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Original Article

Effect of azelastine hydrochloride combined with montelukast sodium in the treatment of patients with allergic rhinitis

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Abstract: Objective: To investigate efficacy of azelastine hydrochloride combined with montelukast sodium in the treatment of patients with allergic rhinitis. Methods: A total of 137 patients with allergic rhinitis in our hospital were divided into two groups, 70 patients in the experimental group received azelastine hydrochloride combined with montelukast sodium treatment, while 67 patients in the control group were given only azelastine hydrochloride treatment. The clinical therapeutic effect, clinical symptom score and serum levels of inflammatory factors were recorded. Results: The clinical therapeutic effect of the two groups after treatment were improved compared to those without intervention ($P < 0.05$), and the total effective rate of the experimental group was 94.3% (66/70), which was higher than that of the control group (83.6%). The clinical symptom score (nasal itching, nasal congestion and runny nose) of two groups was decreased after receiving the intervention, and the scores in the experimental group were much lower than the control group after receiving the intervention ($P < 0.05$). The serum levels of inflammatory factors (IL-6, IL-8 and hsCRP) were obviously lower in the two groups after treatment, and those levels in the experimental group were much lower than the control group after receiving the intervention. Furthermore, after the receiving treatment, the levels of each of the inflammatory and anti-inflammatory factors in the experimental group were significantly ameliorated compared to those in the control group ($P < 0.05$). Conclusion: Azelastine hydrochloride combined with montelukast sodium can effectively improve clinical symptoms and inflammatory reactions in patients with allergic rhinitis; furthermore, this research provides ideas for clinical practice.

Keywords: Azelastine hydrochloride, montelukast sodium, allergic rhinitis

Introduction

Allergic rhinitis (AR) is a non-communicable disease with chronic inflammation of the nasal mucosa mediated by IgE. It is mainly caused by exposure of genetically susceptible individuals to environmental allergens [1, 2]. Allergic rhinitis is a global health problem that affects up to 40% of the general population; besides, its main characteristics vary with the severity and duration of the following symptoms, including nasal congestion, nasal itching, clear water like nose running and sneezing. Some patients often suffer from eye itching, conjunctival congestion, hypo-olfactory sympotoms and other discomfort [3]. AR is also associated with a variety of complications, including allergic conjunctivitis, asthma, sinusitis, otitismedia and so on. Among them, AR is also an independent factor in the development and deterioration of asthma. Some research has demonstrated that AR and asthma often coexist in the same individual; about 38% of allergic rhinitis patients are accompanied with asthma, 78% of asthma patients are accompanied with AR, and the risk of asthma in patients with AR is several times that of patients with non-allergic rhinitis [4-6]. Currently, the treatment of AR mainly includes avoiding specific allergens, symptomatic drug therapy and allergen immunotherapy [7]. If possible, patients should avoid known allergens and reduce allergen levels in the environment, which is an integral part of allergy treatment, but it has no significant effect on symptoms [8].

Azelastine hydrochloride, which is a king of antihistamine, is currently the main drug in the treatment of allergic rhinitis. It can relieve nasal itching, runny nose, sneezing and other symptoms in a short time [9, 10]. Montelukast sodium is a leukotriene receptor antagonist, which can significantly block leukotriene and relieve the clinical symptoms of AR patients [11, 12]. Allergic rhinitis, one type of atopic syndromes, has a predisposition toward an exaggerated immunoglobulin E (IgE) mediated immune response in reaction to environmental allergens such as food and other allergen. In the early phase of inflammation, the allergen is activated by B cells to produce IgE antibodies. The IgE antibody then occupies the surface of mast cells, which subsequently release prostaglandin, histamine, and other chemical mediators into surrounding tissues. Further, release of inflammatory mediators promotes a late-phase reaction which encourages the production of inflammatory mediators, and hence triggers the activation that causes the nasal mucosa cells to be assembled. In our study, we investigated the efficacy of azelastine hydrochloride combined with montelukast sodium in the treatment of patients with allergic rhinitis and its effects on *serum levels of inflammatory factors*.

Data and methods

Clinical data

A total of 137 patients with allergic rhinitis in our hospital from January 2018 to December 2020 met the inclusion and exclusion criteria and were randomized allocated into two groups: the experimental group (n=70 cases) and the control group (n=67 cases). The researchers systematically explained the role, purpose and process of the study to the patients and their families. The patients and their families voluntarily signed the informed consent form to participate in this study. This study was approved and recognized by the ethics committee of our hospital.

