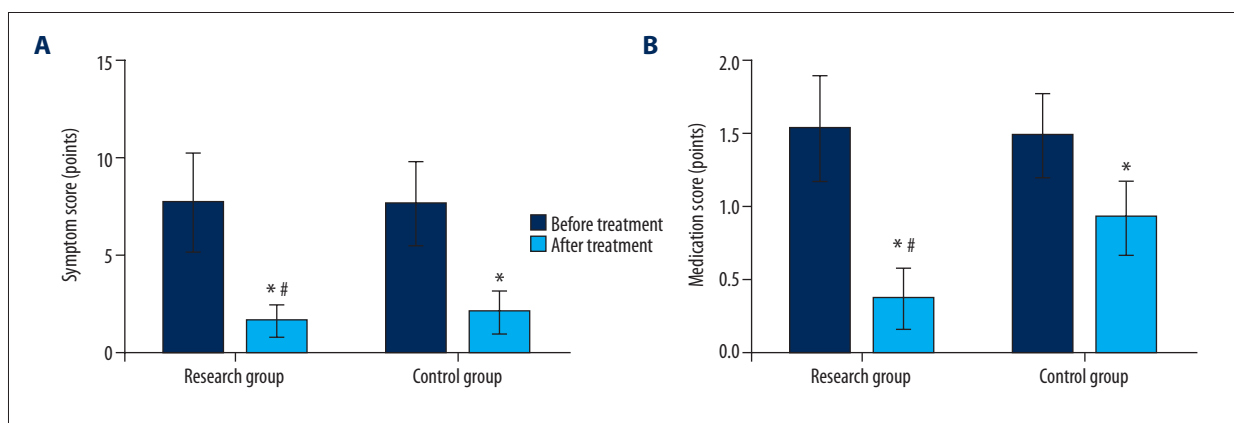


Figure 1. Comparison of symptom and medication scores before and after treatment in the study and control groups. (A) The symptom scores before and after treatment were compared in the study and control groups. (B) Medication status before and after treatment in the study and control groups. * P<0.001 compared to before treatment; # P<0.05 compared to control group after treatment.

Eosinophil counts in the peripheral blood before and after the treatment in the study and control groups

The eosinophil count in the peripheral blood of the study group was 10.93 \pm 3.56% before treatment and 4.03 \pm 1.68% after treatment. The corresponding values in the control group were 10.89 \pm 3.51% and 4.83 \pm 1.82%. Intergroup difference in the eosinophil count in the peripheral blood before the treatment was not significant (P>0.05). The post-treatment eosinophil counts in the peripheral blood in the study and control groups were significantly lower than those before the treatment (t=12.440, P<0.001; t=10.840, P<0.001, respectively). Further, the post-treatment eosinophil count in the peripheral blood of the study group was significantly lower than that in the control group (t=2.308, P=0.023; Figure 2).

Clinical efficacy of the treatment in the study and control groups

Treatment excellence, effectiveness, and ineffectiveness were observed in 49 cases (94.23%), 2 cases (3.85%), and 1 case (1.92%), respectively, with a total effective rate of 98.08% in the study group. The corresponding values in the control group were 29 cases (58.00%), 14 cases (28.00%), and 7 cases (14.00%), with a total effective rate of 86.00%. The total effective rate in the study group was significantly higher than that in the control group ($\chi^2=5.144$, P=0.030; Table 2).

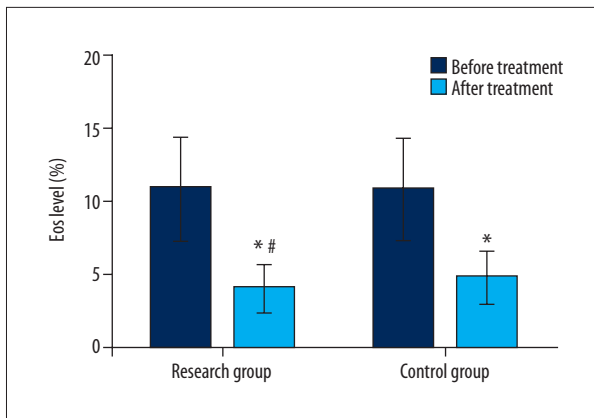


Figure 2. Comparison of eosinophil counts in peripheral blood before and after treatment between the study and control groups. * $P < 0.001$ compared to before treatment; # $P < 0.05$ compared to control group after treatment.

