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Effect of Yupingfeng granule assisted fluticasone propionate nasal spray on patients with AR and its regulation on IL-5, ICAM-1 and ECP

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The present investigation deals with the effect and mechanism of Yupingfeng granule assisted Fluticasone propionate nasal spray in the treatment of patients with allergic rhinitis (AR). Total of 140 patients with AR treated in Yulin Hospital of Traditional Chinese Medicine from December 2019 to July 2020 have been selected for clinical trial. The patients in traditional Chinese medicine (TCM) group were treated with Yupingfeng granule plus Fluticasone propionate nasal spray, while those in routine group are treated with Fluticasone propionate nasal spray. The remaining basic treatment in the two groups remained the same, with 60 patients in each group. Symptom, sign score, TCM syndrome score, quality of life score, interleukin-5 (IL-5), intercellular adhesion molecule-1 (ICAM-1), eosinophil cationic protein (ECP) levels in peripheral blood and clinical treatment effect have been compared between two groups before and after treatment. Before treatment, there is no significant difference in the scores of symptoms, signs and total scores between the two groups; after treatment, these were lower than those of the routine group. There is no significant difference in the scores of TCM symptoms between the two groups ($P > 0.05$) before treatment, while after treatment; these are lower than those of the routine group. The levels of IL-5, ICAM-1 and ECP in the peripheral blood of the patients in the two groups have been compared, and there is no significant difference between the two groups before treatment while after treatment, the levels of IL-5 and ECP in the peripheral blood of the patients in TCM group were lower than those in the routine group, and the difference had statistical significance. Yupingfeng granule assisted Fluticasone oropionate nasal spray can effectively relieve the clinical symptoms of patients with AR, improve the quality of life, regulate the levels of IL-5 and ECP in peripheral blood and improve the clinical effect.

Keywords: Allergic rhinitis, Fluticasone propionate, Immunomodulation, TCM,Yupingfeng granules

Allergic rhinitis (AR) is a common allergic disease caused by allergen, which is mediated by immunoglobulin E (IgE) with the incidence of 10 to 35%[1]. At present, the pathogenesis of the disease has not been fully defined, and most studies suggest that it is mainly related to genetic factors, allergen exposure, autoimmune imbalance and other factors[1]. AR mainly manifests as nasal congestion, sneezing, runny nose and other symptoms, repeated attacks, prolonged and difficult to heal, seriously affecting patients' quality of life. As the disease progresses, severe cases may even cause conjunctivitis, otitis, sinusitis, and even allergic asthma[2]. At present, the western medicine mainly uses glucocorticoids, antihistamines and so on to treat AR. Fluticasone Propionate Nasal Spray is a kind of AR drug with strong anti-inflammatory and anti-allergic effects, but it fails to achieve the ideal effect of complete eradication and has certain side effects[3]. Therefore, there is a need to explore new pharmacological treatment options to improve patients' quality of life. According to the traditional theory of traditional Chinese medicine, AR belongs to the category of "allergic rhinitis" and "rhinopharyngitis", which is closely related to the function of lung, spleen, kidney and other Zang-Fu (viscera) organs[4].

In recent years, many studies have reported that traditional Chinese medicine is effective in treating AR. Interleukin-5 (IL-5), intercellular adhesion molecule-1 (ICAM-1), eosinophil cationic protein (ECP) and other cytokines have been shown to be closely related to the incidence and severity of AR[5]. In the present investigation, Yupingfeng Granule combined with Fluticasone Propionate Nasal Spray was used to treat AR, and the effects of Yupingfeng Granule on IL-5, ICAM-1, ECP and other cytokines were observed, so as to provide reference for the treatment of AR by combination of traditional Chinese and western medicine.

Experimental Section

Data

The rest basic treatments in the two groups were consistent, with 60 cases in each group; the symptom,

sign score, TCM syndrome score and quality of life of the patients in the two groups for the treatment with aerosol were compared before and after treatment, and 140 cases of AR treated in Yulin Hospital of Traditional Chinese Medicine, China from December 2019 to July 2020 were selected for clinical trial. They were randomly divided into TCM group and routine group, with 70 cases in each group.