Inclusion and exclusion standards

Inclusive criteria: ① conformant to the diagnostic standards of allergic rhinitis [13]; ② no history of nasal diseases in the past; ③ age: 18-75 years; ④ no glucocorticoid use within six months; ⑤ subjects were willing to cooperate and implement the experiment.

Exclusion criteria: ① Had a history of mental illness; ② had a history of a deviated nasal septum, acute sinusitis and nasal polyps and other disease; ③ had a history of nasal surgery; ④ had serious cardiac disorders, severe liver malfunction or renal failure; ⑤ had hypersensitivity in response to the drugs or other components in the drug; ⑥ pregnant woman and the breast-feeding woman; ⑦ those unwilling to participate our research.

Methods

The control group (CG): The subjects were only treated with azelastine hydrochloride (Jiangxi Zhenshiming Pharmaceutical Co., Ltd), 2 mg twice a day.

The experimental group (EG): The subjects were treated with azelastine hydrochloride (Jiangxi Zhenshiming Pharmaceutical Co., Ltd) (2 mg twice a day) combined with montelukast sodium (Sichuan Dazhong Pharmaceutical Co., Ltd) (once a day, 10 mg each time).

Evaluation standards of clinical therapeutic effect

① Significantly effective: nasal congestion, nasal itching and runny nose disappeared or almost disappeared after treatment, and there was no recurrence within 2 months.

② Effective: the clinical symptoms were significantly improved compared with those before treatment, and there was no recurrence within one month.

③ Ineffective: there was no improvement in clinical symptoms or recurrence within 1 month.

Total effective rate = (significant effective + effective)/total cases × 100%.

Clinical symptom score standard

The clinical symptoms of the two groups before and after treatment were evaluated, mainly including nasal itching, nasal congestion and runny nose. The specific scoring standards are shown in the **Table 1**.

Serum levels of inflammatory factors

The levels of serum inflammatory factors, including interleukin-6 (IL-6), interleukin-8 (IL-8)

Table 1. Clinical symptom score standard

Clinical symptom	0 score	1 score	2 score	3 score
nasal itching	No symptoms	Mild symptoms, easily tolerated by patients	Moderate symptoms, symptoms more obvious but tolerable	Severe symptoms, intolerable symptoms, affect the patient's life or sleep
nasal congestion	No symptoms	Mild symptoms, easily tolerated by patients	Moderate symptoms, symptoms more obvious but tolerable	Severe symptoms, intolerable symptoms, affect the patient's life or sleep
runny nose	No symptoms	Mild symptoms, easily tolerated by patients	Moderate symptoms, symptoms more obvious but tolerable	Severe symptoms, intolerable symptoms, affect the patient's life or sleep

Table 2. Comparison of clinical data between the two groups

	Experimental group (n=70)	Control group (n=67)	t/X^2	*P*
Age (years)	49±3.01	47±3.83	2.25	0.06
Sex			4.68	0.48
Male (n%)	43 (61.4%)	47 (70.1%)		
Female (n%)	27(38.6%)	20 (29.9%)		
BMI	19.7±1.14	20.1±0.77	3.39	0.35
Average course of disease	4.52±2.53	4.37±2.35	5.52	0.67
Smoking	37 (52.9%)	39 (58.2%)	3.96	0.28
Hypertension	27 (38.6%)	19 (28.4%)	7.79	0.16
Diabetes	18 (25.7%)	21 (31.3%)	6.29	0.29
Coronary heart disease	13 (18.6%)	15 (22.4%)	4.23	0.31

Note: Compared with the control group, significant difference as $P < 0.05$.

and interleukin-10 (IL-10), were detected by enzyme-linked immunosorbent assay.

Statistical analysis

All data were analyzed by SPSS 22.0. The statistical results are expressed by mean ± standard deviation (m ± sd), the data comparison was conducted by t-test and the correlation analysis was conducted by person linear phase. $P < 0.05$ was the difference with statistical significance. Analyses were performed using Graph Pad Prism (Graph Pad Software Inc., CA, USA).

