

Effect of Yupingfeng granules combined with glucocorticoid on eosinophil infiltration and inflammatory factors of lavage fluid in nasal secretion of patients with allergic rhinitis

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Abstract

The purpose of this study was to investigate the effect of Yupingfeng granules, a well-known traditional Chinese medication, combined with glucocorticoids on eosinophil (EOS) number and inflammatory factors in nasal secretions of patients with allergic rhinitis (AR). 76 patients with AR were randomly divided into controls (nasal inhaled corticosteroids alone) and experimental group (combined with Yupingfeng granules orally). The efficacy, symptoms, number of EOS and levels of inflammatory factors in nasal secretions were compared between the two groups after 2 months of treatment. The results showed that in the experimental group (94.73%, 0.48 ± 0.25 points), the effective rate of treatment was obviously higher and the physical sign score was clearly lower compared with controls (81.57%, 0.97 ± 0.36 points); the EOS count in the experimental group was clearly less than that in the controls; the tumor necrosis factor- α (TNF- α) (0.76 ± 0.44 ng/mL), interleukin-6 (IL-6) (11.83 ± 3.72 pg/mL), and interleukin-8 (IL-8) (17.45 ± 6.53 pg/mL) levels were evidently lower in the experimental group than in the controls (1.48 ± 0.72 ng/mL, 14.62 ± 5.19 pg/mL, 22.86 ± 9.35 pg/mL) ($P < 0.05$). In summary, compared with nasal inhalation of glucocorticoids alone, combined with oral administration of Yupingfeng granules, it can more significantly improve the symptoms of nasal obstruction and rhinorrhea in AR patients, reduce nasal mucosal edema, reduce the number of EOS in nasal secretions, and reduce the level of inflammatory factors, which is of positive significance for the clinical treatment of AR patients.

Keywords: AR; EOS; Glucocorticoids; inflammatory factors; Yupingfeng granules

Introduction

In China, the incidence of AR exceeds 140 million people, and the incidence continues to increase every year. If AR is not solved in time, it can also induce a series of complications and endanger people's health (Zhang *et al.*, 2021). AR is caused by exposure of the nasal mucosa to allergens and is mainly characterized by recurrent nasal itching, nasal congestion, continuous episodes of paroxysmal sneezing, and massive watery nasal discharge, sometimes accompanied by ocular symptoms such as ocular itching and lacrimation (Zhou *et al.*, 2021; Siddiqui *et al.*, 2022). People with AR experience nasal obstruction and hyperplasia, reddish or pale nasal mucosa, edema,

Received: 28 Jul 2023. Received in revised form: 01 Sep 2023. Accepted: 18 Sep 2023. Published online: 17 Nov 2023.

From Volume 49, Issue 1, 2021, Notulae Botanicae Horti Agrobotanici Cluj-Napoca journal uses article numbers in place of the traditional method of continuous pagination through the volume. The journal will continue to appear quarterly, as before, with four annual numbers.

and thin nasal secretions. Normal nasal passages are obstructed, and these inflammatory nasal secretions reach the throat downward, and these secretions contain viscous substances and viruses, which can easily cause infection of the throat, and then a variety of complications, and even damage heart and lung function in severe cases (Meng *et al.*, 2020; Steiner and Lorentz, 2021; Meng *et al.*, 2018). It has been shown that more mast cells, IgE-producing cells, and EOS infiltration can be detected in the nasal secretions of AR, suggesting a close relationship between AR and this pleocytosis (Ji *et al.*, 2021). As a special white blood cell in the human immune system, EOS is associated with many inflammatory processes, especially allergic diseases. When the human body is exposed to allergens that cause allergy, EOS responds by entering this area and releasing various toxins, participating in allergic reactions, and regulating inflammatory reactions. EOS is formed only in the bone marrow, then enters the blood circulation from the bone marrow, and then reaches the destination (respiratory tract, gastrointestinal tract, etc.), and may remain in the blood for no more than half a day, but stay in bronchial mucosa and nasal mucosa for a long time. Diseases with increased EOS such as AR occur when the EOS content in various parts of the body is higher than normal levels (Zhang and Li, 2020; Harkema *et al.*, 2020).

