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Clinical evaluation of sublingual administration of dust mite drops in the treatment of allergic asthma and allergic rhinitis of children

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Abstract. – OBJECTIVE: This study focuses on evaluating the clinical effects of sublingual dust mite drops for the treatment of allergic asthma in children.

PATIENTS AND METHODS: 156 pediatric patients with allergic rhinitis and asthma were randomly divided into control and observation groups (78 cases each). For the control group the standard global initiative for asthma (GINA) asthma control scheme was adopted; meanwhile, the observation group patients received the standard GINA combined with sublingual administration of dust mite drops, once per day, gradually increasing the dose to reach a high maintenance level. After six months the sublingual drops were stopped and then the effects of the treatments on both groups of patients were compared.

RESULTS: The symptoms of asthma and rhinitis in the daytime and nighttime for both groups decreased gradually with time. However, the observation group's outcome at the 6th, 12th and 24th month were significantly better than those of the control group ($p < 0.05$). Moreover, the FVC, FEV_1 and PEF values of the two groups increased gradually, but those of the observation group improved more obviously ($p < 0.05$). The total effective rate of the observation group at the 6th and 24th months was significantly higher than that of the control group ($p < 0.05$). The contrast of complete and good control at 6 months had no statistical significance ($p > 0.05$). But at the 24th month, the observation group had significantly higher rates of complete and good control ($p < 0.05$). During the median time of sublingual administration of 20.3 months (ranging from 6 to 36 months), there were no evident adverse reactions. Finally, after the intervention, there were no significant differences between the IgE levels of the two groups ($p > 0.05$); however, the levels of IL-2 increased gradually and improved more in the observation group ($p < 0.05$).

CONCLUSIONS: The results of our study support the notion that sublingual administration of dust mite drops to treat allergic rhinitis and asthma can improve clinical symptoms, increase the efficiency rate and increase the serum IL-2 level, and does not cause an increase in adverse reactions or IgE levels in treated children.

Key Words:

Sublingual dust mite drops, Allergic asthma, Allergic rhinitis, Standard GINA asthma control schemes.

Introduction

Children's allergic asthma is usually related to the presence of allergic rhinitis, dust or dust mite allergies and an autoimmune system imbalance[1,2]. Standard global initiative for asthma (GINA) asthma control schemes recommend the use of bronchial relaxants and glucocorticoids, but according to the statistics, the normal utilization rate is only about 10-30%[3], because parents of asthmatic children worry about side effects of the medication and there is poor adherence to the prescription. This poor patient compliance in many cases results in difficulties in the treatment of allergic asthma, and the frequency of symptoms gradually increase. Specific immune therapy is considered to be the only method that can alleviate symptoms of allergic disease, and change the natural course of the disease[4]. The safety profile and therapeutic effects of the SLIT scheme have been reported to be better than conventional subcutaneous injection[4,5]. This study aims at evaluating the effects of administration of dust mite drops in the treatment of allergic asthma and allergic rhinitis of children, and to provide a reference basis for clinical treatment.

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Patients and Methods

Patients

A total of 156 children with allergic asthma and rhinitis diagnosed in our hospital between January 2013 and January 2015 were successively enrolled in the study. Inclusion criteria included an age between 1. 5 to 18 years; diagnosis in line with the diagnostic criteria for allergic asthma and allergic rhinitis, patients in a mild to moderate acute phase of asthma; a positive result of dust mites skin prick test; a good willingness to adhere to the prescribed medication, finishing the follow-ups, and not participating in other studies; history of normal growth and development, no autoimmune diseases, and normal functions of heart, lung, kidney and other organs.

The hospital Ethics Committee approved the research and the children's guardians signed informed consent forms. The children were divided into two groups of equal size by a method of random numbers. In the control group there were 40 boys and 38 girls; with an age range from 5 to 16 years (10.3 + 4.5 years on average); the course of the disease had a duration ranging from 1 to 6 months (3.3 + 1.5 months on average). In the observation group, there were 42 boys and girls, ranging in age from 5.5 to 17.5 years (11.2 + 4.8 years on average); the course of the disease had had a duration ranging from 1.5 to 6.5 months (3.6 + 1.4 months on average). Comparisons of gender, age, and asthma course between the two groups, yielded no statistically significant differences ($p > 0.05$).

