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Original Article

Effect of acupuncture at Xinwu acupoint combined with loratadine and fluticasone propionate on symptom alleviation, nasal function, and serum histamine level in patients with allergic rhinitis

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Abstract: Objective: To determine the influence of acupuncture at the Xinwu acupoint combined with western medicine (loratadine and fluticasone propionate) on symptom alleviation, nasal mucociliary clearance velocity (MCV), and serum histamine level of patients with allergic rhinitis (AR). Methods: A total of 122 patients with AR treated in Gansu province hospital of TCM and The Third People's Hospital of Gansu Province from April 2019 to April 2021 were retrospectively analyzed. Among them, 54 patients treated with loratadine and fluticasone propionate were assigned to the control group, and 68 patients treated with additional acupuncture at the Xinwu acupoint based on treatment of the control group were assigned to the observation group. The treatment efficacy of the two groups was compared, and the scores of main symptoms and nasal function were also compared before and after therapy. Additionally, the two groups were compared in the levels of histamine, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and immunoglobulin E (IgE) before and after therapy. Results: After therapy, the observation group yielded a higher total effective rate than the control group (P=0.006) and had lower symptom scores than the control group (P<0.001). Additionally, the MCV of the two groups increased (P<0.001), and the nasal mucociliary transit time (MTT) and nasal resistance (NR) of both groups decreased (P<0.001) after therapy. The observation group showed a greatly better improvement of nasal function than the control group (P<0.001). Moreover, after therapy, the observation group showed lower histamine and IgE levels than the control group (P<0.01) and the observation group presented significantly lower levels than the control group, and had lower rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores than the control group (P<0.001). The two groups were not different in the incidence of adverse reactions (P=0.886). Conclusion: Acupuncture at Xinwu acupoint combined with loratadine and fluticasone propionate can deliver a powerful efficacy on AR and alleviate the clinical symptoms, without increasing adverse reactions.

Keywords: Acupuncture, Xinwu acupoint, loratadine, fluticasone propionate, allergic rhinitis, nasal function, histamine

Introduction

Allergic rhinitis (AR), namely, rhinallergosis, is an IgE-mediated inflammatory disease of nasal mucosa, that is stimulated by allergens acting on atopic individuals [1]. It is a common nasal allergic disease worldwide and the most common disease in otolaryngology [2]. According to statistics, AR patients account for approximately 20%-30% of the global population, with an incidence increasing annually. A prolonged unhealed AR course seriously impairs the lung function of patients, and can induce severe respiratory diseases including asthma and chronic obstructive pulmonary disease, compromising patients' health and quality of life

(QoL) [3]. Moreover, AR can be life-long clinically, and is one of the independent risk factors for asthma [4]. Accordingly, it is of profound importance to take effective therapy measures to alleviate the clinical symptoms of AR and improve the QoL of patients.

The optimization of AR therapeutic regimen has become a global focus [5]. Currently, the clinical therapeutic regimen for AR mainly includes allergen avoidance, drug therapy, specific immunotherapy, surgical treatment, and health education [6]. Drug therapy is the main way for AR clinically, which primarily involves nasal glucocorticoids, oral or nasal antihistamines (H1 receptor antagonists), leukotrienes, etc. Among them, nasal glucocorticoids are the most powerful first-line treatment drugs, but the symptoms of some patients cannot be effectively controlled with only these drugs [7]. According to modern medicine, AR is a polygenic disease that is influenced by both heredity and environment. Among them, the genetic susceptibility of individuals is a crucial cause of AR, and allergens are the primary excitation mechanism [8]. Traditional Chinese medicine (TCM) has a long history in treating AR, with favorable clinical effect, showing obvious advantages in treating this disease for a relatively complete and unique theoretical system [9]. Xinwu acupoint, also known as sphenopalatine acupoint, can effectively help treat various nasal diseases, and its body surface marks are obvious [10]. It is an original acupoint for treating nasal diseases, which was found by Mr. Li Xinwu in the late 1960s, based on his personal clinical experience and the theory of modern Chinese and western medicine [11]. Despite only 40 years of clinical research history, it has captured increasing attention for its good achievements. Prior research by Wang et al. [12] has found that acupuncture at Xinwu acupoint can help improving nasal ventilation by increasing sympathetic nerve excitability of healthy volunteers, suggesting a certain effect of acupuncture at the Xinwu acupoint in treating nasal diseases. However, little research has been conducted on the therapeutic effect of acupuncture at the Xinwu acupoint on AR patients.

