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Analysis of the efficacy of azelastine nasal spray combined with mussel mucin in the treatment of allergic rhinitis and the influence of peripheral blood CCL26 and CCR3 levels

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Abstract. – OBJECTIVE: A retrospective study was conducted to investigate the efficacy of azelastine nasal spray combined with mussel mucin in the treatment of allergic rhinitis (AR) and the effects of CCL26 and CC chemokine receptor-3 (CCR3).

PATIENTS AND METHODS: A total of 80 patients with AR admitted to our hospital from March 2020 to March 2022 were included as the research objects. All subjects were divided into two groups according to the different therapeutic strategies by reviewing the patient's treatment. The control group (n = 40) was given azelastine nasal spray, while the study group (n = 40) was treated with a combination of mussel mucin and azelastine nasal spray. The clinical efficacy, clinical symptoms, and sleep quality improvement of the two groups were calculated and compared retrospectively. The serological indexes were compared, and the incidence of adverse reactions between the two groups was calculated retrospectively based on the patient's medical records.

RESULTS: In the study and control groups, the effective rate was 95.00% and 72.50%. After treatment, the symptom scores of nasal congestions, nasal itching, sneezing, and runny nose and the total score of Pittsburgh sleep quality index (PSQI) in the study group were remarkably less. After treatment, the serum levels of sVCAM-1, interleukin-4 (IL-4), and immunoglobulin E (IgE) were decreased, and the levels of IL-12 were upregulated. Following treatment, Minimum nasal cross-section (NMCA) and total nasal resistance (TNR) at 75Pa in the study group were reduced more noticeably ($p < 0.05$). After treatment, the expression levels of CCL26 and CCR3 in peripheral blood were significantly decreased. In the control and study groups, the incidence of adverse reactions was 7.50% and 10.00%.

CONCLUSIONS: Azelastine nasal spray combined with mussel mucin is effective in the treatment of allergic rhinitis, which can effectively improve patients' clinical symptoms, alleviate nasal ventilation disorders, reduce inflammatory reactions, and improve sleep quality. This strategy of combined treatment is safe and, therefore, worth advocating.

Key Words:
Azelastine nasal spray, Mussel mucin, Allergic rhinitis.

Introduction

Allergic rhinitis (AR), also known as allergic rhinitis or allergic rhinitis, is a bridging reaction between allergic substances exposed to patients and immunoglobulin E (IgE) antibodies on the nasal mucosa, resulting in increased vascular permeability, telangiectasia, and other allergic reactions[1,2]. The main clinical symptoms of AR are continuous or intermittent sneezing, runny nose, stuffy nose, temporary loss of sense of smell, etc. Although the disease cannot endanger the life safety of patients, it will seriously affect the quality of life of patients. The incidence of allergic rhinitis is related to a variety of factors, such as exposure to allergens, climate change, environmental factors, seasons, and so on. When the body encounters an allergen, IgE antibodies are produced. Repeated exposure to allergens can cause the production of antibodies that trigger allergic rhinitis. Once the disease sets in, local histamine mediators are released, which enhances the activity of the pterygoid canal nerve and anterior ethmoidal plexus. This

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leads to increased glandular secretion, vascular dilation, and promotion of blood circulation, resulting in various symptoms such as nasal itching, congestion, runny nose, and sneezing. After the onset of the disease, some patients may experience a loss of smell, memory, and other physiological functions, which can negatively impact their daily life and work[3]. In recent years, the incidence of allergic rhinitis has increased significantly under the influence of climate, environment, industrialization, and other factors. The commonly used therapeutic drugs for the disease are glucocorticoids, antihistamines, to name a few. However, the clinical symptoms of patients with allergic rhinitis cannot be significantly improved. Alternatively, some patients cannot be treated with hormonal drugs, and some drugs are prone to adverse reactions. Choosing an appropriate, effective, and safe treatment is very important.

