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Montelukast Combined with Loratadine can Improve The Immune Function and SF-36 Score of Patients with Allergic Rhinitis

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Abstract

Objective: To determine the influence of montelukast combined with loratadine on the immune function and MOS 36-Item Short-Form Health Survey (SF-36) score of patients with allergic rhinitis.

Methods: Patients with allergic rhinitis admitted to our hospital between December 2018 and December 2019 were selected and randomly assigned to a control group (con group) and an observation group (obs group). Patients in the con group were treated with loratadine alone, while those in the obs group were treated with montelukast combined with loratadine. The therapeutic effect, nasal symptom scores, changes in immune function-related indexes, and life quality SF-36 score of the two groups were evaluated.

Results: Before treatment, no remarkable difference was found in nasal symptom scores between the two groups, while after treatment, the nasal symptom scores of the obs group were significantly better than those of the con group, and the effective treatment rate of the obs group was greatly higher than that of the con group. In addition, the changes of immune function indexes in the obs group were also significantly better than those in the con group, and the obs group experienced significantly higher life quality than the con group after treatment. Moreover, there no remarkable difference was found between the two groups in the incidence of adverse reactions (P> 0.05).

Conclusion: Montelukast combined with loratadine can provide relatively high efficacy on patients with allergic rhinitis and can ameliorate the immune function and life quality of the patients.

Keywords: Montelukast, loratadine, allergic rhinitis, immune function, life quality

Introduction

Allergic rhinitis (AR) is a common clinical rhinitis. It is an immunoglobulin E (IgE) -mediated chronic inflammation disease of nasal mucosa involving various immunologically active cells and cytokines in allergic individuals who contact with allergens. The occurrence of AR is related to environmental factors and genetic factors, and its onset is characterized by annuality and seasonality. Clinically, AR is mainly manifested by perennial and recurrent rhinocnesmus, sneezing, nasal obstruction, and rhinorrhea, and it occurs and stops rapidly, with a lingering course and tremendous treatment difficulty (Schuler et al.,2019) Patients with AR often have a hereditary allergic constitution. During the onset of the disease, the patients are prone to comorbid symptoms such as itchy conjunctiva, upper jaw, and external auditory canal, which seriously compromise their health and normal life (Meltzer ,2016). At present, with the deterioration of the global environment, the incidence of AR is also increasing annually, but there is no effective method to cure it in clinical practice at present (Cingi et al.,2019). Serious AR needs drug treatment. One previous study has showed that the effect of monotherapy on AR is unsatisfactory, and long-term use of the same drug will bring about antibodies and will exert weaker curative effect (Mehta,2018).

Loratadine is a long-acting selective peripheral histamine H1-receptor antagonist (Drummond,2018), which acts on the whole

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process of allergic reaction and can effectively relieve AR by inhibiting the release of inflammatory factors, chemokines, and active oxygen free radicals (Wei et al.,2019; Nayak et al.,2017). Many cytokines are involved in the pathogenesis of AR. Cysteinyl leukotriene is a powerful inflammatory mediator released by various cells including mast cells and EOS cells, which can act on leukotriene receptors of smooth muscle cells, macrophages, and EOS (Miyata et al.,2020)Montelukast is a selective leukotriene receptor antagonist, and it is verified to be able to inhibit the release of leukotriene, reduce the aggregation of EOS in the airway, and lower the hyperreactivity of mucous membranes (Shirasaki et al.,2016;Li et al.,2018) , so it is used to treat allergic diseases. Loratadine tablets can alleviate telangiectasia to a certain extent and can also inhibit capillary permeability, thus alleviating allergic symptoms, but its concentration lasts for a short time, so its long-term efficacy is unfavorable, and patients face high incidences of adverse reactions and recurrence in the later period after being treated with it (Nakamura et al.,2019).

Therefore, this study treated patients with AR through montelukast combined with loratadine and evaluated the clinical efficacy of the combination and the effect of the combination on immune function and life quality of the patients.

1 Materials and methods

1.1 Research objects

A total of 125 patients with AR admitted to the otorhinolaryngology department of our hospital between December 2018 and December 2019 were enrolled, and randomly assigned to a control group (con group) and an obs group. The con group consisted of 60 patients (35 males and 25 females), with a mean age of (36.9±9.1) years and a course of disease of 9-17 months, while the observation group (obs group) consisted of 75 patients (42 males and 33 females), with a mean age of (36.5±9.8) years and a course of disease of 10-19 months. The inclusion criteria of the study: Patients conforming to the diagnostic criteria in the *Guidelines for diagnosis and treatment of allergic rhinitis* and suffering from symptoms including rhinorrhea, nasal obstruction, sneezing, and rhinocnesmus, and those with a course of disease longer than 3 months. The exclusion criteria of the study: Patients with contraindications to drugs, patients with severe mental disorders or consciousness disorder, patients whose family members did not agree the participation of the patients, and those during lactation or pregnancy. There was no remarkable difference in general data including age, sex, and course of disease between the two groups (all $P > 0.05$), so the two groups were comparable.