Traditional Chinese medicine (TCM) believes that the human lung and nose are closely related. Lung discomfort, nose will have symptoms, and the same reason, nose with symptoms can indicate lung problems. AR is mostly caused by lung qi is not solid, lung qi deficiency, following lung deficiency, it is easy to be invaded by various external cold pathogens. There are four main approaches to the treatment of AR, including allergen avoidance, drug therapy, specific immunotherapy, and health education (Yang *et al.*, 2021). Among them, drug therapy is convenient and can quickly relieve symptoms, so drug therapy is the most important treatment for AR. Yupingfeng San, from Effective Formulae Handed Down for Generations, was created by Wei Yilin, a physician in the Yuan Dynasty in China, and is a classic formula for supplementing qi and consolidating the root, which has the effect of anti-perspiration and is commonly used for recurrent upper respiratory tract infections and AR (Liu *et al.*, 2021). Modern studies have also shown that Yupingfeng San is able to regulate human immunity and has been widely used in various diseases such as internal medicine, surgery, gynecology, pediatrics in modern clinical practice (Song, 2021). Nasal glucocorticoids are currently the most effective drugs with the strongest anti-inflammatory effect and the most effective treatment of AR, which may relieve symptoms by inhibiting inflammatory factors, reducing edema, and vasoconstriction, with stronger affinity and higher stability, and can effectively reduce various symptoms of nasal discomfort. It has a rapid onset of action and is metabolized by the liver and kidney, with a low chance of developing serious adverse effects (Yang *et al.*, 2021; Lai *et al.*, 2021). Some scholars believe that glucocorticoids can inhibit alveolar and systemic inflammatory response, reduce vascular permeability, reduce exudation, promote the synthesis of alveolar surfactant, reduce late pulmonary fibrosis and loss of lung volume, so they can be used in the early stage of inhalation (Gao *et al.*, 2020; Yang and Li, 2021). The innovation lies in the combined application of Yupingfeng granule oral treatment and nasal inhaled corticosteroids to comprehensively regulate the immune response and inflammation level of allergic rhinitis (AR). It aims to achieve the goal of relieving symptoms, reducing eosinophil infiltration in nasal secretions, and reducing the level of inflammatory factors in lavage fluid. This method is expected to achieve better results in the treatment of allergic rhinitis, and provide a more feasible and effective scheme for the treatment of the disease.

Materials and Methods

Study subjects

76 AR patients (40 males and 36 females, age range 17-64, mean age 30.5 ± 5.4) who visited Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine from June 2022 to March 2023 were selected. They were grouped: controls ($n = 38$) and experimental group

(n = 38). Controls were treated with nasal inhalation of glucocorticoid alone. The experimental group was treated with oral Yupingfeng granules based on controls.

Inclusion criteria: Patients had to meet the following clinical diagnostic criteria for AR: the presence of typical AR symptoms, including frequent sneezing, nasal itching, nasal congestion, and runny nose, lasting more than 4 days per week; Nasal endoscopy found that nasal mucosa edema, pale, or the eosinophilic positive performance; Serum IgE measurement was positive, further confirming the presence of anaphylaxis in the patient. Patients should be between 17 and 64 years of age, ensuring inclusion of patients of different age groups to maintain the diversity of the sample. There was no gender restriction, and a total of 40 males and 36 females were recruited to ensure a balanced distribution of gender. To exclude other confounding factors, patients were required to have not used antihistamines or hormonal drugs in the past month. Patients had moderate-to-severe AR to ensure the generalizability of the results across severities.

Exclusion criteria: Patients with severe organic diseases or other nasal diseases; patients with incomplete clinical data; pregnant and lactating women; patients withdrew from the experiment due to various reasons.

The study subjects agreed to sign the informed consent form with the consent of their family members. The conduct of this experiment was approved by the Hospital Ethics Association (Shanghai Municipal Hospital of Traditional Chinese Medicine, registration number: SMHTC3251, registration date: May 21, 2020). Obtained study subjects and private data are confidential and are for research use only and may not be used for other purposes.