The principles of clinical treatment are to improve the patient's environment, give pharmacological interventions, improve the patient's immune function, and give health education. Some studies[4,5] have shown that a variety of immunoreactive cells are involved in the inflammatory response of nasal mucosa and play an important role in the occurrence and progression of the disease. Pharmacological studies[6,7] have found that azelastine hydrochloride has the effect of anti-histamine H1 receptor in vitro. The mechanism of action of azelastine includes inhibiting the release of histamine from stimulated lymphocytes; inhibiting the release of acetylcholine from vagus nerve; inhibiting the release of inflammatory mediators such as histamine and leukotriene from mast cells. Additionally, the metabolite demethylazolastine also has the effect of anti-H1 receptor. Clinical application showed that the therapeutic dose of azelastine nasal spray did not cause systemic adverse reactions. Topical administration is able to act directly on the nasal mucosa, providing rapid relief, with most patients seeing results within one hour. It is characterized by rapid, safe, low systemic drug concentration and less systemic discomfort reaction[8,9]. Because the use of a single drug is easy to cause recurrent attacks, it is clinically considered that it can be used in combination with other drugs[10].

Mussel mucin is a kind of protein extracted and purified from the foot glands of marine mussels. The medical community has paid more and more attention because of its strong stickiness, good biological safety, and non-toxic side effects. This kind of protein extraction has high biological safety and strong stickiness, and its utilization rate in clinical medicine is gradually increasing[10]. Previous studies[11,12] have shown that mussel mucin has the effects of promoting wound healing, anti-inflammation and antioxidation, which has no irritation to skin, no allergy and cytotoxicity. The antipruritic effect of mussel mucin may be due to the presence of L-Dopa group in its molecule. The L-Dopa group can bind to the receptors of the epidermal nerve endings to play a blocking effect on the cortical nerve endings, thereby achieving an antipruritic effect[13]. In addition, mussel mucin molecules carry many positive charges, which can passivate nerve endings through electrostatic action, thereby achieving antipruritic effect[14]. Although azelastine nasal spray combined with mussel mucin has a certain efficacy in the treatment of allergic rhinitis, the clinical study on the application of azelastine nasal spray combined with mussel mucin in the treatment of allergic rhinitis has not been reported. Further studies are needed to prove its clinical efficacy and to lay the theoretical foundation for its promotion and application.

Patients and Methods

General Information

A total of 80 patients with AR admitted to our hospital from March 2020 to March 2022 were included as the research objects. All subjects were divided into two groups according to the different therapeutic strategies by reviewing the patient's treatment. The control group (n = 40) was given azelastine nasal spray, while the study group (n = 40) was treated with a combination of mussel mucin and azelastine nasal spray. The control group included 25 males and 15 females, who were aged 23 to 66 years old. The control subjects were with body mass index (BMI) of 18.55-28.69 kg/m^2. The disease duration of the cases in the control cohort ranged from 2 months to 12 years, with an average of 5.71±3.42 years. There were 27 males and 13 females in the study group, who aged from 22 to 67 years old, with a BMI of 18.36-28.72 kg/m^2. The patients' course of AR ranged from 3 months to 13 years, with an average of 6.81±3.13 years. The current study was approved by the Medical Ethics Committee of The Sixth Medical Center of PLA General Hospital.

Selection criteria: (1) the patients were diagnosed as AR on admission and confirmed by nasal endoscopy. The diagnostic criteria referred to the relevant literature[15]; (2) the course of disease of

the patients investigated was more than 1 month; (3) the age of the patient was ≥ 18 years old; (4) the liver and kidney function of the patient was normal; (5) by reviewing the treatment methods of AR patients in our hospital, the cases were given azelastine nasal spray alone or combination of mussel mucin and azelastine nasal spray.

Exclusion criteria: (1) patients with allergy to the drugs used in this study (the applicable conditions of azelastine nasal spray and mussel mucin were no history of allergy to the drug); (2) subjects had recently received other drug treatment (within 2 weeks before entering the group); (3) patients with deviation of nasal septum; (4) patients with other types of rhinitis; (5) patients with respiratory tract infection, asthma, congenital heart disease and severe liver and kidney dysfunction.

Methods

The control group was treated with azelastine hydrochloride tablets (Meiluo Pharmaceutical Co., Ltd., Chinese medicine H20041574, each tablet 1 mg), 2 tablets each time, twice a day. Based on the control group, the study group was treated with mussel mucin nasal spray (Su machine injection 20142640069, Jiangyin Beryson biochemical Technology Co., Ltd., Jiangyin City, Jiangsu Province, China), sprayed into the nasal cavity, once or twice a day, 4 sprays each time. The procedure was 1 spray for each nostril, 2 times a day. Patients in both groups were treated continuously for 8 weeks.