Serum IgE, T-IgE, and IgG4 levels before and after the treatment in the study and control groups

The serum levels of IgE, T-IgE, and IgG4 in the study group were 73.52 ± 5.07 kUA/L, 307.57 ± 14.85 kUA/L, and 226.85 ± 7.69 mg/L, respectively, before the treatment; the corresponding post-treatment levels were 23.84 ± 4.25 kUA/L, 162.63 ± 12.74 kUA/L,

and 337.25 ± 8.45 mg/L, respectively. In the control group, the serum levels of IgE, T-IgE, and IgG4 were 74.63 ± 5.15 kUA/L, 309.41 ± 15.63 kUA/L, and 228.14 ± 7.42 mg/L, respectively, before the treatment; the corresponding post-treatment levels were 41.87 ± 5.14 kUA/L, 202.53 ± 13.74 kUA/L, and 287.41 ± 10.07 mg/L, respectively. Intergroup differences in serum levels of IgE, T-IgE, and IgG4 before treatment were not significant ($P > 0.05$). The post-treatment serum IgE levels in the study and control groups were significantly lower than the pretreatment levels ($t = 54.130$, $P < 0.001$; $t = 31.840$, $P < 0.001$, respectively). Further, the post-treatment serum IgE level in the study group was significantly lower than that in the control group ($t = 19.34$, $P < 0.001$). The post-treatment serum T-IgE levels in the study group and the control group were significantly lower than the pretreatment levels ($t = 53.420$, $P < 0.001$; $t = 36.320$, $P < 0.001$). Further, the post-treatment serum T-IgE levels in the study group were significantly lower than those in the control group ($t = 15.220$, $P < 0.001$). The post-treatment serum IgG4 levels in the study and control groups were significantly higher than the pretreatment levels ($t = 69.680$, $P < 0.001$; $t = 33.510$, $P < 0.001$, respectively). The post-treatment serum IgG4 level in the study group was significantly higher than that in the control group ($t = 27.120$, $P = 0.023$; Figure 3A–3C).

Table 2. Comparison of clinical efficacy between the study and control groups [n (%)].

Groups	n	Significantly	Effective	Invalid	Total efficiency (%)
Research group	52	49 (94.23)	2 (3.85)	1 (1.92)	51 (98.08)
Control group	50	29 (58.00)	14 (28.00)	7 (14.00)	43 (86.00)
χ^2	–	–	–	–	5.144
P	–	–	–	–	0.030

