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Original Article

Efficacy of intranasal corticosteroids combined with saline nasal irrigation and Singulair on allergic rhinitis and its influence on serum inflammatory factors

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Abstract: Objective: To observe the efficacy of intranasal corticosteroids combined with saline nasal irrigation and Singulair on allergic rhinitis (AR) and its influence on serum inflammatory factors. Methods: Seventy-eight patients with AR were selected as observation subjects and divided into two groups using a table of random digits, control group and study group, with 39 cases in each group. The control group was treated with intranasal corticosteroids combined with saline nasal irrigation, while the study group received medication of Singulair on the basis of the aforementioned treatments. The clinical efficacy, and the changes of serum inflammatory factors, lung function indices, physiological function of nasal cavity, and the score of quality of life (QoL) before and after treatment were compared. Results: The total effective rate of the study group was higher than that of the control group ($P<0.05$). The levels of serum inflammatory factors, tumor necrosis factor, interleukin-6 (IL-6), and interleukin-12 (IL-12), in the study group were lower than those in the control group (all $P<0.05$). The lung function indices, forced expiratory volume in one second % (FEV_1%) and maximal mid-expiratory flow % (MMEF%), in the study group were higher than those in the control group (both $P<0.05$). The study group was superior to the control group in the physiological function of nasal cavity and QoL (both $P<0.05$). Conclusion: Intranasal corticosteroids combined with saline nasal irrigation and Singulair presented definite efficay on AR, with reduction in inflammatory reaction, improvement in lung function, physiological function of nasal cavity, and QoL, and it is worthy of clinically application and promotion.

Keywords: Intranasal corticosteroids, normal saline, nasal irrigation, singulair, allergic rhinitis

Introduction

Allergic rhinitis (AR) is a non-infectious inflammatory disease occurring in nasal mucosa with nasal itching, nasal congestion, rhinorrhea and sneezing as its main clinical symptoms, which is induced by immunoglobulin E-mediated chemical mediators with the participation of various immunologically competent cells and cytokines after allergen exposure. According to statistics, AR affects 10% to 25% of the global population, and its incidence in China is about 11%, presenting a high proportion in otolaryngology diseases. Asthma appears in about 20%-30% of AR patients, seriously affecting the quality of life (QoL) and mental health of the patients [1, 2]. Moreover, AR is a risk factor for developing nasal polyps and sinusitis, so it should be given timely treatment [3]. Environment and heredity are currently considered to be the main factors inducing AR [4]. The prevalence rate of AR has been on the rise in recent years with the aggravation of air pollution and the deterioration of the environment [5]. AR can be controlled after effective treatment, but it is prone to recurrent attacks, and refractory to complete recovery for its persistence, with the loss of the QoL of patients and passive affection to mental health [6]. Therefore, AR should be treated in an active and prompt way.

Budesonide is the main component of Rhinocort Aqua nasal spray, which is a novel non-halogenated inhaled corticosteroid. Budesonide has strong lipid solubility and water solubility due to the existence of lipophilic groups on the D ring of its sterol structure. It can promptly exert anti-

inflammatory effect and rapidly relieve inflammation after intranasal inhalation [7]. Moreover, budesonide can improve the stability of lysosomal membrane and epithelial cells, thus improving nasal mucosa edema and relieving the pathogenetic condition [8]. In addition, budesonide can in part bind to glucocorticoid receptor, while the rest of it is stored in inactive esterified form and converted into active form under certain conditions for continuous effect on anti-inflammation, thus presenting long-acting effect [9]. Besides, budesonide can be used for a long-term medication due to its small dosage in topical application and less adverse reactions [10]. Nasal irrigation with normal saline can improve the rheological properties of contents in the nasal cavity, clear mucus cilia, and promote the functional recovery of ciliated epithelium [11]. Irrigation with normal saline can also promote dehydration of bacterial protein, thus killing the bacteria. However, combination treatment of intranasal corticosteroids and saline nasal irrigation for AR has limited therapeutic effect with proneness to recurrent attacks.

Singulair belonging to the leukotriene receptor antagonists has the effect of inhibiting expression of cysteinyl leukotriene involved in the pathogenetic process of AR. Thus, the inhibition on the inflammatory medium can effectively reduce airway inflammatory response, nasal mucosal edema, and inflammatory exudation etiologically [12]. Intranasal corticosteroids combined with saline nasal irrigation and Singulair can treat AR in a multi-target way with synergistic effect. The total effective rate of the study group is higher than that of the control group after treatment, suggesting that the treatment of intranasal corticosteroids combined with saline nasal irrigation and Singulair for AR presents obvious improvement, which is basically consistent with the previous studies [13].