This study determined the effects of stimulating the Xinwu acupoint combined with loratadine and fluticasone propionate on symptom alleviation, nasal function, and serum histamine level in patients with AR to provide a novel treatment regimen.

Methods and data

Clinical data of patients

This retrospective analysis was conducted on 443 AR patients treated in Gansu Provincial Hospital of TCM and the Third People's Hospital of Gansu Province from April 2019 to April 2021. Based on the inclusion criteria, we screened a total of 284 patients, and then obtained the clinical data of 122 AR patients according to the exclusion criteria. According to the treatments, the patients were divided into a control group (n=54, treated with loratadine + fluticasone propionate) and an observation group (n=68, treated with loratadine + fluticasone propionate + Xinwu acupoint acupuncture). This study was approved by the Medical Ethics Committee of the Third People's Hospital of Gansu Province.

Inclusion and exclusion criteria

Inclusion criteria: Patients meeting the criteria of *Diagnostic and Therapeutic Guidelines for Allergic Rhinitis* [13]; patients with a course of disease >1 year; patients who had not received anti-inflammatory, antihistamine, or other related treatments in the past month; and patients with detailed clinical data.

Exclusion criteria: Patients comorbid with allergic asthma; patients with comorbid nasal septum deviation, nasal polyps or other nasal lesions; patients comorbid with endocrine disorders or cardiovascular diseases; patients comorbid with liver or kidney dysfunction; or patients who suffered repeated attacks and received treatment with glucocorticoid in the last month.

Sources of drugs and reagents

Loratadine (Shanghai Schering-Plough Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H10970410), fluticasone propionate nasal spray (Glaxo Wellcome, S.A., SFDA approval number: H20140-117), and enzyme-linked immunosorbent assay (ELISA) kits of tumor necrosis factor-α (TNF-α, ml077385), interleukin-6 (IL-6, ml058097), histamine (ml060476) and immunoglobulin E

(IgE, ML060225) from Shanghai MLBIO Co., Ltd.

Therapeutic regimen

Therapeutic regimen for the control group: The control group was orally treated with loratadine tablets (10 mg/time, once a day) plus fluticasone propionate nasal spray (2 sprays (200 μg/d) for each nostril in the morning) [14]. Therapeutic regimen for the observation group: Each patient was treated additionally with acupuncture at the Xinwu acupoint based on the treatment regimen in the control group. Specifically, (1) The position of the Xiaguan acupoint was identified: the lower edge of the zygomatic arch and the posterior edge of mandibular condyle; (2) Needle insertion method: after routine disinfection, the needle insertion position was pressed with the left hand to tighten the skin, and the needle was held with the right hand and inserted with a direction of 15° to the frontal plane, 75° to the sagittal plane, and 15° to the horizontal plane (or to the contralateral frontal angle). When the patient felt inductance or a sense of intranasal radiation, the needle would be withdrawn immediately. The acupuncture was conducted twice a week for 4 consecutive weeks. Both groups were treated for 4 weeks. During the treatment period, any drugs that would affect nasal function and rhinitis treatment were forbidden.

ELISA

The TNF-α and IL-6, histamine and IgE levels were detected using ELISA. Before and after the treatment, the morning fasting venous blood (5 mL) was extracted from each patient, followed by 10-min centrifugation (4°C, 3000 r/min) to separate serum that was saved in the refrigerator at -80°C, and the serum was quantified using corresponding kits under the detection steps listed by kit guidelines.