Inclusion criteria:(i) The diagnostic criteria of AR patients refer to the criteria in the "Guidelines for the Diagnosis and Treatment of Allergic Rhinitis (Edition 2015)"[6]; (ii) The main clinical manifestations of patients were nasal itching, nasal congestion and clear nasal discharge. The patients had edema of nasal mucosa, swelling of nasal turbinates and watery discharge of nasal cavity found by nasal endoscopy; (iii) The patients were aged 18-65 years; (iv) Positive serum IgE and positive specific IgE in the laboratory; (v) The diagnostic standard of traditional Chinese medicine refers to the standard of "Integrated Traditional Chinese and Western Medicine and Otorhinolaryngology"[7], which belongs to "lung-qi deficiency and cold type"; (vi) The disease course of the patient is more than 1 year.

Exclusion criteria: (i) Nasopharyngeal tumor; (ii) History of nasopharyngeal surgery; (iii) Severe heart, liver, kidney and other diseases; (iv) History of cerebrovascular disease and myocardial infarction in the past half a year; (v) Immune system disease; (vi) Deflection of nasal septum and hypertrophy of nasal polyps; (vii) Exfoliated patients.

The study protocols were submitted to the medical ethics committee of Yulin Hospital of Traditional Chinese Medicine, China for review and approval before implementation. The study was conducted after the medical ethics committee decided to receive the study report (No.: LY (P)[2019] No. 08).

Basic treatment

Fluticasone propionate nasal spray (GlaxoWellcome S-A production, Registration No.: H20091100) was sprayed into the nasal cavity once daily for 4 weeks is a treatment course.

TCM treatment

At the same time of above-mentioned basic treatment, Yupingfeng granule (Manufacturer: Guangdong Globe Pharmaceutical Co., Ltd.; Strength: 5g × 12 bags; Lot No.:130902) was flushed with boiling water, 5 g/time, tid.

Observation indicators and evaluation methods

Symptom, sign score, TCM syndrome score, quality of life score and clinical treatment effect were compared between the two groups before and after treatment. The levels of interleukin-5 (IL-5), intercellular adhesion molecule-1 (ICAM-1) and eosinophil cationic protein (ECP) in peripheral blood were measured. Clinical symptoms and signs were scored with reference to the criteria in "Guidelines for Diagnosis and Treatment of Allergic Rhinitis (Edition[6],2015)". Four clinical symptoms of sneezing, runny nose, nasal congestion and nasal itching were given respectively 0, 1, 2 and 3 points according to the severity of symptoms e.g. the higher the score, the more severe the symptoms. Clinical signs consisted mainly of swelling of the inferior turbinate (score 0: no swelling; score 1: mild swelling of the inferior turbinate with visible nasal septum and middle turbinate; score 2: close proximity of the inferior turbinate to the nasal septum with moderate swelling; score 3: close proximity of the inferior turbinate to the nasal base with no visible middle turbinate, polypoid changes or polyposis in the inferior turbinate).

The TCM syndrome score refers to the standard of "Integrated Traditional Chinese and Western Medicine and Otorhinolaryngology"[7], mainly from the main symptoms: sneezing, nasal itching, nasal stuffiness, watery nasal discharge, anosmia; the secondary symptoms: fear of wind and cold, shortness of breath and laziness to speak, pallor, drowsiness of limbs, stagnation of urination and defecation; the main symptoms score ranges from 0 to 6 points, the secondary symptoms score ranges from 0 to 3 points, the higher the score, the more serious the patient's TCM syndrome.

The quality of life scoring criteria refer to the criteria in the "Rhinoconjunctivitis Quality of Life Scale", which includes daily activities (3 questionnaire items), sleep (3 questionnaire items), non-nasal/ocular symptoms (7 questionnaire items), actual problems (3 questionnaire items), nasal symptoms (4 questionnaire items), ocular symptoms (4 questionnaire items), mood (4 questionnaire items), and a maximum score of 6 points for each questionnaire item and a minimum of 0 point.

