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Original Article

Clinical efficacy of ketotifen tablets and montelukast sodium tablets as a combination treatment for children with allergic rhinitis and their effect on serum inflammatory factors

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Abstract: Objective: This study was designed to evaluate the efficacy of Ketotifen Tablets and Montelukast Sodium Tablets as a combination treatment for children with allergic rhinitis and their effect on serum inflammatory factors. Methods: In total, 67 children diagnosed with allergic rhinitis in our hospital from February 2017 to November 2018 were included as study subjects, and divided into the control group (n=32) in which patients were treated with Ketotifen tablets, and the observation group (n=35) in which patients were treated with Ketotifen tablets and Montelukast Sodium tablets. Before and after treatment, patients were assessed for syndromes with TNSS and TNNSS, levels of TNF-α, IL-4 and IFN-γ with ELISA, serum IgE with TINIA; and compared for clinical efficacy and effect on serum inflammatory factors (TNF-α, IL-4 and IFN-γ) and serum IgE. Results: Compared with the control group, the observation group showed significant increases in clinical efficacy ($P<0.05$), levels of serum IL-10 and serum IFN-γ ($P<0.05$), decreases in serum IgE ($P<0.05$), TNSS and TNNSS scores ($P<0.05$), levels of TNF-α, IL-4 and IL-10 ($P<0.05$), serum TNF-α and IL-4 ($P<0.05$). Conclusion: Ketotifen Tablets and Montelukast Sodium Tablets as a combination treatment can better treat allergic rhinitis by reducing TNSS and TNNSS scores, and IgE, and alleviating inflammatory reaction, over Ketotifen tablets alone.

Keywords: Ketotifen tablet, montelukast sodium tablet, allergic rhinitis, serum inflammatory factor

Introduction

Allergic rhinitis is a type of allergic inflammation more common in children [1] since they are have less immunocompetence because of underdeveloped organs [2]. Allergic rhinitis involves multiple kinds of immune cells and cell factors resulting in chronic inflammation in the nasal mucosa, and is characterized by syndromes such as rhinobyon, runny nose, rhinocnesmus and sneezing, etc. [3, 4]. Without proper and effective treatment in a timely manner, the disease may develop into allergic sinusitis, asthma, otitis media, nasal polyps, etc., and can severely threaten the health and QOL of patients [5, 6].

Clinical treatment is dominated by antihistamines, anticholinergic agents and glucocorticoids in most cases. However, those drugs may fail to control the syndromes completely in some children. Therefore, finding a proper way of treating allergic rhinitis is a hot spot in clinical study [7, 8]. Montelukast Sodium Chewable Tablets are a selective LTRA which can inhibit inflammatory cells such as eosinophil granulocytes effectively, lower the incidence of inflammatory reaction, and alleviate clinical syndromes of allergic rhinitis such as rhinobyon [9, 10]. Ketotifen is a general antihistamine used to treat seasonal allergic rhinitis. Studies have proven its ability to effectively inhibit the release of eosinophil granulocytes and labrocytes, efficiently binding with histamine, an antagonist against H1 receptor, and blocking the cascade reaction arising from exciting H1 receptors [11]. Studies in recent years revealed a significant rise of related inflammatory factor levels in peripheral blood (PB) of patients with allergic rhinitis, and a vital role of inflammatory cell factors in the progress of the disease [12].

The significant benefits of Montelukast Sodium and Ketotifen in relieving patients from allergic rhinitis have been demonstrated through previous studies [13-15]. However, little study has been performed with focus on their combined application against the same disease. In this study, Montelukast Sodium and Ketotifen were provided as a combination treatment for children with acute enteritis to observe the changes of inflammatory factors of TNF-α, IL-4 and IgE during treatment, in order to provide references and basis for the treatment of children with allergic rhinitis.

Material and methods

General materials

In total, 67 children diagnosed with allergic rhinitis in our hospital from February 2017 to November 2018 were included as study subjects, and divided into the control group (n=32) with 17 males and 15 females aged between 5 and 12 (average age of 7.23±1.42), who were treated with Ketotifen tablets, and the observation group (n=35) with 19 males and 16 females aged between 4 and 10 (average age of 7.29±1.56), who were treated with Ketotifen tablets and Montelukast Sodium tablets.

Inclusion criteria: Children under 12 diagnosed with pediatric allergic rhinitis characterized by frequent occurrence of stuffy or runny nose, sneezing, throat itching and other syndromes, hyperemia and hydroncus in nasal mucosa as observed through examination, and whose family members have been informed.