Main reagents and instruments

ELISA kit (Beijing Solarbio Technology Co., LTD., China), Anti-TNF- α antibody, anti-IL-6 antibody, anti-IL-8 antibody (Thermo Fisher Scientific Co., LTD., China), Termination solution (Shanghai Kanglong Biotechnology Co., LTD., China), Fiberoptic bronchoscopy (Guangzhou Yunqi Medical Equipment Co., LTD., China), Optical microscope (Beijing Precise Instrument CO., LTD, China), Microplate analyzer (Jinan Laibao Medical Equipment Co., LTD., China), constant temperature water bath (Nanjing Kenfan Electronic Technology Co., LTD., China), fully automatic washing machine (Beijing Perlong New Technology CO., LTD. China); Slide (Beijing Shengkun Haili Technology Development Co., LTD., China); 2% lidocaine (Beijing Zeping Technology Co., LTD., China); Sterile saline (Nanjing SenBeiJia Biological Technology Co., Ltd., China); Microplate (Jiangsu Bomeida Life Science Co., LTD., China); Termination Solution (Jiangsu Huizhi Biotechnology Co., LTD., China).

Detection of eosinophils and inflammatory factors

For eosinophil detection, the patient's inferior turbinate was repeatedly rubbed with a cotton swab under direct vision to allow the secretion to dry on the slide. After HE staining, eosinophils were counted under a microscope, and the criteria were as follows: + (a small number scattered), ++ (a general number or aggregated into clusters), +++ (aggregated into large clusters or the whole was visible).

Bronchoalveolar lavage procedure: After airway examination by fiberoptic bronchoscopy, local anesthesia with 2% lidocaine was performed. Through biopsy hole to inject local anesthetic lidocaine, 37 °C sterilized saline was injected adopting the silicone tube, total 100-250 mL, and the recovery was between 40% and 60%.

For the detection of inflammatory factor levels, a blank control well was set in the microplate, and the standard substance and the tested sample were added in sequence. Enzyme-labeled antibodies were added, incubation at constant temperature, and the plates were washed. The chromogen solution was added, and the color was developed at 37 °C for 15 min before the termination solution was added. The absorbance value was measured by microplate reader, and the concentrations of TNF- α , IL-6, and IL-8 were calculated.

Drug therapy

Glucocorticoids: Patients in both controls and experimental group were treated with nasal inhalation of budesonide (1 spray, twice a day or 2 sprays, once a day) (Shanghai Johnson & Johnson Pharmaceutical Co., LTD., H20171311, China) + loratadine tablets (10 mg, orally, once a day) (Jiangsu Huanghe Pharmaceutical Co., LTD., H20050953, China).

Yupingfeng granules: Based on nasal inhaled corticosteroids treatment, patients in the experimental group were also orally administered with Yupingfeng granules (Sinopharm Group Guangdong Medi-World Pharmaceutical Co., LTD., Z10930036, China), with warm water, 10 g once, twice a day. Both groups continued treatment for 2 months.

Outcome measures and evaluation criteria

The symptoms of AR were scored before and after treatment in both groups (Table 1).

Table 1. Scoring criteria of symptom

Scoring	Nasal obstruction	Nasal itching	Blowing nose (times/day)	Sneezing (time)
1	Deliberate deep breathing	Occasionally	≤3	2-4
2	Occasionally	Tolerable	4-8	5-9
3	Almost every day	Unbearable	≥9	≥10

The physical signs of patients in the two groups were graded and scored according to the following criteria: 3 points: the inferior turbinate was close to the nasal floor and nasal septum, and the middle turbinate was not visible; 2 points: the inferior turbinate was close to the nasal floor and nasal septum, and there were small gaps; 1 point: the inferior turbinate was slightly swollen, and the nasal septum and middle turbinate were still visible; 0 point: none. The actual concentrations of inflammatory cytokines TNF- α , IL-6, and IL-8, as well as the number of EOS before and after treatment were measured by ELISA and recorded.

Calculation of treatment effect: (score before treatment - score after treatment)/score before treatment \times 100%. \geq 69% is significantly effective; 31% to 69% is effective; and \leq 30% is ineffective.

Statistical analysis

All experimental data were analyzed by SPSS 24.0 software (IBM, USA). Measurement data were described as mean \pm standard deviation ($\bar{x} \pm s$), and measurement data with normal distribution were statistically analyzed by t test. Statistical inference of count data was performed using χ^2 test. In terms of comparison between groups, one-way ANOVA was used and SNK-q test was performed for pairwise comparison. In all statistical analyses, a *P* value of less than 0.05 was considered statistically significant.