1.2 Methods

Con group: Each patient in the con group took loratadine tables orally at 10 mg/time, once a day, for 2 consecutive weeks.

Obs group: Each patient in the obs group took montelukast sodium chewable tablets before sleep at 4 mg/ time, once a day, for 2 consecutive weeks based on the treatment for the con group.

Fasting peripheral venous blood (5 mL) was sampled from each patient before and after treatment, and centrifuged to take supernatant, and the supernatant was refrigerated for later analysis.

1.3 Outcome measures

Nasal symptom score: Sneezing (continuous sneezes at one time): 1 point for 3-9 sneezes; 2 points for 10-14 sneezes; 3 points for 15 sneezes or more. Rhinorrhea (times of nose blowing per day): 1 point for 4 times of nose blowing or less, 2 points for 5-9 times of nose blowing; 3 points for 10 times of nose blowing or more. Nasal obstruction: 1 point for occasional mouth breathing; 3 points for nearly all-day mouth breathing; 2 points for situation between nearly all-day mouth breathing and occasional mouth breathing. Rhinocnesmus: 1 point for intermittent rhinocnesmus; 2 points for tolerable formication; 3 points for unbearable formication.

The clinical efficacy on the con group and the obs group was compared, and the clinical efficacy on patients was evaluated according to the change of the symptom score. Markedly effective: The symptom score of the patient was lowered by 50% or more; Effective: The symptom score of the patient was lowered by 20% - 49%; ineffective: The symptom score of the patient was lowered by less than 20%. The effective treatment rate = (the number of markedly effectively treated patients + the number of effectively treated patients) /the total number of patients×100%.

The immune function-related indexes of the two groups were compared: A ELISA was carried out to quantify T helper type 1 (Th1) cytokines (interferon-γ (IFN—γ) and tumor necrosis factor-β (TNF-β)), T helper type 2 (Th2) cytokines (interleukin-4 (IL-4) and interleukin-5 (IL-5)), and IgE.

The MOS 36-Item Short-Form Health Survey (SF-36) was adopted for evaluating the life quality of each patient from eight aspects, bodily pain, physiological functioning, role-physical, mental health, role-emotional, social functioning, vitality,

as well as general health, and the score was proportional to the quality of life.

The adverse reactions were compared between the two groups.

1.4 Statistical analyses

SPSS21.0 was adopted for data processing. Measurement data were presented by the mean ± standard deviation of three independent experiments or more, and compared between two groups using the T test. Enumeration data were presented by (n, %) %, and analyzed through the chi-square test. In addition, GraphPad Prism 6 was adopted for analysis and mapping.

2 Results

2.1 Comparison of nasal symptom scores between the two groups

Comparison of nasal symptom scores between the two groups showed that before treatment, there was no remarkable difference between them in scores of sneezing, rhinorrhea, nasal obstruction, and rhinitis (all $P > 0.05$), while after treatment, the scores obtained by the obs group were greatly lower than those obtained by the con group (all $P < 0.05$).