Exclusion criteria: Children who were suffering from other combined organic diseases in heart, liver and kidney, rhinitis due to bacterial, mycoplasma and virus infection, allergic asthma, dehydration, severe infection, TB, bronchiectasis hemorrhage, severe combined dysfunction of lungs, kidney, liver and heart, combined acute and chronic paranasal rhinitis, vasomotor rhinitis and nasosinusitis, and other such nasal diseases, combined nasal therioma, severe dysgnosia and epilepsia which occurred such that they can't cooperate with the treatment, and children allergic to the drugs studied or demanding nasal surgery due to organic lesions in nasal cavity, were excluded. All patients signed the Informed Consent. The study was submitted to the Ethics Committee of the Fujian University of Traditional Chinese Medicine for review and approval before implementation.

Treatment method

Both groups received symptomatic treatment and supportive treatment after hospitalization. The control group was routinely treated for pediatric allergic rhinitis with Ketotifen tablets (Jiangsu Tianshili Diyi Pharmaceutical Co., Ltd., GYZ Zi H32023660) at a dose of 0.5 mg/time, two times a day for a course of 1 month, while the observation group, on the same basis, received additional treatment with Montelukast Sodium tablets (Shandong Lunan Beite Pharmaceutical Co., Ltd., specification: 5 mg, lot No.: 1312251) at a dosage of 5 mg/po/qd. The treatment lasted for 2 weeks, and the two groups were compared in terms of efficacy, diarrhea response time, defervescence time and time with normal Stool Routine Test results.

Efficacy assessment

The study subjects were assessed for clinical efficacy 72 h after treatment, which can be graded as markedly effective if syndromes such as stuffy or runny nose, rhinocnesmus and sneezing disappear, or effective if significant improvements are observed in the those syndromes except for visible mild swelling of concha nasalis inferior, concha nasalis media and nasal septum, or ineffective if those syndromes and vital signs are not improved. The total effective rate shall be the sum of markedly effective and effective. Improvements in clinical syndromes of both groups were observed before and after treatment by assessing with TNSS and TNNSS.

Main apparatuses and reagents

TNF-α ELISA test kit (Shanghai Hengfei Biotechnological Co., Ltd., China, CSB-E04740h-1); IL-4 ELISA test kit (Shanghai Hengfei Biotechnological Co., Ltd., China, CSB-E04633h-1); IFN-γ test kit (Shanghai Hengfei Biotechnological Co., Ltd., China, CSB-E04577h-1); AU5800 Automated Biochemical Analyzer (Beckman coulter, USA, AU5800), ELISA detector (Molecular Devices, USA, SpectraMaxiD5), and IgE test kit (Shanghai Hengfei Biotechnological Co., Ltd., China, CD-103900GM).

Test methods

The two groups were observed and recorded for improvements in clinical syndromes, tested for indicators such as serum inflammatory fac-

Table 1. General Materials of the Two Groups [n (%)]/($\bar{x}$ ± sd)

Factor	Observation Group (n=35)	Control Group (n=32)	t/X^2 value	P
Gender			0.176	0.674
M	19 (54.29)	19 (59.38)		
F	16 (45.71)	13 (40.62)		
Age (year)	7.29±1.56	7.23±1.42	0.164	0.872
Weight (kg)	20.25±2.34	19.56±2.25	1.228	0.224
Height (cm)	126.12±5.26	125.15±5.45	0.741	0.461
BMI	12.57±2.43	12.28±3.13	0.426	0.672
Domicile			1.101	0.294
Urban	23 (65.71)	17 (53.13)		
Rural	12 (34.29)	15 (46.88)		
Parents' history of excessive drinking			1.473	0.225
Y	16 (45.71)	10 (31.25)		
N	19 (54.29)	22 (68.75)		
Parents' history of smoking			0.005	0.074
Y	20 (57.14)	18 (56.25)		
N	15 (42.86)	14 (43.75)		
Nationality			0.134	0.718
Minority	3 (8.57)	2 (6.25)		
Han	32 (91.43)	30 (93.75)		
Mother's educational background			2.021	0.155
Under high school	12 (34.29)	16 (50.00)		
At or above high school	23 (65.71)	16 (50.00)		
Erythrocyte ($\times 10^{12}$/L)	4.67±0.93	4.59±0.71	0.405	0.687
Pathogenesis (year)	2.24±2.27	2.98±2.35	1.340	0.187