Results*General information and clinical data of the patients*

As presented in Table 2, there was no significant difference in gender composition between the controls and the experimental group (*P* > 0.05), indicating that the two groups were comparable in terms of gender composition. The age of the controls and experimental group also performed *F* test, overall and pairwise comparison, and the results were *P* > 0.05, indicating that there was no significant difference in age composition between the two groups, which was comparable. For AR patients, *F* test and pairwise comparison were performed between the two groups in terms of course composition, and *P* values were also greater than

0.05, indicating that there was no significant difference in course composition between the two groups, which was comparable.

Table 2. Comparison of general conditions between the two groups

Group	Cases	Gender (Male/Female)	Age ($\bar{x}\pm s$)	Disease course ($\bar{x}\pm s$)
Controls	38	21/17	31.3 \pm 4.6	6.3 \pm 1.5
Experimental group	38	19/19	29.6 \pm 5.1	5.9 \pm 1.8
<i>P</i>	-	4.782	5.034	3.269

Comparison of symptoms before and after treatment

Figure 1 shows that there was no significant difference in clinical symptom scores such as sneezing, runny nose, nasal congestion, and itching between the two groups of patients before treatment ($P > 0.05$). After 2 months of treatment, the symptom scores of both groups decreased, and the scores of the experimental group were significantly lower than those of the controls, with a significant difference ($P < 0.05$).

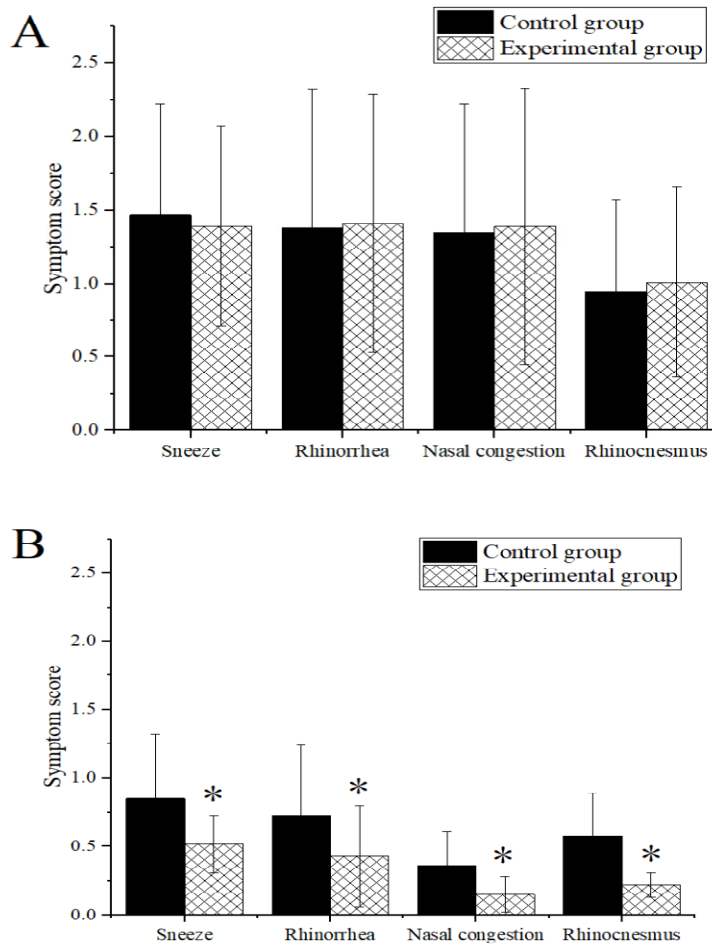


Figure 1. Comparison of symptoms

Note: A: pre-treatment, B: post-treatment

* represents experimental group versus controls, $P < 0.05$

Comparison of treatment effects

As shown in Figure 2, after treatment, the effective rate of the controls was 81.57%; The effective rate of treatment in the experimental group was 94.73%, which was significantly higher than that in the controls ($P < 0.05$).