Data extraction

The clinical data of enrolled patients were collected from the hospital LIS system, including gender, age, course of disease, hypertension history, diabetes history, smoking history, alcoholism history, treatment effect, adverse reactions, nasal function changes, TNF-α, IL-6, histamine, IgE, visual analysis scale (VAS) score, Rhinoconjunctivity Quality of Life Questionnaire (RQLQ) score and Saint George Respiratory Questionnaire (SGRQ) score.

Outcome measures

Primary outcome measures: The efficacy and nasal function, mainly including the changes in nasal mucociliary clearance velocity (MCV), nasal mucociliary transit time (MTT), and nasal resistance (NR), in the two groups were evaluated. The two groups were also compared as to the levels of histamine, TNF-α, IL-6, and IgE before and after therapy.

Secondary outcome measures: The clinical data of the two groups were compared. The visual analogue scale (VAS) [15] was adopted to evaluate the severity of AR in patients. VAS is composed of a line segment that is divided into 10 small squares, with corresponding scores of 0-10 points. The severity of the disease increases from left to right, with 0 for no trouble and 10 for extremely strong trouble. The QoL was evaluated using a RQLQ [16], which involved seven symptoms: activity, sleep, non-nasal/eye symptoms, practical problems, eye symptoms, nasal symptoms, and emotion. Each survey item has 7 options: no trouble (0 point), almost no trouble (1 point), some troubles (2 points), moderate troubles (3 points), strong troubles (4 points), very strong troubles (5 points), and extremely strong troubles (6 points). The SGRQ [17] was adopted to evaluate the patients' QoL, with scores between 0 and 100. A lower score indicates better QoL. The two groups were compared for adverse reactions after therapy.

Evaluation criteria of efficacy

Efficacy index = (total score before therapy - total score after therapy)/total score before therapy × 100%. Cured: an efficacy index ≥90%; Markedly effective: an effective index of 65% (contained)-90%; Effective: an efficacy index of 25% (contained)-65%; Ineffective: an efficacy index <25%. Overall response rate = [(number of cured cases + markedly effective cases + effective cases)/the total number of cases] × 100%.

Statistical analyses

SPSS 19.0 (Asia Analytics, Formerly SPSS China) was used for data analysis, and GraphPad Prism 8 was used for figure rendering. Counted data were described by percentage and analyzed by the Chi-square test. Measured data (mean ± SD) were analyzed by the t test, and their inter-group comparison and intra-

Table 1. Comparison of baseline data

	Control group (n=54)	Observation group (n=68)	χ^2 value	*P* value
Gender			1.575	0.209
Male	24	38		
Female	30	30		
Age			0.155	0.693
≥40 years old	18	25		
<40 years old	36	43		
Course of disease			0.985	0.320
≥6 years	31	45		
<6 years	23	23		
History of hypertension			1.150	0.283
Yes	12	10		
No	42	58		
History of diabetes mellitus			1.939	0.163
Yes	18	15		
No	36	53		
History of smoking			1.575	0.209
Yes	24	38		
No	30	30		
History of alcoholism			0.062	0.802
Yes	8	9		
No	46	59		

group comparison were carried out using the independent-samples T test and paired t test, respectively. P<0.05 implied a significant difference.

Results

Comparison of clinical data

According to inter-group comparison of clinical data, the observation and control groups were similar in clinical data (all P>0.05, **Table 1**).

Clinical efficacy analysis

According to inter-group comparison of clinical efficacy after therapy, the control group showed a significantly lower total effective rate than the observation group (P=0.006, **Table 2**).