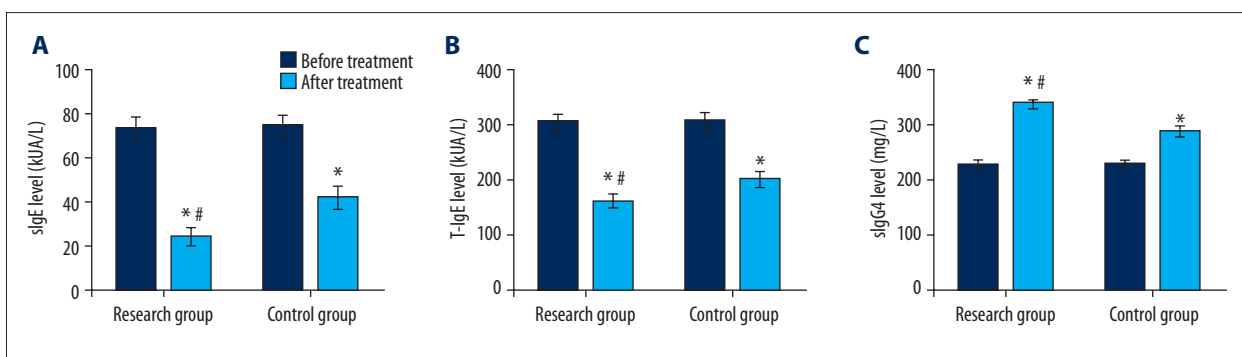


Figure 3. Comparison of serum IgE, T-IgE, and IgG4 levels before and after treatment in the study and control groups. (A) Comparison of serum IgE levels before and after treatment between the study and control groups. (B) Comparison of serum T-IgE levels before and after treatment between the study and control groups. (C) Comparison of serum IgG4 levels before and after treatment between the study and control groups. * $P < 0.001$ compared to that before treatment; # $P < 0.001$ compared to the control group after treatment.

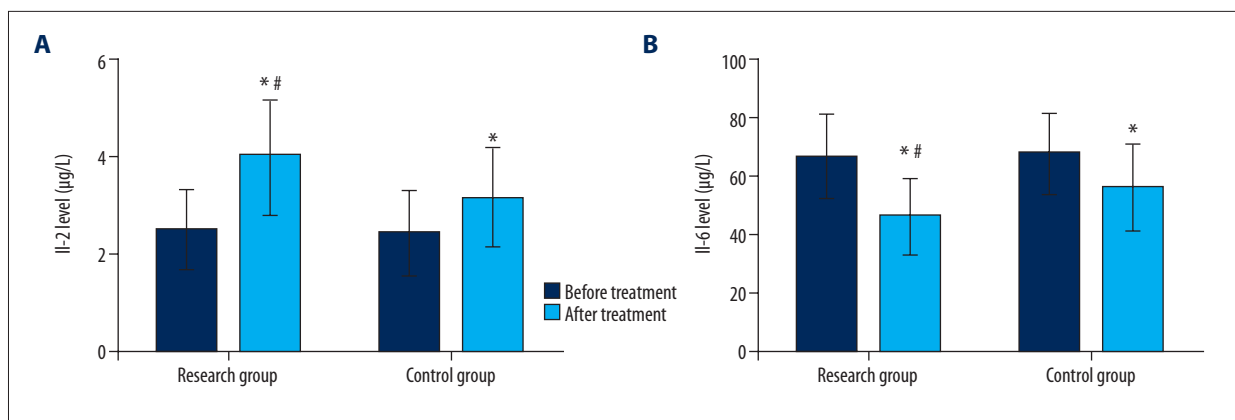


Figure 4. Comparison of serum levels of IL-2 and IL-6 before and after treatment in the study and control groups. Comparison of serum IL-2 levels before and after treatment between the study and control groups (A); comparison of serum IL-6 levels before and after treatment between the study and control groups (B). * $P < 0.001$ compared to before treatment; # $P < 0.001$ compared to control group after treatment.

Serum IL-2 and IL-6 levels before and after the treatment in the study and control groups

The pretreatment serum levels of IL-2 and IL-6 in the study group were 2.51 ± 0.83 µg/L and 66.93 ± 14.52 ng/L, respectively; the corresponding post-treatment levels were 3.99 ± 1.16 µg/L and 46.41 ± 13.58 ng/L, respectively. The pretreatment serum levels of IL-2 and IL-6 in the control group were 2.43 ± 0.87 µg/L and 67.87 ± 13.51 ng/L, respectively; the corresponding post-treatment levels were 3.15 ± 1.01 µg/L and 56.47 ± 14.64 ng/L. Intergroup differences in pretreatment serum IL-2 and IL-6 levels were not significant ($P > 0.05$). Further, the post-treatment serum IL-2 levels in the study and control groups were significantly higher than the pretreatment levels ($t = 7.482$, $P < 0.001$; $t = 3.819$, $P < 0.001$, respectively). The post-treatment serum IL-2 levels in the study group were significantly higher than those in the control group ($t = 3.894$, $P < 0.001$). The serum levels of IL-6 after the treatment in the study and control groups were significantly lower than those before the treatment ($t = 7.443$, $P < 0.001$; $t = 4.046$, $P < 0.001$, respectively). The post-treatment serum IL-6 level in the study group was significantly lower than that in the control group ($t = 3.600$, $P < 0.001$; Figure 4A, 4B).