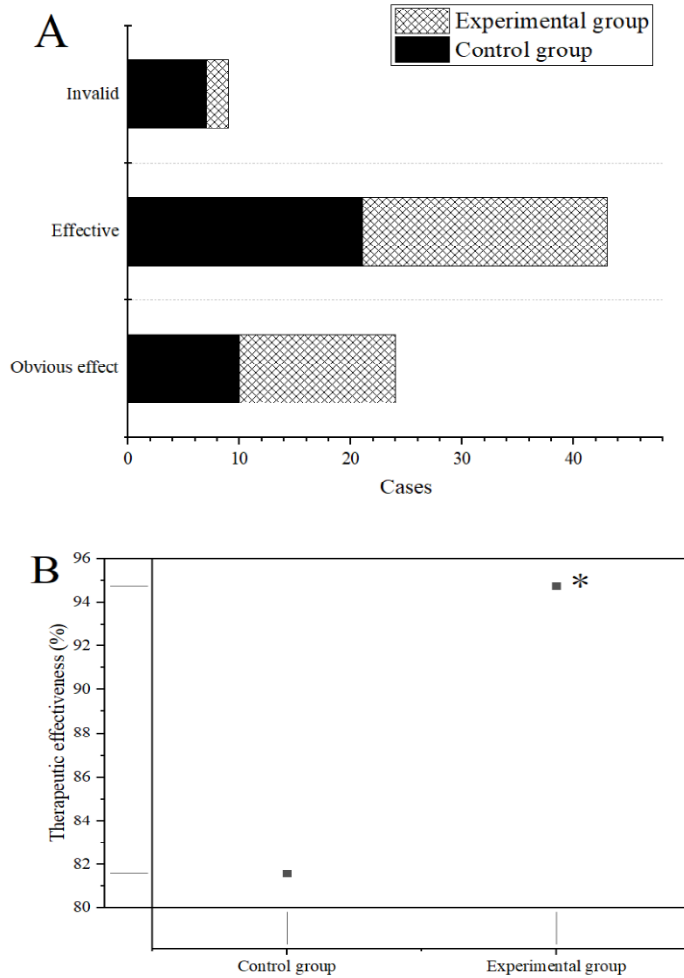


Figure 2. Comparison of patients' treatment effect

Note: A: therapeutic effect, B: therapeutic effective rate

Comparison of physical sign scores

As shown in Figure 3, there was no significant difference in sign scores between the two groups before treatment ($P > 0.05$). After 2 months of treatment, the physical sign scores of both groups decreased, and the experimental group was significantly lower than the controls, with a significant difference ($P < 0.05$).

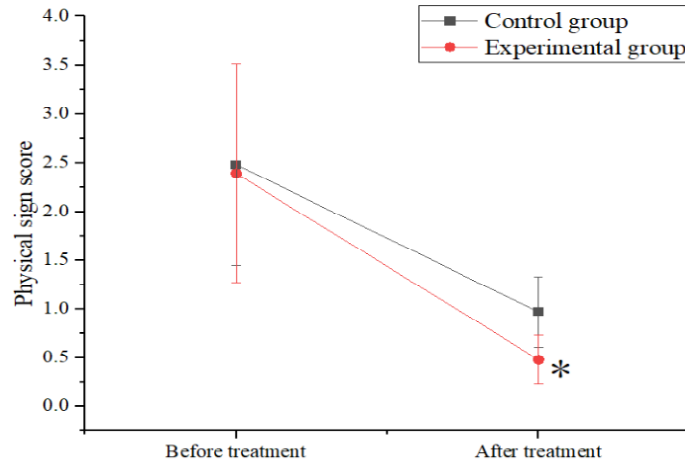


Figure 3. Comparison of physical sign scores before and after treatment

EOS count comparison

Figure 4 shows that the eosinophil count of nasal secretions observed under an optical microscope was similar between the two groups before treatment, with no statistical difference ($P > 0.05$). After treatment, the experimental group had fewer eosinophil counts, which showed a significant difference compared to the controls ($P < 0.05$).