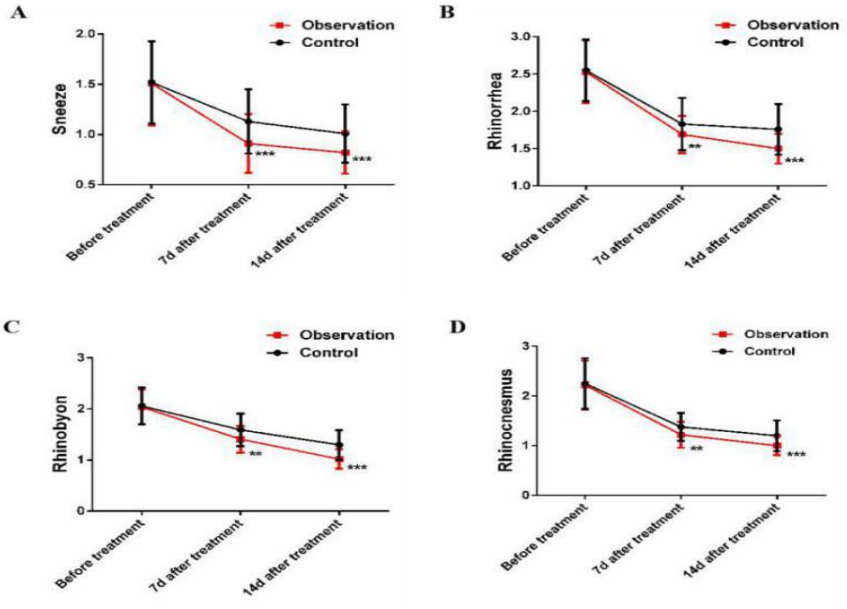

Figure 1. **Comparison of nasal symptom scores between the two groups**

(A, Comparison of sneezing symptom score between the two groups. B, Comparison of rhinorrhea symptom score between the two groups. C, Comparison of nasal congestion symptom score between the two groups. D, Comparison of rhinocnesmus symptom score between the two groups. ** indicates $P<0.01$ vs. the control group; *** indicates $P<0.001$ vs. the control group.)

2.2 Comparison of therapeutic effect between the two groups

The therapeutic effect on the obs group was significantly stronger than that on the con group ($P<0.05$).

Table 1. **Comparison of therapeutic effect between the two groups**

	Patients with markedly effective treatment	Patients with effective treatment	Patients without effective treatment	Total effective rate (the rate of markedly effective treatment + the rate of effective treatment)
The control group (n=60)	29 (48.3)	20 (33.3)	11 (18.4)	49 (81.6)
The observation group (n=75)	45 (60)	26 (34.6)	4 (5.4)	71 (94.6)
χ^2/t				5.7041
P-value				0.0169

2.3 Changes of immune function-related indexes in the two groups

Before treatment, the levels of serum IFN-γ, TNF-β, IL-4, as well as IL-5 in the two groups increased greatly (all *P*> 0.05), while after treatment, the levels of serum IFN-γ and TNF-β in the two groups decreased greatly, the levels of IL-4 and IL-5 increased significantly, and the improvement of the indexes in the obs group was more significant than that in the con group (*P*<0.05).

2.4 Life quality SF-36 score of patients in the two groups

The life quality of each patient was evaluated and scored from vitality, role-physical, physiological functioning, role-emotional, social functioning, mental health, bodily pain, as well as general health. It was found that the life quality scores of the obs group were significantly better than those of the con group after treatment (all *P*<0.05).

Table 2. **Changes of immune function-related indexes in the two groups**

		Th1 cytokine		Th2 cytokine		IgE (kU/L)
		TNF-β (μg/mL)	IFN-γ (pg/mL)	IL-4 (ng/mL)	IL-5 (ng/mL)	-
Before treatment	The control groups(n=60)	47.94±6.37	32.09±5.47	108.85±10.54	39.14±4.78	106.23±18.82
	The observation groups(n=75)	48.19±6.26	31.86±5.59	107.46±10.87	38.67±4.86	106.01±18.74
	χ^2/t	0.2288	0.2398	0.7483	0.5624	0.0677
	P-value	0.8139	0.8108	0.4556	0.5748	0.9462
After treatment	The control groups(n=60)	52.56±7.13	37.96±7.04	88.76±7.19	27.95±3.43	73.87±13.21
	The observation groups(n=75)	59.07±7.34	45.12±7.98	71.78±6.68	16.98±2.73	48.67±9.87
	χ^2/t	5.1859	5.4455	14.1855	20.6955	12.6821
	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Table 3. **Comparison of SF-36 scores between the two groups**

	Energy	Role-physical	Physiological functioning	Role emotional	Social functioning	Mental health	Bodily pain	General health
The control group (n=60)	42.4±17.8	51.2±22.4	77.3±20.4	61.2±21.4	64.3±17.1	47.5±10.8	71.2±22.4	52.5±12.5
The observation group (n=75)	56.9±15.7	67.4±24.3	83.7±16.3	73.5±23.1	82.1±18.7	59.1±11.2	84.2±14.5	63.1±10.9
χ^2/t	5.0237	3.9841	2.0266	3.1757	5.7069	6.0750	4.0731	5.2590
P-value	< 0.0001	0.0001	0.0447	0.0019	< 0.0001	< 0.0001	< 0.0001	< 0.0001

2.5 Incidence of adverse reactions

There was no significant difference between the obs group and the con group in the incidence of adverse reactions (4% *vs.* 6.67%, *P*＞0.05).