Results

Clinical data

Table 2 shows the characteristics of the participants. The research included 137 patients after follow-up, and involved 70 patients in the experimental group, a mean age (49±3.01) years old, while the control group had a mean age (47±3.83) years old. The BMI in the experimental group was (19.7±1.14) kg/m^2, and in the control group it was (20.1±0.77) kg/m^2, there was no statistical significance between two groups (P=0.35). The number of people who smoked in the experimental group was 37 (52.9%), and that in the control group was 39 (58.2%). The average course of disease in experimental group was (4.52± 2.53) years, and in control group was (4.37±2.35) years, there was no statistical significance between the data of two groups (P=0.67). The number of patients who had a history of hypertension in experimental group was 27 (38.6%), and in the control group it was 19 (28.4%). The number of patients who had a history of diabetes in experimental group was 18 (25.7%), and in the control group it was 21 (31.3%). The number of patients who had a history of coronary heart disease in experimental group was 13 (18.6%), and in control group it was 15 (22.4%). The two groups were similar in demographics, clinical characteristics, and there was no statistical significance between characteristics of the two groups.

Clinical therapeutic effect

As shown in **Table 3**, the total effective rate of the experimental group was 94.3% (66/70), which was higher than that of the control group (83.6%), the differences were statistically significant ($P < 0.05$). In the experimental group, the significantly effective rate was 41.4% (29 cases), the effective rate was 52.9% (37 cases), and the ineffective rate was 5.7% (4 cases); in the control group, the significantly effective rate was 35.8% (24 cases), the effective rate was 47.8% (32 cases), and the ineffective rate was 16.4% (11 cases).

Clinical symptom score

The score of nasal itching before treatment in the experimental group was (2.42±0.47) points, and that in the control group was

Table 3. Comparison of clinical therapeutic effect between the two groups after treatment

Group	Number of cases	Significant effective	Effective	Ineffective	Total effective rate
Experimental group	70	29 (41.4%)	37 (52.9%)	4 (5.7%)	66 (94.3%)
Control group	67	24 (35.8%)	32 (47.8%)	11 (16.4%)	56 (83.6%)
T	-	7.268	9.737	4.061	6.378
P	-	0.007	0.012	0.00004	0.00002

Note: Compared with the control group, significant difference as $P < 0.05$.

Table 4. Comparison of Clinical symptom score between the two groups before and after treatment (points, m ± sd)

Clinical symptom	Time	Experimental group (n=70)	Control group (n=67)	t	*P*
nasal itching	Before treatment	2.42±0.47	2.38±0.31	1.478	0.075
	After treatment	0.33±0.05	1.39±0.49	18.333	0.00003
	T	12.458	10.776	-	-
	P	0.0007	0.0005	-	-
nasal congestion	Before treatment	2.23±0.21	2.14±0.17	0.959	0.168
	After treatment	0.45±0.02	1.33±0.48	28.875	0.00002
	T	7.278	6.131	-	-
	P	0.0004	0.0002	-	-
runny nose	Before treatment	2.37±0.37	2.36±0.20	1.303	0.096
	After treatment	0.31±0.09	1.39±0.32	21.738	0.000023
	T	12.458	10.776	-	-
	P	0.0004	0.0001	-	-

Note: Compared with the control group, significant difference as $P < 0.05$.

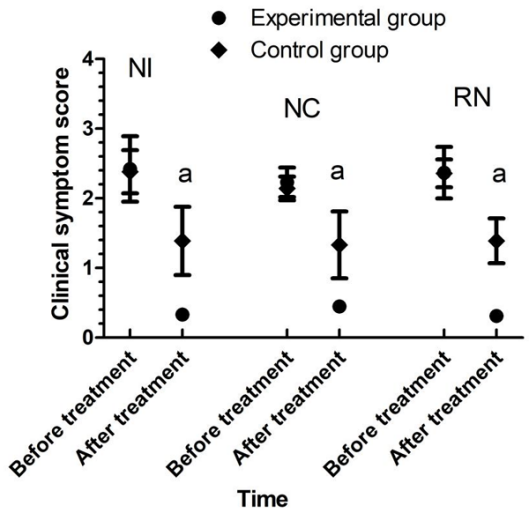

Figure 1. Comparison of clinical symptom scores between the two groups before and after treatment. Note; Compared with experimental group, $^{a}P < 0.05$. NI: nasal itching, NC: nasal congestion, RN: runny nose.