The evaluation of clinical treatment effect is evaluated according to the integral change of clinical symptoms and physical signs of the patient, and the recovery is: the score of symptoms and physical signs of the patient is reduced by ≥ 95% compared with that

before treatment; significant effect: the score of symptoms and physical signs of the patient is reduced by 75% ~ 94% compared with that before treatment; effective: the score of symptoms and physical signs of the patient is reduced by 30% ~ 74% compared with that before treatment; ineffective: the score of symptoms and physical signs of the patient is reduced by less than 30% compared with that before treatment.

Statistical processing

The measurement indexes such as IL-5, ICAM-1 and ECP levels in peripheral blood of this study were tested by normal distribution, and all of them conformed to approximately normal distribution or normal distribution. They were expressed by (± s), and t test in SPPS software was used; χ^2 test was used to analyze the measurement data; Whitney-U test was used to analyze the rank count data; the test level was $\alpha = 0.05$.

Results

Comparison of general data between the two groups

The baseline data of the patients in the TCM group were compared with those in the routine group, and the differences between the two groups had no statistical significance (P>0.05) (Table 1).

Comparison of symptoms and physical signs between the two groups before and after treatment

Before treatment, there was no significant difference in symptom score, physical sign score and total score between the two groups (P>0.05); after treatment, the symptom score and total score of patients in TCM group were lower than that in routine group, and the difference had statistical significance (P<0.05) (Table 2).

Comparison of TCM syndrome scores before and after treatment between the two groups

Before treatment, there was no significant difference in the scores of TCM syndromes between the two groups (P>0.05); after treatment, the scores of symptoms, the scores of secondary syndromes and the total scores of TCM syndromes in the TCM group were lower than those in the routine group, and the difference had statistical significance (P<0.05)(Table 3).

Comparison of quality of life scores between the two groups before and after treatment

Before treatment, there was no significant difference in the scores of quality of life between the two groups (P>0.05); after treatment, the total scores of daily activities, actual problems, nasal symptoms, mood and quality of life in the TCM group were lower than those in the routine group, and the difference had statistical significance (P<0.05) (Table 4).

Table 1 — Comparison of general information of the two groups of patients

Normal information	Chinese medicine group（n=60）	Regular group（n=60）	t/χ^2	P
Age (Years)	36.9±9.6	38.2±8.8	-0.773	0.441
Course of disease (Years)	5.1±2.0	5.5±2.2	-1.042	0.299
Sex (%)			0.845	0.358
Male	36(60.00)	31(51.67)		
Female	24(40.00)	29(48.33)		
Smoking(%)			0.862	0.353
Yes	22(36.67)	27(45.00)		
No	38(63.33)	29(48.33)		
Drinking (%)			1.386	0.239
Yes	22(36.67)	16(26.67)		
No	38(63.33)	29(48.33)		
Shedding case (%)	2(3.33)	4(6.67)	0.702	0.402

Table 2 — Comparison of the scores of symptoms and signs between the two groups of patients before and after treatment

（$\bar{x}$±s，Scores）

Group	n	Symptom score		Physical sign score		Total score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Chinese medicine group	58	9.84±1.50	3.81±0.84	2.30±0.56	0.84±0.30	12.14±2.51	4.65±1.44
Regular group	56	10.21±1.28	4.77±1.10	2.18±0.61	0.92±0.28	12.39±2.74	5.69±1.62
t		-1.414	-5.248	1.095	-1.471	-0.508	-3.626
P		0.160	0.000	0.276	0.144	0.612	0.000

Table 3 — Comparison of treatment compliance scores before and after intervention in the two groups (±s, points)

Group	n	Main card		Secondary card		Total score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Chinese medicine group	58	21.83±3.96	7.88±2.03	11.32±2.06	4.52±1.38	33.15±5.76	12.40±2.57
Regular group	56	21.41±4.22	9.77±2.63	10.95±2.11	5.73±1.50	32.36±5.14	15.50±3.03
t		0.548	-4.304	0.947	-4.485	0.772	-5.898
P		0.585	0.000	0.345	0.000	0.442	0.000