Observation Index

Clinical curative effect

After 8 weeks of treatment, the efficacy was evaluated retrospectively according to the symptom score (including sneezing, runny nose, stuffy nose and itching 4 dimensions, each dimension 1-3 points). The score reduction rate ≥ 66% was judged to be significantly effective, ≥ 26% and < 66% was effective, and < 26% was ineffective, and the significant effect and effectiveness were included in the total effective rate.

Clinical symptom score

Symptom included itching, stuffy nose, sneezing, runny nose. Each score was 0-6 points. The patients were evaluated after 8 weeks of treatment retrospectively.

Sleep quality

Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI)[16], including 7 dimensions, such as sleep latency, sleep efficiency, hypnotic drugs, sleep time, sleep quality, sleep disorders, and daytime function, with a score of 0 to 3 for each item, a total of 21 points. The total PSQI score of the two groups was calculated and compared retrospectively. The evaluation was performed based on the records of pre-treatment and post- 8 weeks of treatment.

Serum index

5 mL was collected from fasting elbow vein blood before and 8 weeks after treatment. The serum from 5 mL blood sample of patients was used to re-exam by centrifugation (rotational speed 3,000 r/min, centrifugal 15 min). Soluble vascular cell adhesion molecule-1 (sVCAM-1) and immunoglobulin E were detected by enzyme linked immunosorbent assay (ELISA). Interleukin-4 (IL-4) and interleukin-12 (IL-12) were detected by chemiluminescence. The experimental procedure was carried out according to the instructions.

Minimum nasal cross section (NMCA) and total nasal resistance (TNR)

Before treatment and 8 weeks after treatment, nasal acoustic reflectometer A1 (Jim instrument Co., Ltd., 20162073142) was used to detect NMCA. And nasal resistance meter NR6 (GM Instruments Ltd., injected 20162213143) was used to detect total nasal resistance (TNR) under 75Pa.

The chemokine C-Cmotif ligand 26 (CCL26) and CC chemokine receptor-3 (CCR3) expression in peripheral blood

The expression level of CCL26 in the peripheral blood of subjects in each group was determined by ELISA method, carried out strictly according to the instructions of the kit. The CCL26 kit was purchased from Shanghai Walan Biotechnology Co., Ltd. The relative expression of CCR3 in peripheral blood was detected by flow cytometry. First, CCR3-FITC (10 mL) reagent was added to the index tube, and then plasma 100 mL was added to the test tube with the same type of control tube. After shaking, the 20 min was incubated at 25°C, then 2 ml of hemolysin was added to put 5 min away from light at 25°C. After centrifugation (1,000 r/min centrifugation 5 min), the supernatant was discarded and phosphate buffer solution (PBS) 2 mL was added. After another centrifugation, the supernatant was removed, and 300 mLPBS solution was added and shaken well. The expression of CCR3 was detected by flow cyto-

metry (model: BDFACS Calibur, BD Bioscience, Franklin Lake, NJ, USA). The flow cytometry analyzer (model: BDFACS Calibur, BD Bioscience, Franklin Lake, NJ, USA) was purchased from BD Company. The patients were tested before treatment and 8 weeks after treatment.

Adverse reaction

The incidence of adverse reactions such as epistaxis, somnolence, dry mouth, and cough were counted retrospectively based on the patient's medical records.

Statistical Analysis

SPSS 19.0 software (IBM Corp., Armonk, NY, USA) was used for data analysis, in which the measurement data with normal distribution and uniform variance were expressed as ($\bar{x}\pm s$). Independent sample t-test was used for comparison between the two groups, and paired t-test was used for intra-group comparison. The counting data were expressed as percentage or number of cases [n (%)] and were tested by χ^2 test. The difference was statistically significant ($p < 0.05$).

Results

The Therapeutic Effects Between the Two Groups

The effective rate in the study and control groups was 95.00% and 72.50%. The treatment effective rate in the study group was lower than that in the control group (Figure 1).

The Clinical Symptom Scores Between the Two Groups

After 8 weeks of treatment, the scores of nasal congestions, nasal itching, sneezing and runny nose in the study group were significantly lower (Table I).

PSQI Total Score Between the Two Groups

After treatment, the total PSQI score of the study group was significantly lower than that of the control group ($p < 0.05$). All results are shown in Table II.