Discussion

Although AR does not induce a severe disease state, it seriously affects the quality of life of patients and affect the normal development of children if the disease onset is in early childhood [14]. Previous studies have shown that SCIT improves clinical symptoms in children. However, because of the suboptimal drug delivery routes and poor compliance by children, it might take a long time to show a curative effect [15]. The application of SLIT is very convenient and *D. farinae* drops can inhibit the degranulation of T lymphocytes in the human body, reduce the

tension bronchial smooth muscles, and alleviate symptoms such as breathlessness and cough [16].

D. farinae drops contain active proteins of the allergens, which stimulate the immune response in the body and gradually induce tolerance to the allergen so as to alleviate nasal discomfort in AR patients [17]. *Dermatophagoides* mites possess strong allergens and can cause adenoid hypertrophy. *D. farinae* drops can eliminate clinical symptoms in children with AR by binding the allergens [18].

D. farinae drops is an SLIT and induces the production of blocking antibodies with specificity, including IgE, T-IgE, and IgG4, which combine with the allergens to block the interaction between the IgG on the surface of the mast cells and the basophil and the antigens so as to reduce the occurrence of type I hypersensitivity reaction [19,20]. The results of this study indicated that the scores of the symptom and medications in the study group and the control group were significantly lower than those before treatment, and the scores of symptom medications in the study group were significantly lower than those in the control group after treatment; the total effective rate of the treatment group was significantly higher than that of the control group. The eosinophil count in the peripheral blood and the serum levels of IgE and T-IgE after treatment in the study and control groups were significantly lower than those before the treatment. The serum IgG4 level after treatment was significantly higher than that before the treatment. Further, the eosinophil count in the peripheral blood and the serum levels of IgE and T-IgE after treatment in the study group were significantly lower than those in the control group. In addition, the serum IgG4 level in the study group was significantly higher than that in the control group. These findings suggest that the sublingual *D. farinae* drops can regulate the immune function of children with AR and improve their clinical symptoms by

combing the blocking antibodies with the allergens, which is similar to the results of Cao et al. [21].

Studies have also shown that SLIT can reduce sIgE, and allergen-specific T cells in patients with allergic rhinitis are shifted from TH1 to TH2 by activating inflammatory cells in the mucosa [22]. Therefore, sublingual *D. farinae* drops may regulate the immune function of children with adenoid hypertrophy by blocking the binding of antibodies to allergens, thereby improving clinical symptoms.

AR is a non-infective inflammatory disease involving many cytokines, and in cases of AR, inflammatory cell infiltration may be observed in the nasal mucosa, which is mainly caused by the imbalance of functions and proportions of Th1/Th2 cells in the body [23]. AR is an inflammatory response induced by immune cells and can cause a decrease in interferon- γ , IL-2, and other cytokines in Th1 cells, and increase cytokines including IL-4, IL-6, and IL-9 in Th2 cells [24]. IL-2 has an immunomodulatory effect and can activate and induce multiple immune cells in the body to play a dual role in regulating immune responses [25]. IL-6 is an inflammatory cytokine that mediates the proliferation and activation of T lymphocytes and promotes the aggregation of inflammatory cytokines during inflammatory reactions to achieve the release of inflammatory mediators [26,27]. The results of this study show that the serum IL-2 levels after treatment in the study and control groups were significantly higher than those before treatment. Further, the serum level of IL-6 after treatment was significantly lower than that before treatment, and the serum level of IL-2 after treatment in the study group was significantly higher than that in the control group. Additionally, the serum level of IL-6 in the study group was significantly lower than that in the control group. Thus, the sublingual administration of *D. farinae* drops can promote the formation of Th1 cells, inhibit the activity of Th2, and restore the balance of Th1 and Th2 cells by regulating the expression of IL-2 and IL-6 to improve immune function