Nasal spray of corticosteroids and nasal irrigation with normal saline are the main treatments for AR. Yang *et al*. used normal saline at normal temperature (25°C) alone for treating 35 AR patients, and the rate of symptomatic improvement was 74.3% [14]. A study showed that nasal spray using corticosteroids alone in 47 patients with AR presented a total clinical effective rate of 80.85%, but this single treatment was prone to relapse after drug withdrawal, with approximately 65% of the patients receiving treatments giving satisfactory feedback on the efficacy [15]. Shan *et al*. adopted nasal irrigation with 3% sodium chloride solution combined with fluticasone propionate nasal spray for AR patients, with an effective rate of 91.25%, presenting better outcomes compared with AR patients in the control group using fluticasone propionate nasal spray alone, indicating that the combination therapy could effectively improve the curative effect of AR [16].

Therefore, the present study aimed to explore whether the combined application of nasal spray using intranasal corticosteroids, nasal irrigation with normal saline and oral medication of Singulair in the treatment of AR is superior to the effect of single application.

Materials and methods

Baseline characteristics

A total of 78 patients with AR admitted to Ganzhou People's Hospital from June 2017 to June 2018 were selected as observation subjects and divided into control group and study group using a table of random digits, with 39 cases in each group. The included patients were diagnosed with AR according to the *Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis* revised in 2015 by the Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery, and the Society of Otorhinolaryngology Head and Neck Surgery of Chinese Medical Association, and their conditions were at the onset stage, and they were at the age of 18-79 years old [17]. The exclusion criteria were: (1) patients with tuberculosis; (2) subjects with nasal polyps or sinusitis and other complications requiring surgery; (3) subjects with asthma; (4) subjects with serious dysfunction in vital organs like heart, liver, kidney, and lung; (5) sujects with malignant tumor or hematological diseases; (6) subjects undergoing desensitization therapy; (7) subjects allergic to the drugs used in this study; (8) subjects who were in prenatal and lactational periods. The study was approved by the Medical Ethics Committee of Ganzhou People's Hospital, and informed consents were obtained from all the patients or their families.

Methods

The control group was treated with Rhinocort Aqua nasal spray (AstraZeneca, Sweden) twice a day and nasal irrigation with normal saline once a day for four weeks. Besides the treatments in the control group, the study group was additionally treated with oral Singulair (DSM, Dutch) at night before sleep, one bag a time. Both groups were continuously treated for 21 days as one course of treatment, with a total of three courses [15].

Outcome measures

Primary outcome measures: Evaluation was carried out according to the *Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis* [17]. The visual analogue scale (VAS) was applied before and after treatment on all the included patients. In this scale, judgements by the patients through feeling on nasal congestion, sneezing, watery nasal discharge, nasal itching, and overall symptoms were collected. VAS=0 was counted as 0 point, VAS=1-5 as 1 point, VAS=6-10 as 2 points, and VAS=10 as 3 points. The efficacy was evaluated by the reduction of integral. The reduction rate of integral=(pre-treatment integral-post-treatment integral)/pre-treatment integral * 100%. The reduction rate of integral ≥66% was re-garded as being markedly effective, the rate of 26%-66% as being effective, and the rate < 26% as being ineffective. The total effective rate = 1 - the rate of inefficacy A total of 5 mL venous blood from each included patient was collected before treatment, and the same amount was taken after treatment for detection of serum inflammatory factors. The tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12) were determined by enzyme-linked immunosorbent assay through microplate reader (HR 801; Shenzhen Highcreation Technology Co., Ltd., Guangdong, China). The determination operation was carried out according to the instructions of the kits (Shanghai Chenyi Biotechnology Co., Ltd., China). For detection of physiological function of nasal cavity, Nasal resistance (NR) before and after treatment was measured by RhinoCeros™ DIFRA rhinomanometer (S.A. Instrumentation DIFRA, Belgium) [18]. As to physiological function of nasal cavity, nasal mucociliary clearance rate (MCR) and nasal mucociliary transport time (MTT) before and after treatment were measured by saccharine clearance test.

Secondary outcome measures: Before and after treatment, lung function indices, forced expiratory volume in one second % (FEV_1%) and maximal mid-expiratory flow % (MMEF%), were measured using the MasterScreen™ Pneumo PC spirometer (Vyaire; German). As to QoL, the included patients were investigated with questionnaires, and their QoL was evaluated with the Allergic Rhinitis-Specific Quality of Life Scale [19], with a total of 40 items for scoring. Each item included four grades, grade 1, 2, 3, and 4, representing 1, 2, 3, and 4 points respectively. The higher the score, the lower the QoL.