tors (TNF-α, IL-4 and IFN-γ) and E (Ig E) level with Automated Biochemical Analyzer and serum IgE with TINIA, levels of serum TNF-α, IL-4 and IFN-γ with ELISA before and after treatment via the following steps: control wells and study wells were set up. Into the control wells 50 μL standard substance of different concentrations were added respectively, and the study wells were filled with 10 μL sample to be tested which was then diluted with 40 μL sample diluent; next, 100 μL HRP-marked detection antibody was injected into all wells which were then covered with film, cultivated in water-bath or incubator of 37°C for 60 min, removed of liquid, dried with absorbent paper, and refilled with cleaning solution, left still for 1 min before removal of the cleaning solution by centrifugation, and drying again with absorbent paper. The plates were washed 5 times following the same steps; afterwards, substrates A and B were added into each well in the amount of 50 μL respectively, incubated at 37°C away from the light for 15 min; the last step was addition of stop buffer into each well with an amount of 50 μL and measurement of the OD at the wavelength of 450 nm within 15 min to calculate the concentrations of TNF-α, IL-4 and IFN-γ.

Statistical method

SPSS 22.0 (IBMCorp, Armonk, NY, USA) was adopted for statistical analysis. Nominal data were expressed in [n (%)] and subject to X^2 test between groups. Measurement data were expressed in $\bar{x}$ ± sd, and subject to independent-samples T test between groups or paired t-test in the same group for pre-and-post comparison. P<0.05 indicates a statistically significant difference.

Results

The two groups showed no significant difference in baseline data

No significant difference was observed between the two groups in general clinical materials of gender, age, weight, height, BMI, domicile, parents' history of smoking and excessive drinking, nationality, and mother's educational background (P>0.05, **Table 1**).

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

Type [n (%)]	Observation Group (n=35)	Control Group (n=32)	X^2 value	P
Markedly effective	14 (40.00)	10 (31.25)	0.557	0.456
Effective	18 (51.43)	13 (40. 63)	0.785	0.375
Ineffective	3 (8.57)	9 (28.13)	4.347	0.037
Total effective rate of treatment	32 (91.43)	23 (71.88)	4.347	0.037

Table 3. Comparison of serum TNSS and TNNSS Scores before and after treatment ($\bar{x} \pm sd$)

Group	n	TNSS		TNNSS	
		Before treatment	After treatment	Before treatment	After treatment
Control Group	35	7.65±0.64	4.66±0.47	2.39±0.32	0.84±0.22
Observation Group	32	7.47±0.91	2.13±0.36	2.41±0.38	1.26±0.24
t value	-	0.943	24.560	0.234	7.474
P	-	0.349	<0.001	0.816	<0.001