Nasal function analysis

The MCV, MTT, and NR were compared between the two groups before and after therapy. Before the therapy, the two groups showed no obvious difference in MCV, MTT or NR (all P>0.05). After the therapy, MCV in both groups increased greatly, while MTT and NR decreased greatly (all P<0.001, **Figure 1**). Furthermore, the observation group showed a greatly higher MCV level but lower MTT and NR levels than the control group after the therapy (all P<0.001, **Figure 1**).

Comparison of inflammatory indexes

The two groups were compared in TNF-α and IL-6 before and after the therapy. Before the therapy, the two groups showed no obvious difference in TNF-α and IL-6 levels (both P>0.05). After the therapy, TNF-α and IL-6 levels in both groups decreased (both P<0.001), with greatly lower levels in the observation group than in the control group (both P<0.001, **Figure 2**).

Comparison of immune indexes

The two groups were compared in histamine and IgE levels before and after therapy. Before the therapy, the two groups showed no difference in histamine and IgE levels (both P>0.05). After the therapy, the histamine and IgE levels in both groups decreased (both P<0.001), with lower levels in the observation group than those in the control group (both P<0.01, **Figure 3**).

Comparison of function scores

According to comparison of the two groups in VAS, RQLQ and SGRQ scores before and after therapy, there was no difference in VAS, RQLQ and SGRQ scores between the two groups before the therapy (all P>0.05), and after the therapy, VAS, RQLQ and SGRQ of the two groups decreased (all P<0.001, **Figures 4** and **5**), with lower scores in the observation group than in the control group (all P<0.05, **Figures 4** and **5**).

Comparison of adverse reactions

According to inter-group comparison of adverse reactions, the incidence of adverse reactions of the two groups was comparable (P=0.886, **Table 3**).

Table 2. Evaluation of clinical efficacy

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=54)	12 (22.22%)	25 (46.29%)	6 (11.11%)	11 (20.38%)	43 (79.62%)
Observation group (n=68)	18 (26.47%)	32 (47.05%)	15 (22.05%)	3 (4.43%)	65 (95.57%)
χ^2 value		9.000			7.546
P value		0.029			0.006

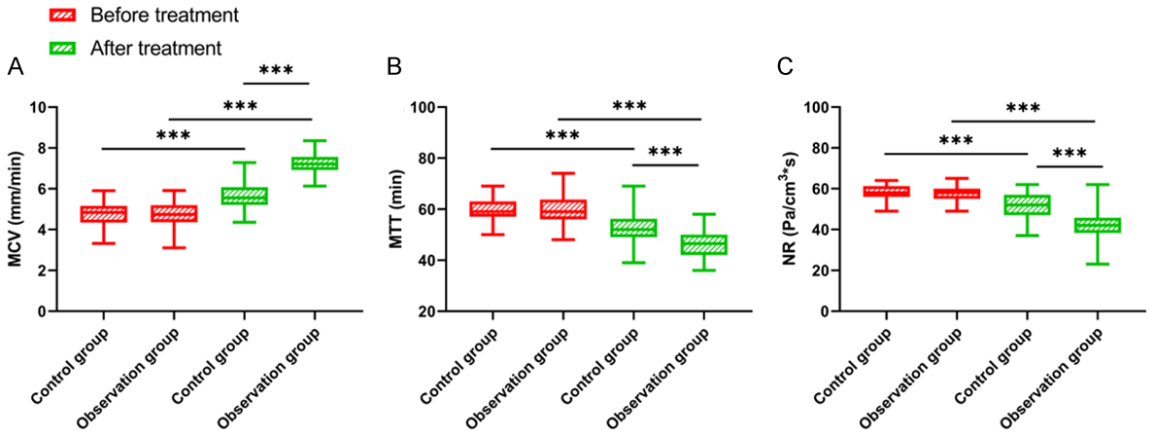

Figure 1. Changes in nasal function in patients before and after therapy. A: Changes of MCV in patients before and after therapy; B: Changes of MTT in patients before and after therapy; C: Changes of NR in patients before and after therapy. Note: ***P<0.001. MCV: Mucociliary clearance velocity; MTT: Nasal mucociliary transit time; NR: nasal resistance.