Statistical analysis

The data obtained in this study were analyzed using the SPSS software version 19.0. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm sd$). Intra-group comparison of data was performed by paired t-test. Inter-group comparison was performed by independent t-test. The enumeration data was expressed cases/percentage (n/%), on which the χ^2 test or Fisher's exact test was perfomed. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline data

There were no significant differences between the two groups in sex, age, duration of disease, prior treatment history, and severity of disease (all $P>0.05$), presenting comparability. See **Table 1**.

Significant improvement on clinical efficacy

The total effective rate in the study group was 94.87 %, higher than that in the control group (79.49%; $P<0.05$). See **Table 2**.

Significant deduction of serum inflammatory factors

There were no significant differences in levels of TNF-α, IL-6 and IL-12 between the two groups before treatment (all $P>0.05$). After treatment,

Table 1. Comparison of baseline data ($\bar{x}$±sd, n)

		Study group (n=39)	Control group (n=39)	t/χ^2	P
Sex (cases)	Male	22	25	0.482	0.488
	Female	17	14		
Age (years)		39.4±8.7	38.9±9.2	0.233	0.817
Duration of disease (years)		5.1±3.5	5.3±3.4	0.194	0.847
Prior treatment history	Yes	28	25	0.530	0.467
	No	11	14		
Severity of disease	Mild	5	7	0.407	0.816
	Moderate	10	9		
	Severe	24	23		

Table 2. Comparison of clinical efficacy (n, %)

	Marked effectiveness	Effectiveness	Ineffectiveness	Total effective rate
Study group (n=39)	22 (56.41)	15 (38.46)	2 (5.13)	37 (94.87)
Control group (n=39)	18 (46.15)	13 (33.33)	8 (20.51)	31 (79.49)
χ^2				4.129
P				0.042

Table 3. Comparison of levels of serum inflammatory factors ($\bar{x}$±sd, ng/L)

		Study group (n=39)	Control group (n=39)	t	P
TNF-α	Before treatment	3.52±0.71	3.48±0.65	0.260	0.796
	After treatment	1.23±0.18	2.33±0.26	21.723	0.000
IL-6	Before treatment	14.32±2.47	14.69±2.25	0.692	0.491
	After treatment	5.69±0.53	8.71±0.68	21.876	0.000
IL-12	Before treatment	28.59±7.06	27.93±7.11	0.411	0.682
	After treatment	16.48±3.37	20.24±4.35	4.267	0.000

Notes: TNF-α, tumor necrosis factor; IL-6, interleukin-6; IL-12, interleukin-12.

the levels of TNF-α, IL-6 and IL-12 in both groups were significantly reduced, and the study group presented significantly lower levels in those inflammatory factors compared with the levels in the control group (all P<0.05). See **Table 3.**

Significant decrease in lung function indices

No significant differences were shown in FEV_1% and MMEF% between the two groups before treatment (both P>0.05). After treatment, the FEV_1% and MMEF% in both groups were significantly elevated, and the study group showed significantly higher elevation in those lung function indices compared with the indices in the control group (both P<0.05). See **Table 4**.

Significant improvement in physiological function of nasal cavity

There were no significant differences between the two groups in NR, MTT and MCR before treatment (all P>0.05). After treatment, the levels of NR, MTT and MCR in both groups were significantly reduced, and the study group showed a significantly larger reduction in those physiological function indices compared with the indices in the control group (all P<0.05). See **Table 5**.

Improvement in the quality of life of the patients

No significant difference was shown between the two groups in QoL before treatment (P>0.05). After treatment, the QoL scores in both groups were significantly lowered, and the study group presented significantly lower score in QoL compared with the score in the control group (all P<0.05). See **Table 6**.

Discussion

AR characterized by persistent nasal itching, sneezing, rhinorrhea, and nasal congestion is mainly caused by allergic reaction of nasal mucosa, with nasal capillary dilatation and increased gland secretion as the pathological basis for the onset of AR [20]. The nose is closely related to the trachea from the perspective of anatomy and physiology, so AR can cause an increase in bronchial resistance and decrease in pulmonary compliance, thus affecting lung function [21]. Studies have proven that the abnormality of inflammatory factors is closely related to the occurrence of AR. Among the inflammatory factors, IL-6 and IL-12 partici-

Table 4. Comparison of lung function indices

	FEV_1%		MMEF%	
	Before treatment	After treatment	Before treatment	After treatment
Study group (n=39)	61.74±11.65	93.18±7.55	45.72±12.46	80.47±15.32
Control group (n=39)	60.82±10.91	89.26±7.73	46.58±11.85	62.32±14.64
t	0.360	2.266	0.312	5.349
P	0.720	0.026	0.756	0.000

Notes: FEV_1%, forced expiratory volume in one second %; MMEF%, maximal mid-expiratory flow %.