Methods

For the control group standard GINA asthma control schemes were adopted, using intravenous drip, inhaled or oral hormones, leukotriene receptor antagonists, antihistamines, bronchial beta agonists, theophylline and so on the basis of disease severity.

For the observation group the same standard GINA schemes were used but in combination with sublingual administration of dust mite drops (trade name Chang Di, produced by Zhejiang WOWU Biology Co., Ltd., Shanghai, China) The protein concentrations of solutions 1 to 5 were 1, 10, 100, 333 and 100 mg/l, solutions 1 to 3 were used at the initial increasing phrase, and 4 to 5 at a later maintenance phase. Treatment began with the solution 1, administering one drop under the tongue and then swallowing and then repeating as appropriate, using the medicine once per day at the same time point in the morning on an empty stomach or before going to bed. The doses were gradually increased daily (doses of 1st to 7th day were 1, 2, 3, 4, 6, 8 and 10 drops respectively). Solution 2 was used in the second week, solution 3 the third week. Finally, the maintenance phase began from the forth week on, at this point patients took three drops of solution 4 once before sleep; patients over 12 years of age took solution 5 to maintain treatments. Any patient, who got an acute attack of asthma or fever during the treatment, suspended the dust wax drops. If the suspension time was less than two weeks long, the last dosage was resumed to continue the treatment; if the suspension time was longer and happened during the initial increasing phase, then starting from solution 1 was necessary, if the suspension happened during the maintenance phase, then patients re-started taking solution 3. If dose increasing caused a worsening of rhinitis symptoms or asthma attacks, lower doses were maintained for a period of time before slowly increasing them. The effects of treatment were compared between the two groups after a sustained maintenance period of 6 months. Patients were recommended to continue treatment for 2 years in order to achieve optimal results.

Observation Targets

Several clinical and laboratory markers were evaluated and the group averages were compared among groups.

Asthma symptoms were given a score according to the presence of daytime or nighttime symptoms: Asymptomatic days or nights were assigned 0 points. One point was given to instances when a few symptoms were present for a short time; the patient woke up once or woke up too early. Two points meant the patient experienced mild symptoms for a longer time in a day, but no impact on life and work, or woke up many times. Patients with heavier symptoms for a longer time in a day, affecting life and work, or presenting an inability to sleep at night were assigned four points. And finally, five points were given to patients with severe symptoms that obstruct normal work and life.

Similarly, a classification was used to assign points for allergic rhinitis' signs: the maximal 3 points were given in the presence of an inferior turbinate close to the nasal floor and nasal septum, without a visible middle turbinate, or middle turbinate mucosa covered in polyps. Two points were given in the presence of an inferior turbinate close to the nasal septum or the nasal floor, and small gaps between the inferior turbinate and septum. One point meant there was only mild

swelling of the inferior turbinate, with a visible nasal septum and middle turbinate.

The tests for lung function were based on the MS-IOS lung function tester in children; they included the ventilation function (FVC), the forced expiratory volume in the first second (FEV_1) and the maximum peak expiratory flow (PEF).

An asthma control questionnaire (ACQ) was used to assess the curative effect of therapies. The questionnaire assigned points based on the answers. A score of less than 0.75 meant that cough and asthma symptoms disappeared within one week and no relapses occurred during the following three months of treatment. A score between 0.75 and 1.5 meant there was good control with treatment, cough and asthma symptoms were reduced after one week and disappeared within a month. Finally, a score greater than 1.5 points meant that there had been no control with treatment.

Screening for adverse reactions was done looking at laboratory tests for abnormal blood chemistry, doing routine urinary tract, liver and kidney function tests, and examining patients clinically for fatigue, gastrointestinal discomfort, headache, rash, diarrhea, asthma, or anaphylactic shock.

The ELISA method was used to detect IgE, and IL-2 levels in the blood, kits were bought from the British Binding Site Company, and the manufacturer's instructions were strictly followed.

Statistical Analysis

The SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were represented using mean ± standard deviation, and the inter-group comparisons using the independent sample t-test. Comparisons in the group were done using variance analysis of repeated measurement data. Categorical data were expressed using cases or percentages. Comparisons between groups were performed adopting chi-square tests, and hierarchical data comparisons using rank and inspection. Differences were assumed to have statistical significant when $p < 0.05$.