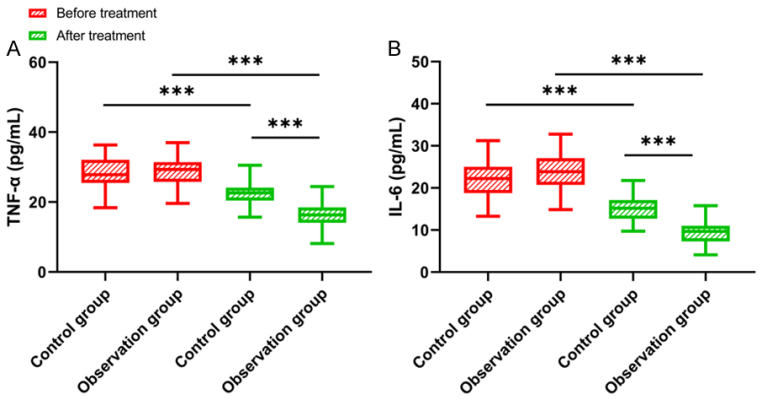

Figure 2. Changes in inflammatory indexes in patients before and after therapy. A: Changes of TNF-α in patients before and after therapy; B: Changes of IL-6 in patients before and after therapy. Note: ***P<0.001. TNF-α: Tumor necrosis factor; IL-6: Interleukin-6.

Discussion

Allergic rhinitis (AR), as a chronic disease with high incidence, long course, and high recurrence rate, has become a global health problem [18, 19]. How to effectively control AR and improve QoL of patients is an urgent problem [20, 21]. Th0 cells induced by specific allergens differentiate into Th2 lymphocytes and release various interleukin and colony stimulating factors that promote the conversion of B lymphocytes into IgE plasma cells, which then bind to specific antibodies on the surface of mast cells and basophils, resulting in AR [22]. Accordingly, clinical therapy for AR mainly consists of allergen avoidance, drug treatment, immunotherapy, publicity and education.

Local application of corticosteroids combined with short-term oral antihistamines is a common clinical treatment regimen for AR [23]. Fluticasone propionate nasal spray is a second generation nasal glucocorticoid, with strong local anti-inflammatory and anti-allergic effects, which has marked efficacy on AR, low toxic and side effects and high safety for long-term treatment, but it cannot act on systemic inflammatory processes [24]. With high selectivity to peripheral H1 receptors and weak affinity to central H1 receptors, lorata-

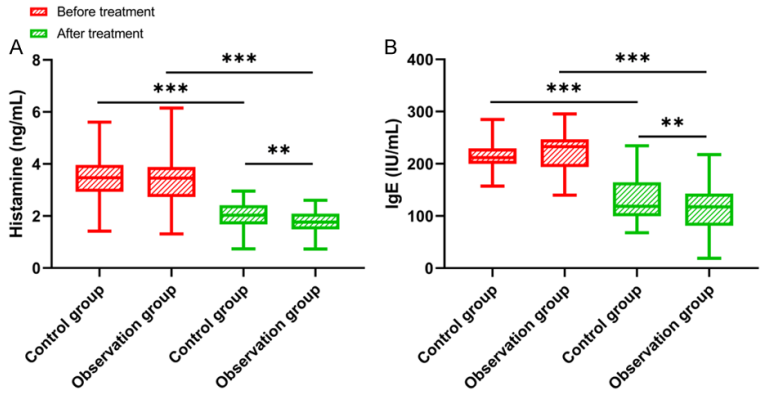

Figure 3. Changes in immune indexes in patients before and after therapy. A. Changes of histamine in patients before and after therapy. B. Changes of IgE in patients before and after therapy. Note: **P<0.01, ***P<0.001. IgE: Immunoglobulin E.