and clinical symptoms of AR in children. Zhao et al. [28] suggested that water-soluble chitosan nasal sprays can improve perennial AR by affecting the levels of IL-6 and IL-10 in the serum; as in the present study, the goal was to improve allergic rhinitis by regulating inflammatory factors, but the selected therapeutic drugs differed from those used in the present study. Bohle et al. [29] found that SLAIT can induce regulatory T cell inhibition by IL-10 in the early stage of treatment, and induce allergen-specific T cell-specific anergy and immune deviation in the late stage of treatment. However, this study did not explore the allergen specificity of the immune mechanism induced by sublingual dust mites, and it remains to be elucidated in subsequent research.

In the present study, subjects were strictly selected according to the inclusion and exclusion criteria, and the general clinical baseline data, including the sex, age, disease course, body weight, Hb, RBC count, PLT count, and DBil and TBil levels, were not significantly different between the study and control groups to ensure the rigorousness and reliability of the study. This study has some limitations, in that we did not explore the regulatory mechanism of serum IgE, T-IgE, IgG4, IL-2, and IL-6 in children with AR. In future studies, animal experiments should be carried out to clarify the specific regulatory mechanisms of these indicators in AR to further verify the results of this study.

Conclusions

Sublingual *D. farinae* drops can improve immune function and clinical symptoms of AR caused by *Dermatophagoides* mites in children.

Conflict of interest

None.

References:

1. Seidman MD, Gurgel RK, Lin SY et al: Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*, 2015; 152: 51–43
2. Frohlich M, Pinart M, Keller T et al: Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis. *Clin Transl Allergy*, 2017; 7: 44
3. Rajakulasingam RK, Farah N, Huber PAJ et al: Practice and safety of allergen-specific immunotherapy for allergic rhinitis in the UK national health service: A report of “real world” clinical practice. *Clin Exp Allergy*, 2018; 48: 89–92
4. Leger D, Bonnefoy B, Pigearias B et al: Poor sleep is highly associated with house dust mite allergic rhinitis in adults and children. *Allergy Asthma Clin Immunol*, 2017; 13: 36
5. Caimmi D, Baiz N, Tanno LK et al: Validation of the MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis control. *Clin Exp Allergy*, 2017; 47: 1526–33
6. Roberts G: Quality of life, when to step down asthma therapy and remembering allergic rhinitis. *Clin Exp Allergy*, 2017; 47: 440–41
7. Scadding GW, Calderon MA, Shamji MH et al: Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: The GRASS randomized clinical trial. *JAMA*, 2017; 317: 615–25
8. Zielen S, Devillier P, Heinrich J et al: Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: A retrospective, real-world database analysis. *Allergy*, 2018; 73: 165–77
9. Wagoner WW, Burchfield SS, Ebeling MD et al: Treatment of maize-based occupational rhinitis by phleum pratense subcutaneous immunotherapy. *J Allergy Clin Immunol*, 2017; 139: AB152
10. Rondon C, Blanca-Lopez N, Campo P et al: Specific immunotherapy in local allergic rhinitis: A randomized, double-blind placebo-controlled trial with Phleum pratense subcutaneous allergen immunotherapy. *Allergy*, 2018; 73: 905–15