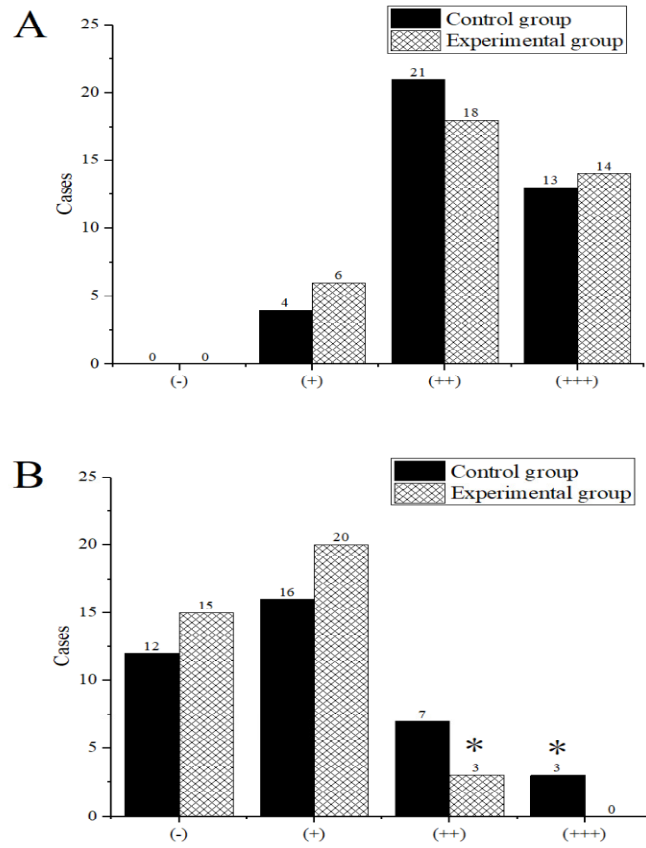


Figure 4. Comparison of EOS count before and after treatment
Note: A: before treatment, B: after treatment

Comparison of inflammatory cytokine levels

Figure 5 shows that there were no significant differences in TNF- α , IL-6, and IL-8 levels between the two groups before treatment ($P > 0.05$). After 2 months of treatment, the levels of inflammatory cytokines in the experimental group were significantly lower than those in the controls ($P < 0.05$).