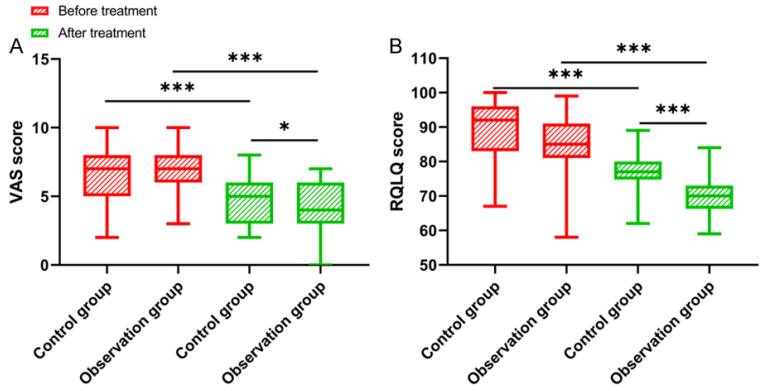

Figure 4. Changes in patients' VAS and RQLQ scores before and after therapy. A. Changes of patients' VAS scores before and after therapy; B. Changes of patients' RQLQ scores before and after therapy. Note: *P<0.05, ***P<0.001. VAS: Visual analogue scale. RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire.

dine, as a third generation long-acting antihistamine, can inhibit mast cells from releasing leukotrienes and histamine, and can also inhibit immune response and reduce airway hyperresponsiveness [25]. Reportedly, fluticasone propionate nasal spray combined with loratadine tablets can deliver better efficacy on AR than fluticasone propionate nasal spray or loratadine tablets alone, and can contribute to low recurrence rate with few adverse reactions [26]. Acupuncture is one of the complementary and alternative medical treatments advocated by the World Health Organization, which comes from traditional Chinese Medicine (TCM) [27]. In this study, the observation group presented a higher total effective rate than the control group, and showed more improved nasal function and QoL. The results suggest acupuncture at the Xinwu acupoint can improve the efficacy in patients with AR and improve their nasal function and QoL. In the research by Fu et al. [28], acupuncture on sphenopalatine ganglion acupoint alone has demonstrated potential effect in relieving nasal symptoms, improving patients' QoL and treating AR, which verifies our research results. Anatomically, the sphenopalatine ganglion originates from the maxillary branch of trigeminal nerve and the sympathetic and parasympathetic branches of pterygoid nerve, and its postganglionic nerve fibers dominate the glands and blood vessels in the nose, pharynx, palate, and orbit [29]. Stimulation of the Xinwu acupoint by acupuncture can regulate and control the central nervous system and restore the dynamic balance of sympathetic nerve and parasympathetic nerve, thus alleviating the clinical symptoms of AR [30].

Research shows that AR belongs to type I allergic diseases. The primary reason for AR is the invasion of allergens into the body, binding to IgE, releasesing inflammatory mediators and related cytokines, promoting mast cell degranulation, etc. Additionally, it is due to the disruption of the Th1/Th2 balance, which causes increased pro-inflammatory factors and decreased anti-inflammatory factors, and an abnormal immune response [31, 32]. This will give rise to an increase in the levels of IgE and inflammatory factors in patients. The production of IL-6, an important inflammatory factor, mainly depends on macrophages and T lymphocytes, etc. IL-6 plays a crucial role in information transmission, immunomodulation, activation, proliferation and differentiation of T cells and B cells, and inflammatory reaction [33]. TNF-α is a systemic inflammatory cytokine secreted by macrophages,