11. Wu YJ, Wang P, Liu ZX, Qiu SQ: [Efficacy of sublingual immunotherapy with dermatophagoides farinae drops in children with allergic rhinitis and the change of TGF-beta and IL-13 mRNA level]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*, 2018; 32: 256–59 [in Chinese]
12. Patel M, Wu M-M, Turner H, Franklin K: Oral Cetirizine 10 mg significantly improves highest perennial allergic rhinitis symptom severity score (s) in posthoc analysis. *J Allergy Clin Immunol*, 2017; 139: AB252
13. Zheng XL, Tian YP, Luo HY et al: [Effect of warm acupuncture on the levels of serum immunoglobulin E, Interleukin-1 beta and tumor necrosis factor-alpha in rats with allergic rhinitis]. *Zhen Ci Yan Jiu*, 2018; 43: 35–38 [in Chinese]
14. Dykewicz MS, Wallace DV, Baroody F et al: Treatment of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. *Ann Allergy Asthma Immunol*, 2017; 119: 489–511.e41
15. Jerzynska J, Stelmach W, Rychlik B et al: The clinical effect of vitamin D supplementation combined with grass-specific sublingual immunotherapy in children with allergic rhinitis. *Allergy Asthma Proc*, 2016; 37: 105–14
16. Anderson HM, Wood RA, Busse WW: Dust mite-induced perennial allergic rhinitis in pediatric patients and sublingual immunotherapy. *J Allergy Clin Immunol Pract*, 2017; 5: 46–51
17. Durham SR, Creticos PS, Nelson HS et al: Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. *J Allergy Clin Immunol*, 2016; 138: 1081–88.e4
18. Demoly P, Emminger W, Rehm D et al: Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*, 2016; 137: 444–51.e8
19. Demoly P, Parkes A, Abiteboul K: P60: Treatment with house dust mite sublingual tablets in allergic rhinitis subjects: House dust mite specific IgE and IgG4 results. *Internal Medicine Journal*, 2017; 47: 23
20. Thiele J, Steacy LM, Soliman M et al: The allergic rhinitis clinical investigator collaborative (AR-CIC)-A correlation analysis of specific IgE levels and skin prick testing with symptoms induced via the nasal allergen challenge model of allergic rhinitis. *J Allergy Clin Immunol*, 2017; 139: AB162
21. Cao LF, Lu Q, Gu HL et al: [Clinical evaluation for sublingual immunotherapy of allergic asthma and atopic rhinitis with *Dermatophagoides Farinae* Drops]. *Zhonghua Er Ke Za Zhi*, 2007; 45: 736–41 [in Chinese]
22. Moingeon P, Batard T, Fadel R et al: Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy*, 2006; 61: 151–65
23. De la Cruz-Mosso U, Garcia-Iglesias T, Bucala R et al: MIF promotes a differential Th1/Th2/Th17 inflammatory response in human primary cell cultures: Predominance of Th17 cytokine profile in PBMC from healthy subjects and increase of IL-6 and TNF-alpha in PBMC from active SLE patients. *Cell Immunol*, 2018; 324: 42–49
24. Komori T: The significance of proinflammatory cytokines and Th1/Th2 balance in depression and action of antidepressants. *Neuropsychiatry*, 2017; 7: 57–60
25. Utomo BSR, Hatta M, Sirait RH et al: The role of cytokine interleukin-2, transcription factor of FoxP3 in the immunological regulation of allergic rhinitis. *International Journal of Otolaryngology and Head & Neck Surgery*, 2017; 7: 7
26. Brożek JL, Bousquet J, Agache I et al: Allergic rhinitis and its impact on asthma (ARIA) guidelines – 2016 revision. *J Allergy Clin Immunol*, 2017; 140: 950–58
27. Charnock DR, Settipane RA: *Epidemiology of rhinitis: Allergic and nonallergic. Nonallergic Rhinitis*. CRC Press, 2016; 45–56
28. Zhao H, Li H, Zhou C et al: Aqueous nasal spray of chitosan oligosaccharide ameliorates perennial allergic rhinitis by affecting serum levels of interleukin-6 and interleukin-10. *Int J Clin Exp Med*, 2018; 11: 539–48
29. Bohle B, Kinaciyan T, Gerstmayr M et al: Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol*, 2007; 120: 707–13