The Serum Indexes Between the Two Groups Before and After Treatment

After treatment, the serum levels of sVCAM-1, IL-4, and IgE in the two groups were lower than

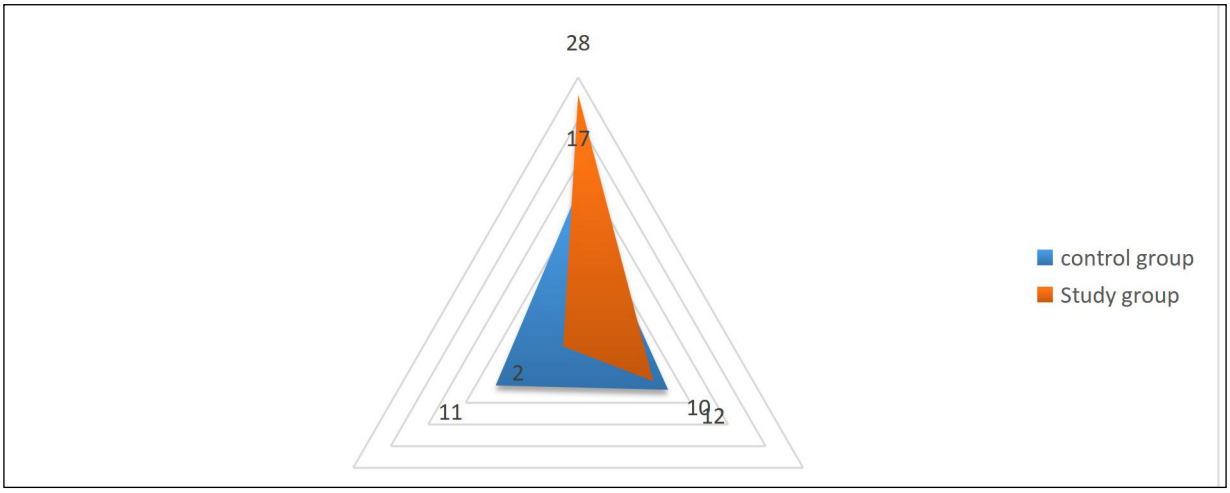

Figure 1. The therapeutic effects between the two groups.

Table I. The clinical symptom scores between the two groups [$\bar{x}\pm s$, points].

Group	N	Nasal itching	Nasal congestion	Sneeze	Runny nose
C Group	40	2.28 ± 0.34	1.12 ± 0.42	2.73 ± 0.78	2.27 ± 0.54
S Group	40	1.24 ± 0.21	0.43 ± 0.17	1.15 ± 0.57	1.47 ± 0.48
t		16.459	9.631	10.344	7.003
p		< 0.05	< 0.05	> 0.05	< 0.05

C: control group, S: study group.

those before treatment. The levels of IL-12 were higher than those before treatment (Table III). Moreover, the levels of SVCAM-1 and IgE in the study group were obviously lower than those in the control group ($p < 0.05$), while the levels of IL-4 and IL-12 were considerably higher than those in the control group ($p < 0.05$) after treatment.

Comparison of NMCA and TNR Between the Two Groups Before and After Treatment

After treatment, NMCA and TNR at 75Pa in both groups were lower than those before treatment, and TNR in the study group was much lower, ($p < 0.05$), as shown in Table IV.

Expression Levels of CCL26 and CCR3 in Peripheral Blood Before and After Treatment

After treatment, the expression levels of CCL26 and CCR3 in the peripheral blood of the two groups were significantly decreased, and the study group was lower than the control group ($p < 0.05$), as shown in Table V.

Comparison of Adverse Reactions Between the Two Groups

In the control and study groups, the incidence of adverse reactions was 7.50% and 10.00%. There was no significant difference between the two groups ($p > 0.05$), as shown in Figure 2.

Table II. Pittsburgh sleep quality index total scores between the two groups [$\bar{x}$±s, points].

Group	N	Before treatment	After treatment
C Group	40	14.91 ± 3.05	8.05 ± 2.11
S Group	40	14.87 ± 3.01	9.95 ± 2.65
t		0.059	3.547
p		0.953	0.001

C: control group. S: study group.

Table III. The serum indexes before and after treatment [$\bar{x}$±s].