(2.38±0.31) points; while the score of nasal itching after treatment in the experimental group (0.33±0.05) points, and that in the control group was (1.39±0.49) points, there was a statistical significance between two group after treatment ($P < 0.05$). The scores of nasal congestion in the experimental group before and after treatment were respectively (2.23±0.21) and (0.45±0.02) points, while that in the control group were respectively (2.14±0.17) and (1.33±0.48) points, the results indicated that the nasal congestion symptoms were improved after treatment in two groups. The score of runny nose before treatment in the experimental group was (2.37±0.37) points, and that in the control group was (2.36±0.20) points; while the score of runny nose after treatment in the experimental group was (0.31±0.09) points, and that in the control group was (1.39±0.32) points, there was statistical significance between two groups after treatment ($P < 0.05$) (**Table 4** and **Figure 1**).

Serum levels of inflammatory factors

The level of IL-6 before treatment in the experimental group was (9.82±1.83) ng/L, and that in the control group was (9.78±1.74) ng/L;

Table 5. Comparison of Serum levels of inflammatory factors between the two groups before and after treatment (m ± sd)

Inflammatory factors	time	Experimental group (n=70)	Control group (n=67)	T	*P*
IL-6 (ng/L)	Before treatment	9.82±1.83	9.78±1.74	0.238	0.093
	After treatment	3.57±0.89	6.32±1.15	6.323	0.0002
	t	32.458	10.776	-	-
	P	0.0001	0.0002	-	-
IL-8 (ng/L)	Before treatment	168.13±31.97	172.87±35.72	3.359	0.054
	After treatment	87.26±18.02	129.63±21.48	43.255	0.0004
	t	67.138	73.331	-	-
	P	0.0002	0.0003	-	-
IL-10 (ng/L)	Before treatment	8.16±1.37	7.89±1.20	1.303	0.096
	After treatment	15.10±2.88	11.39±2.25	21.738	0.0005
	t	8.438	9.176	-	-
	P	0.0001	0.0002	-	-
hsCRP (mg/L)	Before treatment	5.42±1.37	5.36±1.26	4.323	0.074
	After treatment	0.68±0.12	2.19±1.32	10.778	0.0009
	t	22.438	16.576	-	-
	P	0.0002	0.0001	-	-

Note: Compared with the control group, significant difference as P < 0.05. hsCRP: high-sensitivity C-reactive protein.

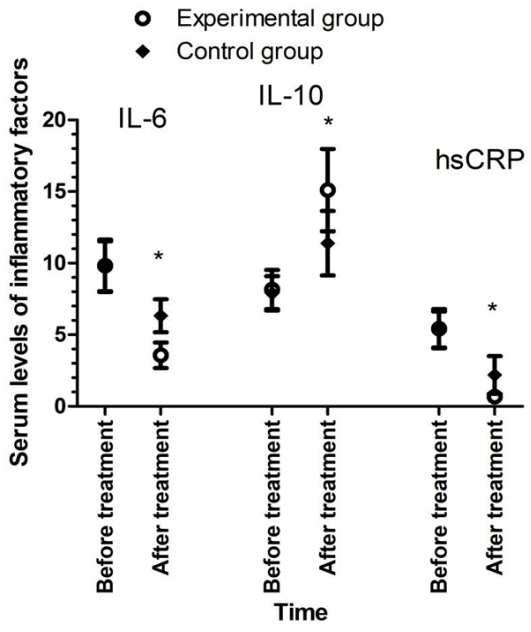

Figure 2. Comparison of Serum levels of inflammatory factors between the two groups before and after intervention. Note: Compared with experimental group, $^{*}P < 0.05$.

while the level of IL-6 after treatment in the experimental group (3.57±0.89) ng/L, and that in the control group was (6.32±1.15) ng/L, there was statistical significance between two groups after treatment (P < 0.05). The level of IL-8 in the experimental group before and after treatment were respectively (168.13±31.97) and (87.26±18.02) ng/L, while that in the control group were respectively (172.87±35.72) and (129.63±21.48) ng/L, the results indicated that the level of IL-8 and IL-6 were decreased after treatment in two groups. The level of IL-10 before treatment in the experimental group was (8.16±1.37) ng/L, and that in the control group was (7.89±1.20) ng/L; while the level of IL-10 after treatment in the experimental group (15.10±2.88) ng/L, and that in the control group was (11.39±2.25) ng/L, there was statistical significance between two group after treatment (P < 0.05). The level of hsCRP in the experimental group before and after treatment were respectively (5.42±1.37) and (0.68± 0.82) mg/L, while that in the control group were respectively (5.36±1.26) and (2.19±1.32) mg/L, the results indicated that the level of hsCRP was decreased after treatment in both groups (**Table 5** and **Figure 2**).