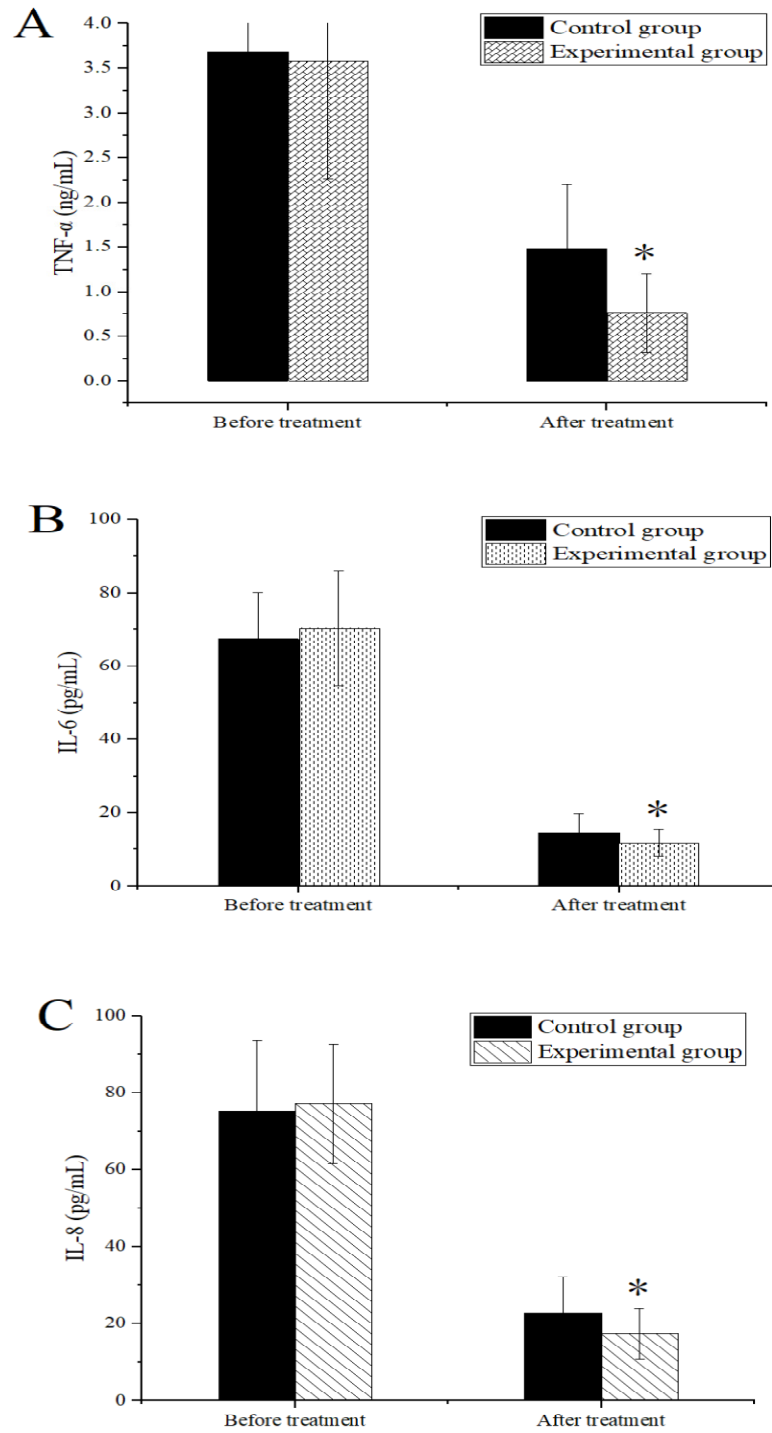


Figure 5. Comparison of inflammatory cytokine levels
Note: A: comparison of TNF- α levels, B: comparison of IL-6 levels, C: comparison of IL-8 levels before and after treatment

Discussion

Mediator involved type I allergic disease characterized by paroxysmal sneezing, nasal itching, and nasal congestion. AR can seriously affect the quality of life of patients. AR incidence has been increasing in recent years and has become a global health concern (Chen *et al.*, 2020; Zeng *et al.*, 2022). Normally, there were only a few epithelial cells and lymphocytes in nasal secretions. When AR occurs, more EOS, basophils, and goblet cells may be present in nasal secretions. EOS is an innate class of immune cells in the human body that has cytotoxic effects and acts on airway epithelial cells and cardiomyocytes, which can lead to tissue damage and organ dysfunction in people with such diseases (Yamashita *et al.*, 2020). The results of the references introduced the pathological characteristic of AR and the influence on patients' quality of life, and this article emphasized the main symptoms of AR, such as nasal congestion, runny nose, and the impact on the quality of life of patients. Moreover, both mentioned the rising incidence of AR has become a global health concern. However, the focus of this article is to explore the Yupingfeng granules with nasal inhaled corticosteroids therapy in patients with AR. This article highlights the specific treatment method of these factors, the combined use of Yupingfeng granules oral and nasal inhaled corticosteroids treatment, to realize the comprehensive therapeutic effect. AR generally causes high EOS, and it may be because allergens come into contact with the nasal mucosa, triggering allergic reactions. EOS on the surface of the nasal mucosa is stimulated to split more EOS and phagocytose allergens, limiting allergic reactions. Infiltration of the nasal mucosa and hyperreactive allergic lesions by EOS are important features of AR (Yildiz *et al.*, 2020; Shao *et al.*, 2021), often accompanied by respiratory epithelial detachment, basement membrane thickening, mucous cell hyperplasia, and interstitial edema, which are one of the important causes of the occurrence, development, and protracted healing of allergic diseases.

In this article, patients were treated with glucocorticoids for 2 months, and the results showed that the symptoms of patients were alleviated, and the physical sign score, EOS number, and inflammatory factor levels were clearly decreased. It confirmed that glucocorticoids can induce EOS reduction, which may be the basis for the clinical use of glucocorticoids in the treatment of AR. Hong *et al.* (2020) did relevant experiments and revealed that glucocorticoids rapidly induced bone marrow homing in EOS, and selective blockade of CXCR4 reduced or abolished glucocorticoid-induced early blood EOS reduction. In contrast to this article, both deal with the mechanism of action of glucocorticoids on eosinophils, especially in relation to eosinophil bone marrow migration. Both this article and the results of experiments by Hong *et al.* show the effect of glucocorticoids in regulating the number of eosinophils. Specifically, Hong and other scholars found that glucocorticoids can perform selective blocking CXCR4 to reduce or eliminate glucocorticoid induced early blood eosinophils reduction, thus revealing the mechanism of glucocorticoid inducing eosinophils reduction. However, there are some differences to note. This article focuses on the application of Yupingfeng granules oral treatment with inhaled corticosteroids in patients with AR, in order to reduce nasal secretions acidophilic granulocyte infiltration and reduce lavage inflammatory factor levels. This article pays more attention to the treatment scheme of the disease, especially the application of the Yupingfeng granules. Although both articles dealt with the relationship between glucocorticoids and eosinophils, there were differences in research objectives and methods.