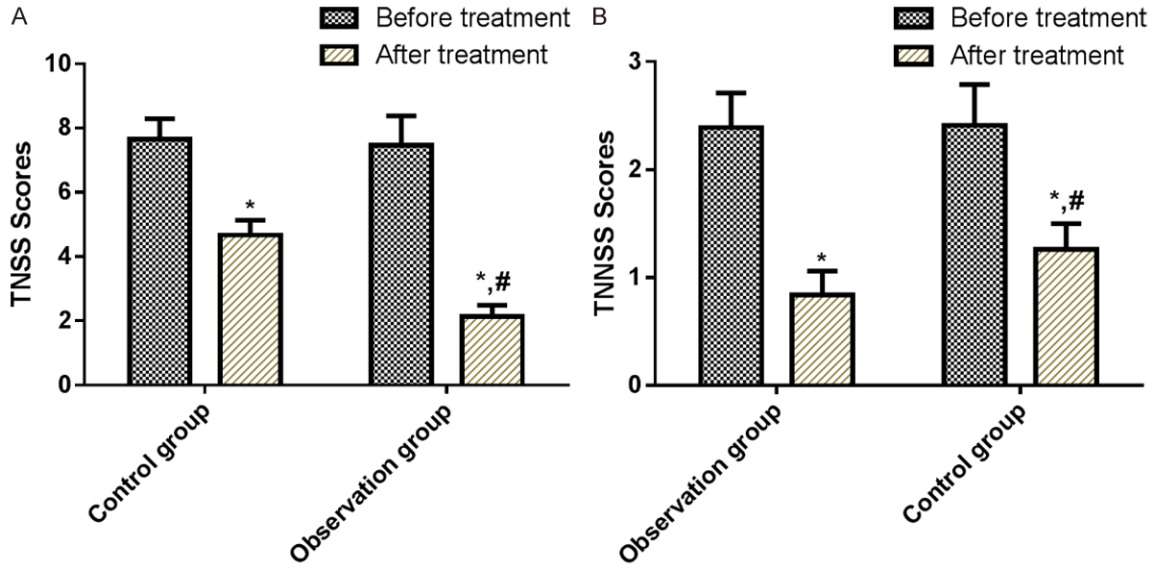

Figure 1. Comparison between the two groups in TNSS and TNNSS Scores before and after treatment. TNSS (A) and TNNSS (B) scores in the two groups were compared, and significantly reduced by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly lower than the control group (P<0.05).

Better clinical efficacy was found in the observation group

After treatment, the observation group reported 14 markedly effective cases (40.00%), 18 effective cases (51.43%) and 3 ineffective cases (8.56%), with total effective rate of 91.43%; while the control group reported 10 markedly effective cases (31.25%), 20 effective cases (40.63%) and 16 ineffective cases (28.13%), with total effective rate of 71.88%. The observation group was significantly higher than the control group (P<0.05) (**Table 2**).

Lower TNSS and TNNSS scores were shown in observation group

Serum TNSS and TNNSS scores in the two groups were significantly reduced by treatment (P<0.05) as compared with those before treatment when there was no significant difference (P>0.05), and the observation group was sig-

Table 4. Comparison of Serum IgE between the Two Groups before and after Treatment ($\bar{x}$ ± sd)

Group	n	IgE (IU/mL)	
		Before treatment	After treatment
Control Group	35	1425.73±214.34	1221.28±317.57*
Observation Group	32	1416.08±223.41	1021.05±312.49*
t value	-	0.180	2.598
P	-	0.857	<0.012

Note: compared with conditions before treatment, *P<0.05.

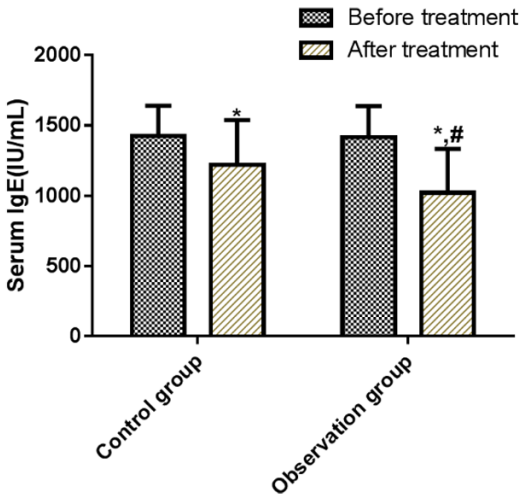

Figure 2. Comparison between the two groups in serum IgE before and after treatment. Serum IgE in the two groups was significantly reduced by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly lower than the control group (P<0.05). Note: compared with conditions before treatment, *P<0.05. Compared with the control group after treatment, #P<0.05.

nificantly lower than the control group (P<0.05) (**Table 3** and **Figure 1**).

Lower IgE level was found in the observation group

Serum IgE in the two groups was significantly reduced by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly lower than the control group (P<0.05) (**Table 4** and **Figure 2**).

TNF-α, IL-4 and IFN-γ levels were significantly increased in the observation group

Serum TNF-α and IL-4 in the two groups were significantly reduced by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly lower than the control group (P<0.05). Serum IFN-γ in the two groups was significantly increased by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly increased than the control group (P<0.05) (**Table 5** and **Figure 3**).

Discussion

In recent years, social development is impacted by industrialization and climatope, leading to a rising trend of cases of pediatric allergic rhinitis increasing year by year [16, 17]. Allergic rhinitis, a type I allergic disease mediated by IgE, attacks depending on seasonal, environmental and climate factors [18], and may cause local release of histamine and increasingly exciting anterior nerve plexus and nerve of the pterygoid canal, which accelerates blood circulation, leading to angiectasis and increases glandular secretion. Consequently, syndromes such as sneezing, runny nose, rhinobyon and rhinocnesmus manifest themselves, and some patients may experience temporary loss of olfactory sensation and reduction in memory, or compromise their lives in serious cases [19, 20].