Table 4 — Comparison of quality of life scores between the two groups before and after treatment (±s, points)

Group	n	Daily activities		Sleep		Non-nasal/eye symptoms		Practical problems	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Chinese medicine group	58	13.29±2.80	5.74±1.54	9.68±2.44	5.00±1.68	27.50±5.03	14.81±3.74	10.58±2.86	5.11±1.86
Regular group	56	12.78±3.12	6.44±1.85	9.94±2.16	5.41±1.88	25.94±4.16	15.68±3.82	10.13±2.90	6.38±1.91
t		0.919	-2.199	-0.602	-1.229	1.801	-1.229	0.834	-3.597
P		0.360	0.030	0.549	0.222	0.074	0.222	0.406	0.000

Group	n	Nasal symptoms		Eye symptoms		Mood		Total score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Chinese medicine group	58	17.58±4.41	9.42±2.64	16.72±3.37	9.81±2.85	14.37±3.00	8.19±2.23	108.56±11.61	58.41±8.45
Regular group	56	19.02±4.85	11.03±2.97	16.13±3.52	10.84±3.00	15.42±3.76	10.02±3.41	105.41±13.28	69.44±9.52
t		-1.660	-3.062	0.914	-1.880	-1.651	-3.403	1.350	-6.548
P		0.100	0.003	0.363	0.063	0.102	0.001	0.180	0.000

Comparison of laboratory parameters between the two groups before and after treatment

Before treatment, there was no significant difference in the levels of IL-5, ICAM-1 and ECP in peripheral blood between the two groups (P>0.05); after treatment, the levels of IL-5 and ECP in peripheral blood of patients in TCM group were lower than those in routine group, and the difference had statistical significance (P<0.05) (Table 5).

Comparison of treatment effect between the two groups of patients

After treatment, the recovery rate of the patients in the TCM group was 50.00%, the significant effective rate was 37.93%, the effective rate was 10.34%, the ineffective rate was 1.72%. The recovery rate of the routine group was 26.79%, the significant effective rate was 51.79%, the effective rate was 17.86%, and the ineffective rate was 3.57%. The curative effect of the TCM group was better than that of the routine group (P<0.05); (Table 6).

Discussion

Allergic rhinitis is a chronic inflammatory disease of the nasal mucosa. Exposure of atopic individuals to allergens can result in a marked increase in the secretion of IgE-mediated mediators such as histamine in the body, causing edema of the nasal mucosa, causing a series of pathological changes such as increased permeability, telangiectasia and increased glandular secretion, inducing eosinophil accumulation. It also included infiltration, leading to a severe inflammatory reaction in the nasal cavity[1]. Anti-inflammatory therapy is an important treatment for AR in western medicine. Fluticasone Propionate Nasal Spray is a glucocorticoid topical agent with potent anti-inflammatory effects, down-regulating the synthesis and release of cytokines and chemokines, blocking multiple steps in the inflammatory reaction process, and thereby improving the clinical symptoms of AR. However, in clinical practice, it was found that some patients could not spray at the focus, which affected the therapeutic effect; some patients with AR, especially those with multiple allergies, did not receive Fluticasone Propionate Nasal

Table 5 —Comparison of laboratory indicators before and after treatment between the two groups（$\bar{x}$±s）

Group	n	IL-5（ng/mL）		ICAM-1（ng/mL）		ECP（pg/mL）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Chinese medicine group	58	43.82±7.64	24.11±4.85	6.57±1.84	7.88±1.90	498.5±34.7	244.1±25.8
Regular group	56	41.40±8.11	27.53±5.90	6.83±1.90	7.55±1.84	509.4±41.6	267.5±28.5
t		1.640	-3.386	-0.742	0.942	-1.521	-4.599
P		0.104	0.001	0.459	0.348	0.131	0.000

Table 6 —Comparison of treatment effect between two groups of patients [n（%）]