Bruscoli *et al.* (2021) pointed out that glucocorticoids have rapid, powerful, and non-specific anti-inflammatory effects, and they are effective against various inflammations, which mainly play an anti-inflammatory role by inducing the synthesis of anti-inflammatory factors. In addition, they also inhibit the production of leukocyte inflammatory proteases by inducing the synthesis of inflammatory proteins, and inhibit the production of leukocyte inflammatory proteases and fundamentally inhibit the production of inflammation, so they can achieve anti-inflammatory effects. Then, it also inhibits the synthesis of inflammatory factors. In the early stage of inflammation, glucocorticoids reduce inflammation by inhibiting telangiectasia, reducing exudation and edema, and inhibiting the infiltration and phagocytosis of white blood cells. In the later stage of inflammation, it inhibits the proliferation of capillaries and fibroblasts, and delays the

generation of granulation tissue, thus reducing inflammatory sequelae such as scars. Moreover, it can also induce apoptosis of inflammatory cells and inhibit the release of proteolytic enzymes by vasoconstriction to play an anti-inflammatory role. It also explains the significant decrease in levels of inflammatory cytokines TNF- α , IL-6, and IL-8 in patients treated with nasal inhaled corticosteroids (Kim *et al.*, 2020).

In addition to glucocorticoid treatment, Yupingfeng granules were orally administered to patients in the experimental group, and the results suggested that not only the symptoms of patients were greatly improved, but also the number of EOS and the level of inflammatory factors were lower in the experimental group in contrast with controls. It is due to AR, in the view of TCM, mainly because the lack of righteousness in the human body, exogenous pathogens take advantage of deficiency to enter, Promoting the dispersing function of the lung drugs can be used to treat AR. The main components of Yupingfeng are Astragalus membranaceus, Atractylodes macrocephala Koidz, and divaricate saphoshnikovia, which has effects of strengthening pulmonary qi, invigorating spleen, and expelling wind. Therefore, Yupingfeng has a positive auxiliary effect for the treatment of AR. The TCM ingredients of drugs in the treatment of rhinitis, patients formed less drug dependence, and the chance of recurrence is also relatively small, while the side effects on the body are also small. Chen *et al.* (2021) experimentally measured the effect of Chinese herbal compound plus Yupingfeng on ovalbumin induced AR mice in order to investigate the efficacy of Yupingfeng San alone or in combination with other components in the treatment of AR. The results suggested that after treatment, ovalbumin specific IgE and histamine levels were evidently decreased, IL-4 and transforming growth factor- β levels were clearly decreased, while interferon- γ levels were increased in mice, which showed that Chinese herbal compound plus Yupingfeng had a potential therapeutic effect on AR by regulating the rebalance of T helper 1 and T helper 2.

Conclusions

The results showed that oral administration of Yupingfeng granules based on nasal inhalation of glucocorticoids could improve the symptoms of rhinitis, reduce the edema of nasal mucosa, and effectively reduce the number of EOS and the level of inflammatory factors in nasal secretions to a great extent. The shortcomings are that due to the limitation of objective factors such as funding and time, the collected sample size is small, the compared indicators are limited, and the relevant animal experiments have not been performed. The symptom score and sign score before and after treatment can't be evaluated by objective laboratory indicators, which are expressed by the patients themselves. In the future, the sample size should be expanded and animal models should be established to obtain more comprehensive and objective data. It provides some reference for the selection of clinical treatment options for AR.

Authors' Contributions (Please add)

RH is responsible for the preliminary analysis and statistical processing of experimental data, including data collection, experimental procedures, and sample handling, to ensure the reliability of the data. YG is responsible for the design and execution of clinical experiments, as well as summarizing relevant literature on the research topic and overseeing the entire experimental process to ensure its feasibility. LHW serves as the primary supervisor and guide for this research project, providing valuable advice and insights, and directing the overall direction and progress of the experiment. All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

The research project has obtained approval from Shanghai Municipal Hospital of Traditional Chinese Medicine (Registration number: SMHTC3251, registration date: May 21, 2020) and is conducted strictly in accordance with ethical principles. In this study, we respect and protect the rights and privacy of participants, ensuring the confidentiality of their personal information.

Acknowledgements

This work was supported by the: The Clinical Research Special Project of the Shanghai Municipal Health Commission on the Health Industry "Clinical Study on the Treatment of Allergic Rhinitis with Tiantu Acupoint Water Acupuncture Therapy Combined with Du Moxibustion" (No. 20194Y0345).

Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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