		SVCAM-1 (ng/L)		IL-4 (ng/L)		IL-12 (ng/L)		IgE (g/L)	
Group	N	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
C Group	40	86.43 ± 12.27	53.73 ± 10.14[a]	79.08 ± 13.26	39.51 ± 10.26[a]	24.27 ± 6.83	50.87 ± 10.57[a]	0.69 ± 0.11	0.44 ± 0.09
S Group	40	87.02 ± 14.51	47.69 ± 10.43[b]	78.84 ± 14.53	44.66 ± 10.08[b]	25.76 ± 7.35	58.93 ± 11.79[b]	0.67 ± 0.13	0.32 ± 0.07
t		0.196	2.626	0.077	2.265	0.939	3.219	0.743	6.656
p		> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

[a]$p < 0.05$ in the control group and [b]$p < 0.05$ in the study group before and after treatment. C: control group. S: study group. SVCAM-1: Soluble vascular cell adhesion molecule-1; IL-4: Interleukin-4; IL-12: interleukin-12; IgE: Immunoglobulin E.

Table IV. NMCA and TNR between the two groups before and after treatment [$\bar{x}$±s].

		NMCA (cm^2)		TNR ($Pa \cdot cm^{-3} \cdot s$)	
Group	N	Before treatment	After treatment	Before treatment	After treatment
C Group	40	1.12 ± 0.15	1.04 ± 0.12[a]	0.47 ± 0.18	0.43 ± 0.14[a]
S Group	40	1.09 ± 0.14	0.32 ± 0.17[b]	0.45 ± 0.15	0.21 ± 0.06[b]
t		0.925	21.884	0.540	9.135
p		> 0.05	< 0.05	> 0.05	< 0.05

[a]$p < 0.05$ in the control group and [b]$p < 0.05$ in the study group before and after treatment. C: control group. S: study group. NMCA: nasal cross-section TNR: total nasal resistance.

Table V. The expression levels of CCL26 and CCR3 before and after treatment [$\bar{x}$±s].

Group	N	CCL26 (ng/L)		CCR3 (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
C Group	40	4.61 ± 1.02	4.03 ± 0.38	40.56 ± 9.23	34.21 ± 8.72[a]
S Group	40	4.58 ± 1.06	3.13 ± 0.41[b]	40.21 ± 9.41	28.56 ± 9.81[b]
t		0.172	10.182	0.168	2.723
p		> 0.05	< 0.05	> 0.05	< 0.05

[a]$p < 0.05$ in the control group and [b]$p < 0.05$ in the study group before and after treatment. C: control group. S: study group. CCL26: C-Cmotif ligand 26; CCR3: CC chemokine receptor-3.

Discussion

The pathological mechanism of AR is related to genetic factors and susceptibility of nasal mucosa to antigenic substances, whose pathogenesis is type I allergy[17]. Moderate to severe AR with a long course of the disease can be accompanied by nasal polyps, bronchial asthma, otitis media, sinusitis, allergic pharyngitis, sleep disorders, memory, and olfactory loss, intelligence decline, long-lasting nasal inflammation is a risk factor for tumor, but also has a serious negative impact on the psychology of patients, patients often have a sense of inferiority, do not want to communicate with others[18]. The current method of treating moderate-severe AR is drug-based. The survey has shown that there are three low and one high phenomena in clinical practice, including low rates of patient visits and follow-up, low rate of satisfaction with curative effects, and high recurrence rates[19].

Azelastine hydrochloride is a new generation of H1 receptor antagonists, which can exert the effect of anti-histamine and anti-inflammation after entering the body and effectively improve airway hyper response[20]. Azelastine hydrochloride tablets can inhibit the release of