Results

Comparison of Asthma and Rhinitis Symptoms Scores

The comparison of asthma and rhinitis symptoms scores of the two groups before intervention in the daytime and nighttime showed the differences had no statistical significance ($p > 0.05$). After the beginning of the intervention, the scores gradually decreased with time; it became clear that the scores in the observation group at the 6^{th}, 12^{th} and 24^{th} months were significantly lower than those of the control group ($p < 0.05$) (Table I).

Table I. Comparison of asthma and rhinitis symptoms scores

Groups		The control group	The observation group	*t*	*p*
Asthma score in the daytime	Before intervention	4.0±0.6	4.2±0.7	0.632	0.747
	At six months	2.6±0.5	2.3±0.5	4.453	0.041
	At twelve months	1.7±0.4	0.8±0.3	4.968	0.036
	At twenty-four months	1.5±0.6	0.5±0.2	5.321	0.030
	F	5.320	6.548		
	p	0.030	0.017		
Asthma score in the nighttime	Before intervention	3.1±0.7	3.2±0.6	0.326	0.421
	At six months	1.9±0.5	1.6±0.4	4.526	0.040
	At twelve months	1.3±0.6	0.9±0.3	5.201	0.031
	At twenty-four months	1.0±0.3	0.6±0.2	5.637	0.025
	F	5.427	6.965		
	p	0.026	0.010		
Rhinitis symptom scores					
	Before intervention	2.4±0.7	2.5±0.6	0.529	0.867
	At six months	2.2±0.5	2.0±0.4	4.857	0.037
	At twelve months	1.6±0.5	1.3±0.3	5.246	0.032
	At twenty-four months	1.0±0.4	0.6±0.3	5.758	0.023
	F	5.758	7.201		
	p	0.022	0.009		

Table II. Comparison of lung function indexes.

Groups		The control group	The observation group	*t*	*p*
FVC (l)	Before intervention	0.90±0.14	0.89±0.17	0.457	0.602
	At six months	1.10±0.16	1.16±0.15	4.312	0.042
	At twelve months	1.23±0.18	1.45±0.16	4.652	0.040
	At twenty-four months	1.25±0.17	1.58±0.16	5.127	0.033
	F	5.214	6.336		
	p	0.032	0.019		
FEV1 (%)	Before intervention	23.4±5.2	23.3±5.6	0.124	0.326
	At six months	25.6±5.5	28.9±5.4	5.120	0.036
	At twelve months	28.7±5.6	33.4±5.5	5.527	0.028
	At twenty-four months	30.6±5.3	36.7±5.7	5.965	0.017
	F	5.865	7.123		
	p	0.022	0.006		
PEF (l/min)	Before intervention	95.6±15.6	96.3±15.2	0.825	0.769
	At six months	102.3±16.3	105.7±15.7	4.325	0.040
	At twelve months	106.8±16.6	113.2±15.9	5.012	0.035
	At twenty-four months	110.2±17.0	125.4±14.8	5.658	0.026
	F	6.230	7.458		
	p	0.019	0.003		

The Comparison of Lung Function index

The differences in FVC, FEV_1 and PEF between the two groups before the intervention showed no statistical significance ($p > 0.05$). However, all the above indexes increased after intervention in both groups, but the improvement in the observation group was more obvious ($p < 0.05$) (Table II).

Comparison of the Total Effective Rate of Treatment and the Occurrence Rate of Adverse Reactions

The total effective rate in the observation group was significantly higher than that in the control group at six and twenty-four months ($p < 0.05$). Comparing the complete control and good control rates at six months, there were no statistically significant differences ($p > 0.05$); however, at twenty-four months, the rates in the observation group were significantly higher than those in the control group ($p < 0.05$) (Table III). At twenty-four months, there were no evident adverse reactions reported during follow-ups in the observation group; the sublingual administration time ranged from 6 to 36 months (with a median time of 20.3 months).