Montelukast Sodium tablet is a selective LTRA which disables the leukotriene's function of inflammation by blocking its binding with the receptors, and inhibits the maturation-promoting effect of peptidyl growth factor on basophile and eosinophile granulocytes to further reduce the number of eosinophile granulocytes in the air passage and PB. More noteworthy is that no important organ or system has showed significant adverse reaction to this drug [20, 21]. Ketotifen, a H1 receptor antagonist for histamine, is generally administered to treat various allergic responses mediated by IgE. It can protect the cell membranes of labrocytes or basophile granulocytes by changing membrane structure and eliminating the release of allergic active medium in the case of allergen attack. It is a powerful, durable and effective antiallergic drug [22, 23].

In this study, the better efficacy of Montelukast and Ketotifen as a combination treatment for

Table 5. Comparison of levels of serum TNF-α, IL-4 and IFN-γ between the two groups before and after treatment ($\bar{x} \pm sd$)

Group	n	TNF-α (ng/mL)		IL-4 (ng/mL)		IFN-γ (ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control Group	35	17.73±5.64	13.02±2.91*	114.19±4.72	92.94±6.55*	33.27±2.46±2.43	56.08±2.21
Observation Group	32	16.66±4.29	10.13±2.37*	115.85±5.57	73.16±3.86*	32.76±2.68	60.05±3.47
t value	-	0.868	4.432	1.320	14.880	0.812	5.635
P	-	0.389	<0.001	0.192	<0.001	0.420	<0.001

Note: compared with conditions before treatment, *P<0.05.