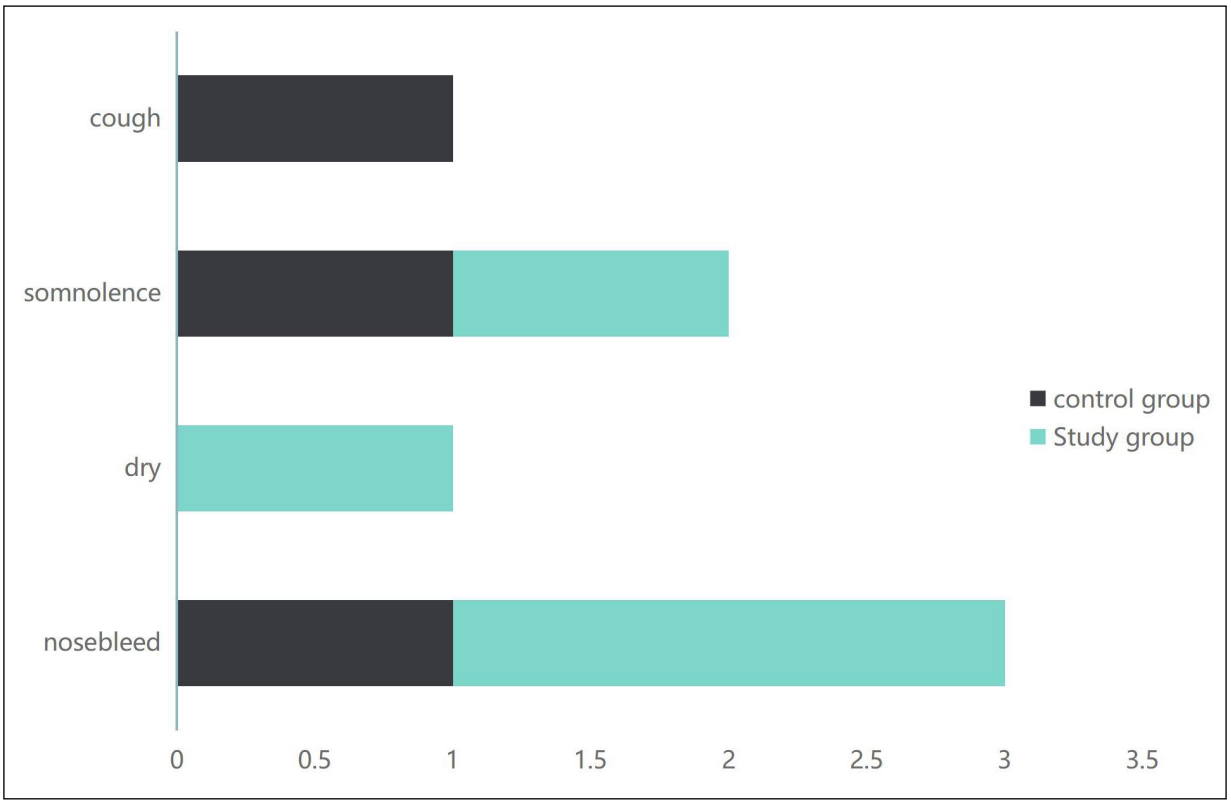

Figure 2. The incidence of adverse reactions between the two groups.

inflammatory factors in the airways and reduce the production of inflammatory mediators such as leukotrienes and histamine by regulating the stability of cell membranes. However, the therapeutic effect of azelastine hydrochloride tablets alone is not obvious, so we still need to find more effective treatments.