The comparison of serum IgE and IL-2 level

The comparisons of serum levels of IgE and IL-2 between the two groups before intervention showed no statistically significant differences ($p > 0.05$). Also, after the intervention, the comparisons of IgE levels at each time point showed the differences had no statistical significance ($p > 0.05$). In contrast, the levels of IL-2 increased gradually in the two groups after the intervention, with the levels in the observation group being sig-

Table III. Comparison of total effective treatment [case (%)]

Groups	Cases	Complete control	Good control	No control	Effective rate at six months	Complete control	Good control	No control	Effective rate of twenty-four months
The control group	78	20 (25.6)	27 (34.6)	31 (39.7)	47 (60.3)	23 (29.5)	29 (37.2)	26(33.3)	52 (66.7)
The observation group	78	29 (37.2)	30 (38.5)	19 (24.4)	59 (75.6)	32 (41.0)	38 (48.7)	8 (10.3)	70 (89.7)
	χ^2	4.691			4.238	12.211			12.185
	p	0.096			0.040	0.002			0.000

nificantly higher at each time point than the levels in the control groups ($p < 0.05$) (Table IV).

Discussion

Research shows that sublingual desensitization can significantly reduce nasal membrane inflammation and clinical symptoms of asthma, and reduce the sensitivity to the allergen[6]; the effects on allergic rhinitis may be excellent. Other researches have deemed sublingual administration and subcutaneous injections both to achieve similar effects, and combining their application with antihistamines can produce synergies against the bronchial hyper-responsiveness[7]. Wilson and Durham[8] took 22 randomized, double-blind and placebo-controlled studies including 979 cases of allergic rhinitis and found a decrease in symptoms and in the requirement for additional medications in all those subjected to immunotherapy.

This research concludes that after the intervention, asthma and rhinitis symptoms scores of the two groups during daytime and nighttime gradually decreased with time. However, the scores in the observation group at 6, 12 and 24 months are significantly better than those in the control group. Also, after the intervention, the FVC, FEV1 and PEF values of the two groups increased gradually, but the values in the observation group improved to a greater extent. At months 6 and 14, the total effective rates in the observation group were significantly higher than those in the control group. Importantly, after 24 months the complete and good control rates were higher in the observation group, and no obvious adverse reactions occurred during the follow-up period. Finally, although the comparison of IgE levels at each time point showed no significant differences between the two groups, the levels of IL-2 were significantly higher in the observation group.

Our results confirmed that using sublingual administration of dust mite drops to treat allergic asthma and rhinitis in children can improve clinical symptoms, improve the efficiency of other treatments and increase the serum level of IL-2, without increasing adverse reactions or IgE levels. Some research even suggests that SLIT therapy can adjust IgE levels or reduce the IgE/IgG ratio, and stimulate mucosal inflammatory cells, to switch the T cell response from Th1 to Th2[9].

Factors influencing the treatment outcome include the patient's compliance, social, economic and family factors, etc[10]. In addition, when sublingual administration gives 6 to 10 drops at once, it is very easy to swallow the medication into the stomach. The best candidates for the sublingual desensitization therapy include children with intermittent mild-to-moderate asthma and rhinitis caused by single trigger allergies that have been controlled[11]. A study on the safety of SLIT meta-analysis concluded that in a total of 240000 administrations to 1200 patients, there were no serious adverse reactions[12].

Conclusions

Choosing appropriate desensitization, informing the patients well to improve the compliance to treatment and closely monitoring adverse reactions are all effective means of ensuring an effective sublingual administration of dust mite drops to treat allergic asthma and rhinitis in children.

Table IV. Comparison of serum IgE and IL-2 level.

Groups		Control group	Observation group	*t*	*p*
IgE (IU/ml)	Before intervention	256.8±56.3	262.3±63.2	0.638	0.768
	At six months	176.5±52.4	185.4±64.7	0.957	0.125
	At twelve months	152.3±45.6	163.2±54.9	1.230	0.639
	At twenty-four months	124.7±42.3	130.3±53.2	1.524	0.754
	F	6.203	6.003		
	p	0.030	0.032		
IL-2 (IU/ml)	Before intervention	42.6±7.3	42.0±7.6	0.563	0.948
	At six months	44.7±7.7	48.9±7.9	5.302	0.030
	At twelve months	46.9±7.5	51.3±7.4	5.758	0.024
	At twenty-four months	47.0±7.0	56.6±7.3	6.314	0.015
	F	4.532	7.123		
	p	0.043	0.006		

Conflicts of interest

The authors declare no conflicts of interest.

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