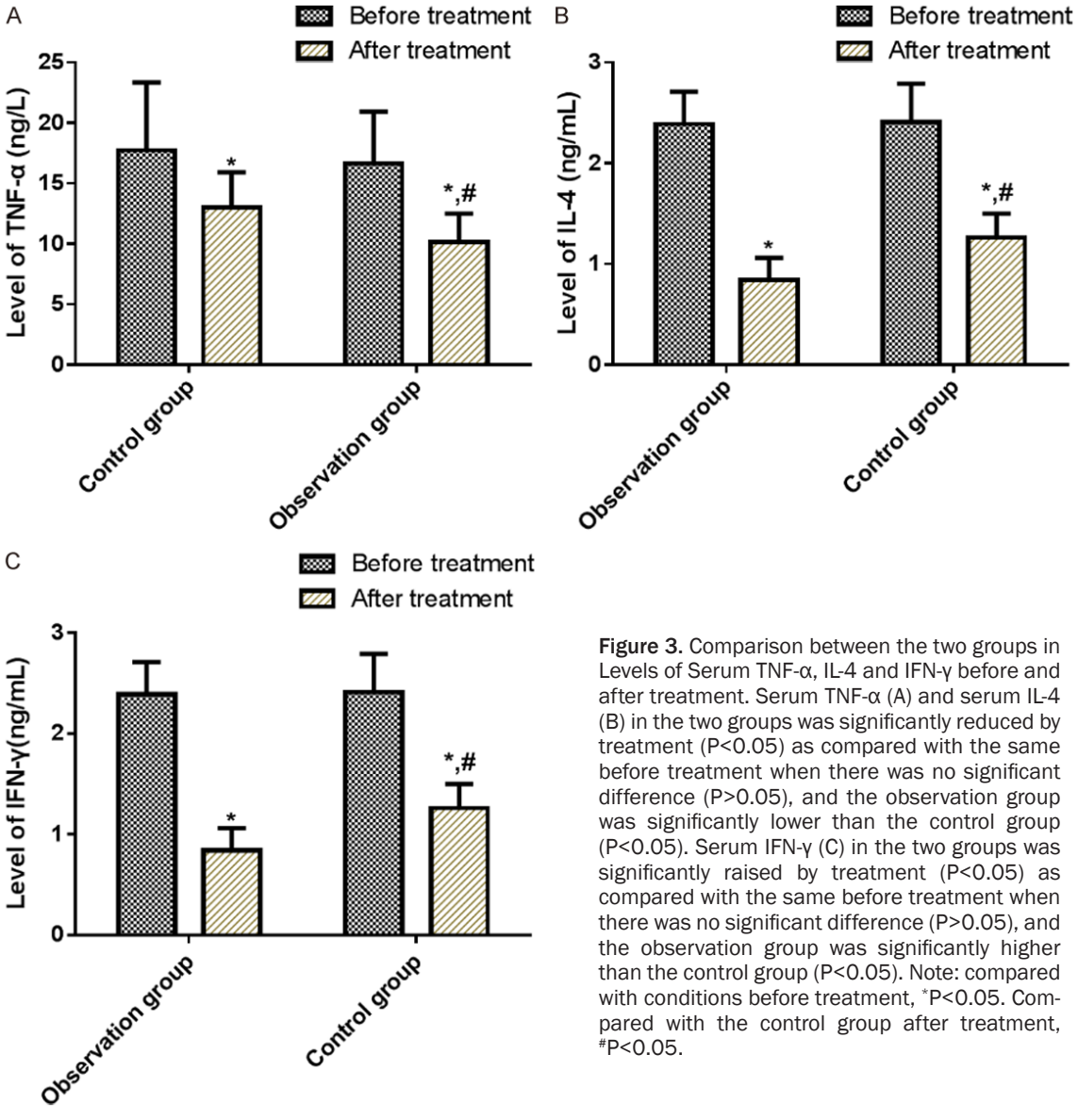

Figure 3. Comparison between the two groups in Levels of Serum TNF-α, IL-4 and IFN-γ before and after treatment. Serum TNF-α (A) and serum IL-4 (B) in the two groups was significantly reduced by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly lower than the control group (P<0.05). Serum IFN-γ (C) in the two groups was significantly raised by treatment (P<0.05) as compared with the same before treatment when there was no significant difference (P>0.05), and the observation group was significantly higher than the control group (P<0.05). Note: compared with conditions before treatment, *P<0.05. Compared with the control group after treatment, #P<0.05.

children with allergic rhinitis has been demonstrated through a significantly higher total effective rate of the observation group as compared with the control group, significant decrease in serum TNSS and TNNSS scores which were not so prominently different between the

two groups before treatment, and serum IgE, which is more prominent in the observation group as compared with the control group ($P<0.05$). Petigara et al [24] investigated and indicated the satisfaction of patients with allergic rhinitis to Montelukast oral disintegrating tablets in their study.

Andhale et al [25] compared the efficacy of Montelukast when it is combined with levocetirizine or Montelukast, and held the ground that Montelukast alone is cost effective and avoids the adverse reactions of levocetirizine, while Phan et al [13] assessed the application data associated with antihistamines and Montelukast, based on which, they pointed out the possibly better resistance and less cardiac toxicity of the 2nd generation of antihistamines and Montelukast, which accords with this study. This evidence supports that the combination treatment with Montelukast and Ketotifen may be ideal and a feasible option for children with allergic rhinitis. TNF-α, IL-4 and IFN-γ are multifunctional inflammatory cell factors which play vital roles in the inflammatory reaction of the body and immune reaction according to existing studies. In this study, treatment contributed to a significant decrease in the levels of serum TNF-α and IL-4, and an increase in the level of IFN-γ, which were more prominent in the observation group compared with the control group, indicating that the combination treatment with Montelukast and Ketotifen can improve the inflammatory reaction in children with allergic rhinitis. Li et al [26] found in their study that Ketotifen bears the potential of reducing FeNO in patients with allergic rhinitis or asthma syndromes significantly, and easing inflammation in the air passage, etc., while Ebrahim et al [27] conducted a study on oral administration of Montelukast which can significantly mitigate the allergic syndromes, reduce ovalbumin-specific immunoglobulin E (IgE) in rats with allergic rhinitis, inhibit chemotactic factors including IL-4, TNF-α and VCAM-1, up-regulate the expression of TGF-β in the Montelukast group, and benefit MSCs, which indicate that the combination treatment with Montelukast and Ketotifen can alleviate inflammation by the possible mechanism of inhibiting inflammatory factor level.

The study testified the prominent benefits of Montelukast and Ketotifen as a combination treatment for children with allergic rhinitis. However, the study is not inclusive since it fails to observe the hazards in children with allergic rhinitis when the disease attacks, and research the specific control and regulation mechanism of TNF-α, IL-4 and IFN-γ in allergic rhinitis, which shall be points demanding more efforts in the future study, in order to provide more evidence to support the study.

In conclusion, Montelukast and Ketotifen as a combination treatment has showen its efficacy in children with allergic rhinitis and ability of improving the patient's QoL by the possible mechanism of inhibiting TNF-α and IL-4 and promoting IFN-γ.

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Disclosure of conflict of interest

None.

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