Table 4. **Incidence of adverse reactions in the two groups**

	Headache	Dry mouth	Sleepiness	The total incidence
The control group (n=60)	1 (1.67)	2 (3.33)	1 (1.67)	4 (6.67)
The observation group (n=75)	0 (0)	2 (2.67)	1 (1.33)	3 (4)
χ^2/t				0.4821
P-value				> 0.05

Discussion

AR is mainly caused by contact with allergens, and IgE plays a key mediating role in the pathogenesis of the disease. Its main pathological changes are increased glandular secretion and telangiectasia (Bernstein et al.,2016). For patients with allergic constitution exposed to allergens, the allergens will activate mast cells and eosinophils and cause a release of histamines, which will result in endocrine disorders and immune dysfunction. In the state of immune dysfunction, more specific IgE antibodies will be secreted and allergic reactions will be triggered. The allergic reactions can cause imbalance in secretion of Th cells, trigger inflammatory reactions, and lead to inflammatory damage of nasal mucosa, eventually leading to AR (Wang et al.,2019). Therefore, during the treatment of AR, it is required to avoid contact with allergens and rationally adopt drugs such as antihistamine drugs, glucocorticoid, anti-leukotriene drugs, nasal

decongestant, anticholinergic drugs, and traditional Chinese medicine preparations according to the efficacy, safety, and cost/effect ratio of the drugs (Sur et al.,2015;(Morjaria et al.,2018). Loratadine is a long-acting and powerful tricyclic antihistamine, which can inhibit allergic reaction. Its affinity with H1 receptor on the cell surface of peripheral organs is higher than that of central H1 receptor, so it is selective to H1 receptor on the cell surface of peripheral organs. Loratadine is effective in treating rhinocnesmus and sneezing, but its effect on nasal obstruction and rhinorrhea is not satisfactory (Folwarczna et al.,2019). Montelukast is a generation of novel leukotriene receptor antagonist, which can specifically inhibit cysteinyl leukotriene receptor, and can also block the pro-maturation effect of peptide growth factors on basophils and eosinophils, reduce eosinophils in respiratory tract and peripheral blood, and alleviate inflammatory response (Hoxha et al.,2017). In addition, montelukast can also effectively alleviate the symptoms such as rhinocnesmus, sneezing, nasal obstruction, and rhinorrhea. When applied in combination with loratadine, montelukast can play a synergistic and complementary role with definite effect (Wei.,2016).

According to comparison of efficacy between patients with AR treated by loratadine alone and those treated by montelukast combined with loratadine, before treatment, there was no remarkable difference in nasal symptom score between the two groups, while after treatment, the nasal symptom score of the obs group was significantly better than that of the con group, and the effective treatment rate of the obs group was significantly higher than that of the con group. In addition, as a leukotriene receptor antagonist, montelukast can effectively block cysteinyl leukotriene receptor, reduce the contents of mast cells and eosinophils in respiratory tract, and alleviate the inflammatory response (Kozer et al.,2012). As a piperidine antihistamine, loratadine can selectively antagonize peripheral histamine H1 receptor, effectively inhibit allergic reaction caused by histamine, and relieve clinical symptoms. It also has a good antihistamine effect and long-lasting and fast-acting curative effect. Combination of the two drugs can exert the synergistic effect of them, delay the contraction response of free nasal mucosa tissue induced by IgE, reduce the contraction amplitude, and effectively inhibit nasal mucosa tissue to relieve symptoms such as rhinorrhea, nasal congestion, sneezing, and rhinocnesmus, thus achieving the therapeutic purpose (Wei et al.,2019). We evaluated the changes of immune function-related indexes in the two groups, finding that the changes of immune function indexes in the obs group were also significantly better than those in the con group. Th cells can be classified into Th1 cells and Th2 cells, of which Th1 cells can mainly increase the secretion of inflammatory factors, causing hypersensitivity, while Th2 cells can promote the production of antibodies by B cells. For patients with AR, the inflammatory reaction is aggravated and the Th1/Th2 level is obviously increased. IgE can mediate the occurrence of AR (Meng et al.,2019; Fan et al.,2019). Montelukast combined with loratadine can inhibit the production and release of IgE and bioactive substances released by mast cells, and can correct immune dysfunction caused by preferential reaction of Th2 cells, which plays a crucial role in maintaining Thl/Th2 balance (Imoto et al.,2019). In this study, the life quality of the obs group was significantly higher than that of the con group after treatment, and there was no remarkable difference in the incidence of adverse reactions between the two groups, which implies that montelukast combined with loratadine can strongly ameliorate the clinical symptoms of patients and improve their life quality, and such a medication is safe and reliable, without bringing about significant adverse reactions.

To sum up, montelukast combined with loratadine can ameliorate the symptoms of patients with AR and provide a relatively good curative effect for them. In addition, the combination of them can effectively ameliorate the immune function of patients with AR, lift their life quality, and provide a high drug safety, without increasing the incidence of adverse reactions.

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