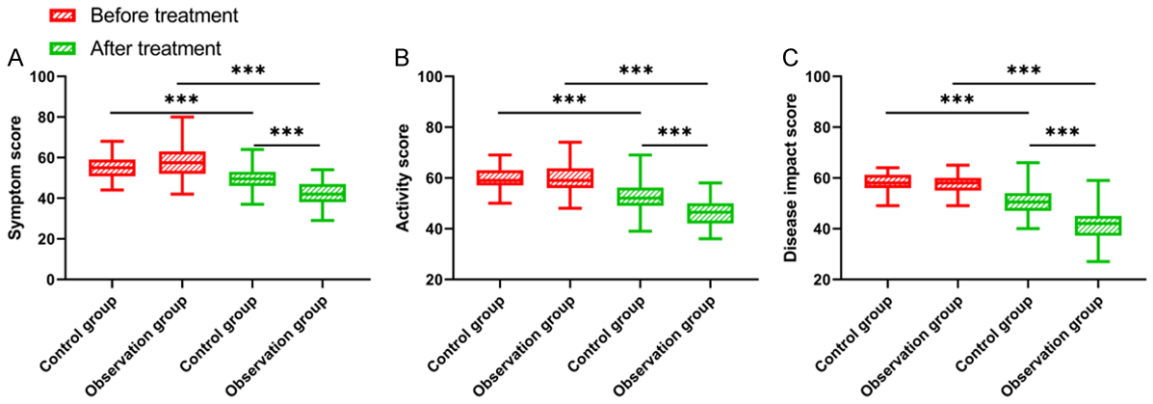

Figure 5. Changes of SGRQ score before and after treatment. A. Changes of symptom score before and after treatment. B. Changes of activity score before and after treatment. C. Changes of disease influence score before and after treatment. Note: *P<0.05, **P<0.001. SGRQ: Saint George Respiratory Questionnaire.

Table 3. Comparison of adverse reactions

Group	Chest distress	Facial flushing	Nausea and vomiting	Rash	Fever	Total response rate
Control group (n=54)	2 (3.70%)	1 (1.85%)	2 (3.70%)	1 (1.85%)	3 (5.55%)	9 (16.65%)
Observation group (n=68)	3 (4.41%)	2 (2.94%)	1 (1.47%)	3 (4.41%)	3 (4.41%)	12 (17.64%)
χ^2 value	0.038	0.148	0.625	0.622	0.084	0.020
P value	0.844	0.699	0.428	0.430	0.771	0.886

which is closely bound up with the proliferation and maturation of B lymphocytes. When AR patients are exposed to related allergens again, the body will produce a large number of effector B lymphocytes, which will participate in humoral immunity and inflammatory reaction [34]. Histamine is abundant in mast cells of skin, lung, and intestinal mucosa, and will be released when tissues are damaged or inflammation and allergic reactions occur [35]. In addition, histamine is also implicated in the regulation of sleep, appetite and memory. Lowering the histamine level can effectively alleviate itching, sneezing and runny nose, as well as improve children's sleep quality and appetite, and promote the recovery of immune function and growth and metabolism in children. In this study, after treatment, the observation group showed lower levels of TNF-α, IL-6, histamine, and IgE than the control group. This is primarily because the stimulation of sphenopalatine nerve causes the reduction of vasoactive intestinal peptide release and improvement of immunity, and thus inhibits allergic reaction [36]. Lastly, we counted the adverse reactions of patients and found no difference in the incidence of adverse reactions between the two groups, indicating that acupuncture at Xinwu acupoint didn't increase adverse reactions.

This study has verified, through retrospective analysis, that acupuncture at Xinwu acupoint can alleviate the symptoms of patients with AR, effectively improve their nasal function, and lower their serum levels of inflammation and immune factors. However, this study has some limitations. First, in this study, the patients had not been followed up for a long time, so the AR recurrence still requires investigation. Secondly, in such a single-center study, with a small sample size, the results of the retrospective study may be biased. Finally, the relevant mechanism of acupuncture at Xinwu acupoint in treating AR is still unclear. We hope to carry out more research in the future to solidify the conclusion.

To sum up, acupuncture at Xinwu acupoint combined with loratadine and fluticasone propionate can deliver a powerful efficacy on AR and alleviate clinical symptoms, without increasing adverse reactions.

Disclosure of conflict of interest

None.

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