Group	n	Get well	Significantly effective	Effective	Invalid
Chinese medicine Group	58	29(50.00)	22(37.93)	6(10.34)	1(1.72)
Regular group	56	15(26.79)	29(51.79)	10(17.86)	2(3.57)
Z			-1.993		
P			0.046		

Spray at early stage[3], which affected the confidence of treatment and even interrupted the treatment. Traditional Chinese medicine treatment improves the constitution of patients by regulating Qi-blood-Yin-Yang of Zang-Fu organs, with lasting effect and little side effect. Therefore, it is an important way to explore combined Chinese and western medicine treatment scheme to improve the efficacy of AR treatment.

According to the theory of TCM, the AR should belong to the category of "allergic rhinitis" and "rhinopharyngitis", which is caused by the deficiency of the function of Zang-Fu, the deficiency of Yangqi of Ying and Wei, and the looseness of exterior deficiency[4]. Positive Qi deficiency mainly embodies in Qi Yang deficiency of the lung, the spleen, the kidney; deficiency-cold body feels the external evil, the evil is easy to become the cold, then nasal obstruction becomes the disease. The treatment should strengthen the Qi and strengthen the positive Qi, provide internal support and external protection, then the wind-evil goes away without restitution[8]. Yupingfeng is a traditional Chinese medicine formula, with astragalus membranaceus good for tonifying the spleen and lung, and can consolidate the exterior and stop sweating; Rhizoma Atractylodis Macrocephalae invigorating the spleen and invigorating the Qi, removing dampness and consolidating the exterior; Divaricate Saposhnikovia Root walking through the muscle and dispersing the wind and evil; the combination of these medicines can jointly exert the effects of replenishing Qi and consolidating dispelling evil.

Inflammatory reaction plays an important role in the development of AR, and it has been shown that multiple cytokine levels are abnormal in AR patients, leading to repeated episodes of the disease[9]. IL-5 is an important cytokine involved in immune regulation which has multiple biological activities. Elevated levels of serum IL-5 can promote eosinophil proliferation and differentiation, and interact with other inflammatory factors to aggravate the inflammatory reaction[10]. ICAM-1 is an important adhesion factor, which can combine with specific receptors on vascular endothelial cells on the body surface to improve the adhesion of white blood cells, inflammatory cells and tumor cells in vivo[11]. ECP is an eosinophil, and its cytotoxic effect is a key factor in the development of AR[12]. It has been confirmed that the levels of IL-5, ICAM-1 and ECP can reflect the serious condition of AR[5]. The results of present investigation showed that the scores of symptoms, total scores and syndrome scores of TCM in the TCM group were lower than control, where as the scores of daily activities, practical problems, nasal symptoms, mood and quality of life in the TCM group were lower than those in the routine group. This finding indicates that the combined application of Yupingfeng Granule can improve the clinical symptoms and quality of life of the patients. The levels of IL-5, ICAM-1 and ECP in TCM group were lower than those in routine group. In recent years, pharmacological studies have proved that astragalus membranaceus can improve immune ability, promote lymphocyte proliferation and phagocytosis of macrophages, while Rhizoma Atractylodis Macrocephalae can exert antihistamine effect and effectively inhibit the secretion of various factors mediating allergic reaction[13]. Zhang Dan *et al.*[14] believed that Yupingfeng granule has various pharmacological effects such as immune regulation, anti-oxidation and regulation of cytokines. BaiShangjie *et al.*[15] reported that the addition of Yupingfeng can

effectively inhibit the level of cytokines, improve the Th1/Th2 immune imbalance in AR patients, and overall regulate the immune function of patients and reduce the level of serum IgE.

The conclusion of this study is consistent with the above study, and further confirms that Yupingfeng Granule has the function of regulating immune function and inhibiting inflammatory reaction. Fluticasone Propionate Nasal Spray combined with Yupingfeng Granule can rapidly improve the clinical symptoms, improve the therapeutic effect and improve the quality of life of patients with AR, and its mechanism may be related to the down-regulation of IL-5, ICAM-1, ECP and other cytokines.

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