Some clinical studies[21] have shown that mussel mucin has significant antioxidant, anti-inflammatory, and repair-promoting effects, with high safety and no cytotoxicity and allergy. In addition, mussel mucin also has a certain antipruritic effect. This protein can form a biofilm on the mucous membrane or skin, which is both elastics, waterproof and breathable. When mussel mucin nasal spray is used, the biofilm generated blocks inflammation and promotes repair. The present study showed that in the research group, 28 cases were markedly effective, 10 cases were effective, and 2 cases were ineffective, and the effective treatment rate was 95.00%. In the control group, 17 cases were markedly effective, 12 cases were effective, and 11 cases were ineffective, and the effective treatment rate was 72.50%. This can indicate that azelastine nasal spray combined with mussel mucus has definite efficacy in patients with allergic rhinitis, and the combination of the two drugs can play a synergistic role to significantly improve the clinical symptoms and promote the recovery of RA patients. The overall efficacy was better than that of azelastine nasal spray alone. Combined use can improve clinical efficacy because mussel mucin has good antioxidant, anti-inflammatory, and promote repair effects. The combination therapy plays a synergistic role and achieves complementary advantages. It has been reported that CCL26 can play an important role in inflammatory and allergic reactions[22]. After binding to CCR3, it can specifically activate eosinophils to chemotaxis toward inflammation, releasing inflammatory mediators such as histamine to participate in inflammatory and allergic reactions. CCR3 is a non-specific receptor protein. In addition to functioning as a receptor for CCL26, it can also function as eosinophil chemotactic factor-1 (eotaxin-1), eosinophil chemokine 2 (eosinophil chemotactic factor-2, eotaxin-2) and other CC chemokines receptors to play different biological functions[23]. A study[24] pointed out that the expression levels of CCL26 and CCR3 are related to the occurrence of AR and can be used as biomarkers for the diagnosis of AR patients. Alleviate inflammatory response can be found in AR patients. sVCAM-1 can bind to receptors on the surface of eosinophils and exert the biological activity of promoting the directional movement of eosinophils, and eosinophils can release histamine, thereby aggravating the condition of AR patients[25]. IL-4 can enhance the effect of B cells on T cells in the body, promoting the immune response in the body and aggravating allergic reactions in patients. IL-12 is mainly produced by B cells and macrophages, which can promote the differentiation of Th2 cells and regulate the balance of Th1/Th2 cells, thereby controlling the development of the disease. Allergic rhinitis patients will stimulate the humoral immunity in the body after allergen stimulation, activate B lymphocytes, and produce IgE, so the IgE level in the patients will increase. In this study, the patients were treated with azelastine hydrochloride tablets combined with mussel mucin treatment, and the level of IgE decreased significantly, which fully confirmed the efficacy of this treatment. The serum indexes of the patients in the observation group were significantly improved. The reason was that azelastine hydrochloride tablets could selectively bind to the H1 receptor and inhibit the release of histamine from lymphocytes, thereby relieving the nasal cavity inflammation of the patients, improving ventilation, and improving ventilation. It can inhibit the excitation of the vagus nerve, thereby reducing the synthesis and release of acetylcholine (ACh) and nasal inflammation[26]. On this basis, mussel mucin can form a biofilm on the surface of the nasal cavity, which can avoid the re-invasion of the nasal mucosa by microorganisms. The protein molecule contains 20% lysine, which makes the molecule carry many "+" charges, thereby forming a molecule. The potential difference can promote the recovery of sick cells to relieve itching. At the same time, it can passivate the nerve endings and relieve itching through static electricity. The protein is also an adhesive, which can adsorb pollutants in the nasal cavity and block allergens and nasal passages. Mucosal contact to inhibit inflammation and repair damaged nasal mucosa[27,28].

NMCA and TNR can directly reflect the nasal ventilation in AR patients. The current results showed that after treatment, the TNR at NMCA and 75Pa in the two groups were lower than those before treatment, and the TNR in the observation group was lower, indicating that azelastine hydrochloride tablets combined with mussel mucin treatment can effectively improve the nasal ventilation in AR patients. The reason may be that the submucosa of the nose contains mucous glands,

connective tissue, nerves, etc., and has a rich vascular network. When capillary dilation increases permeability, plasma extravasation can easily lead to nasal congestion and a runny nose. Fluticasone propionate reduces microvascular permeability and inhibits glandular secretion and histamine release. The stability of leukocyte lysosomal membranes was improved, reducing humoral immunity, relieving nasal edema, and improving nasal ventilation in AR patients[29,30]. In addition, the nasal spray in this study can act directly on the lesion site, binding to the local receptor to act, with a low risk of adverse effects. The present results also showed that there was no statistically significant difference in the incidence of adverse reactions between the two groups, indicating that azelastine hydrochloride tablets combined with mussel mucin treatment did not increase the occurrence of adverse reactions, which fully reflected the safety of this treatment regimen. Certain limitations of this investigation can be found as well. The number of patients included in each group is relatively small, which may cause certain biases in the specific data and statistical calculation results, which will need to be further clarified by subsequent large-sample studies.

Conclusions

Azelastine nasal spray combined with mussel mucin is effective in the treatment of allergic rhinitis, which can effectively improve patients' clinical symptoms, alleviate nasal ventilation disorders, reduce inflammatory reactions, and improve sleep quality. This strategy of combined treatment is safe and worth promoting.

Ethics Approval

The current study was accepted by the Medical Ethics Committee of The Sixth Medical Center of PLA General Hospital with approval number: 60713.

Conflicts of Interest

No conflicts of interest.

Funding

None.

Data Availability

The data used for this study can be obtained from The Sixth Medical Center of PLA General Hospital.

Authors' Contributions

Yang Liu conceived the study design and the content concept; Liu Shuo performed the data collection, extraction and analysis of the data. Lu Shuangfeng interpreted and reviewed the data and drafts. Zang Gui Ming reviewed the final draft.

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Informed Consent

The informed consent was waived due to the retrospective design of the study.

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