Table 5. Comparison of physiological function of nasal cavity

		Study group (n=39)	Control group (n=39)	t	P
NR (Pa/(cm^3·s))	Before treatment	0.28±0.06	0.27±0.07	0.677	0.500
	After treatment	0.15±0.03	0.20±0.04	6.245	0.000
MTT (min)	Before treatment	21.46±5.21	20.82±5.45	0.530	0.598
	After treatment	13.05±2.67	17.69±3.32	6.801	0.000
MCR (mm/min)	Before treatment	7.82±1.21	7.76±1.19	0.221	0.826
	After treatment	4.17±0.53	5.20±0.68	7.461	0.000

Notes: NR, nasal resistance; MCR, mucociliary clearance rate; MTT, mucociliary transport time.

Table 6. Comparison of quality of life ($\bar{x}$±sd, point)

	Before treatment	After treatment	t	P
Study group (n=39)	86.63±18.72	48.34±7.66	9.334	0.000
Control group (n=39)	85.97±19.26	57.67±8.95	6.621	0.000
t	0.130	4.429		
P	0.897	0.000		

pate in the regulation of the immune response, and TNF-α has the function of mediating leukocyte chemotaxis and activation, so the elevation of levels of the three factors can reflect the aggravation of the body's inflammatory reaction [15, 22]. Local application of intranasal corticosteroids combined with saline nasal irrigation and Singulair can effectively relieve nasal inflammatory reaction and reduce irritation of inflammatory reaction and nasal secretions. Meanwhile, nasal irrigation with normal saline can clean away nasal secretions to avoid deposition, improve local environment of nasal cavity, increase sinus ventilation and mucociliary clearance rate, accelerate repair of inflammatory mucosae, thus improving the physiological function of nasal cavity. Alleviation on the nasal inflammatory reaction of AR can relieve airway hyperresponsiveness, and further reduce bronchial resistance, improve pulmonary compliance, and increase blood oxygen saturation, thus improving lung function.

In this study, the levels of TNF-α, IL-6 and IL-12 in the study group were lower than those in the control group. Meanwhile, the study group presented significantly higher elevation in FEV1% and MMEF%, and larger reduction in NR, MTT and MCR after treatment compared with those indices in the control group, with superiority over the control group in physiological function of nasal cavity and lung function. Rao *et al*. found that symptoms like sneezing, rhinorrhea, nasal obstruction and itching induced by AR were obviously improved three months after combination treatment of glucocorticoid with Flixonase and Singulair among patients with asthma complicated with moderate and severe AR, with total effective rate of 94% [23]. Ye et al. found that the levels of IL-4, IL-6, and IL-8 were significantly reduced with effective improvement on AR symptoms and clinical total effective rate of 100% after combination treatment of the Singulair and leukotriene receptor antagonist in treating patients with AR, similar to the finding in this study [24]. Those findings indicated that Singulair combined with intranasal corticosteroids and saline nasal irrigation presented definite synergistic effect on AR, with reduction in inflammatory factors in patients with AR, improvement in lung function and physiological function of nasal cavity.

The QoL scores in both groups after treatment were significantly decreased, and the study group presented significantly lower score compared with that in the control group, suggesting that the clinical symptoms of the patients were gradually improved with obvious improvement in QoL after medication of Singulair combined with intranasal corticosteroids and saline nasal irrigation, which was basically consistent with the previous studies [25]. The total effective rate of the study group was higher than that of the control group after treatment, suggesting that the treatment of intranasal corticosteroids combined with saline nasal irrigation and Singulair for AR presents obvious improvement, which is basically consistent with the previous study [13].

In this study, combination treatment of intranasal corticosteroids with saline nasal irrigation and Singulair are effective for treating AR. However, there are still some limitations or shortcomings such as short observation period, unclear drug dependence, small sample size, and unclear applicability to pediatric patients. Therefore, the sample size needs to be expanded for further researches.

In conclusion, intranasal corticosteroids combined with saline nasal irrigation and Singulair presented definite efficay on AR, with reduction in inflammatory reaction, improvement in lung function, physiological function of nasal cavity, and QoL, and it is worthy of clinically application and promotion.

Disclosure of conflict of interest

None.

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