Discussion

Allergic rhinitis (AR) is an allergic disease, in which people with it are allergic to specific allergens. The main symptoms of AR are nasal congestion, nasal itching, sneezing and nasal discharge; it has the characteristics of repeated attacks and delayed healing, and seriously

affects the work, study and life of patients [14]. In recent years, with the aggravation of environmental pollution, the incidence of AR is increasing. The clinical treatment of AR mainly includes drug therapy, desensitization therapy, local treatment and surgical treatment to alleviate its symptoms [15].

Leukotriene is an important inflammatory transmitter, which plays an important role in the pathogenesis of AR. It can increase vascular permeability, contract airway smooth muscle and gather inflammatory cells, promote the secretion and exudation of mucosa, and cause airway hyperresponsiveness and airway reconstruction [16]. Montelukast sodium can bind with the leukotriene receptor, thus blocking the binding of leukotriene and leukotriene receptor. It has obvious inhibitory effects of an immediate type, which can reduce inflammatory reaction, relieve airway hyperresponsiveness, and improve AR symptoms [17-19]. Azelastine hydrochloride is the second generation of antihistamines, in which the active ingredient is azelastine [20]. It is a long-acting antiallergic drug with dual effects of both an antihistamine and being anti-inflammatory. It takes 15 minutes after administration for effect, and it can effectively treat allergic rhinitis [21, 22]. The curative effect of the nasal dosage form is better than that of the oral dosage form, with less adverse reactions. Some studies have shown that azelastine hydrochloride can block the histamine reaction by inhibiting histamine release from mast cells and basophils, antagonizing H_1 receptor [23]. In our study, the total effective rate of the experimental group was significantly higher than that of the control group ($P < 0.05$); after treatment, the nasal itching, nasal congestion, sneezing, nose blowing scores and total scores of the two groups were significantly lower than those before treatment, and the above scores of the experimental group were significantly lower than those of the control group ($P < 0.05$). The results indicated that the combination therapy can play a synergistic effect, improve the clinical symptoms and signs, and improve the curative effect. During the course of treatment, no obvious adverse reactions occurred in any patients, indicating that it is safe to combine the therapies.

The pathogenesis of AR is still unclear. The traditional view is that AR is a type I allergy mediated by immunoglobulin E (IgE). The imbalance of the serum helper T cell Th1/Th2 ratio is closely related to AR [24]. The combined therapeutic mechanism in treating AR is unclear. As presently reported, we deduced that it may be related to its anti-inflammation reaction [25]. Montelukast sodium can also induce Th1 cells, inhibit inflammatory cells and body allergens, and it can inhibit the formation of antigen-presenting cells, monocyte macrophages and mast cells, thus alleviating the occurrence and development of the inflammatory cascade and type I allergies [26]. As shown on our study, the serum levels of IL-6 and IL-8 in the two groups were significantly lower than those before treatment; furthermore, the level of IL-10 was significantly higher than that before treatment, and the above indexes in the experimental group were significantly better than those in the control group, the differences were statistically significant ($P < 0.05$). This data supports our inferences.

Our study has some limitations that deserve comments. Firstly, the number of consecutive patients was small and were adults, in which we didn't include children (age < 18 years). Secondly, the during time of study is limitated and we didn't observed the long-term efficacy and recurrence of the patients. Thirdly, although our results are promising, the explanation is limited by the self-control study design. Therefore, further study of azelastine hydrochloride combined with montelukast sodium in the treatment of patients with allergic rhinitis is still needed.

In conclusion, azelastine hydrochloride combined with montelukast sodium can effectively improve clinical symptoms and inflammatory reactions in patients with allergic rhinitis, furthermore, it provides research ideas for follow-up in clinical practice.

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Disclosure of conflict of interest

None.

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