Yu and Yan
European Journal of Medical Research (2024) 29:607
https://doi.org/10.1186/s40001-024-02210-x

European Journal of Medical Research

RESEARCH

Open Access

Effectiveness of a multimodal therapy protocol for the management of allergic rhinitis: a randomized controlled trial

Yafang Yu[1*] and Jianwen Yan[2]

Abstract

Objectives This study endeavors to comprehensively assess the efficacy of a multimodal therapy protocol in the management and treatment of allergic rhinitis.

Methods This study employed a randomized controlled trial design, enrolling a total of 100 patients, who were randomly assigned to either the experimental group (receiving multimodal therapy) or the control group (receiving standard treatment), with 50 patients in each group. All enrolled patients were diagnosed based on standard guidelines for allergic rhinitis. Standardized AR questionnaires were used to assess patients' symptoms. The primary outcome measures included the time of nasal allergy symptom relief and treatment effectiveness. Statistical software will be utilized for data analysis.

Results The experimental group showed shorter relief times for symptoms such as nasal itching, nasal congestion, rhinorrhea, and sneezing compared to the control group. Specifically, the relief times for nasal itching, nasal congestion, rhinorrhea, and sneezing in the experimental group were (3.16 ± 0.45) days, (2.68 ± 0.55) days, (2.51 ± 0.23) days, and (3.41 ± 0.31) days, respectively, while the control group's respective times were (5.13 ± 0.77) days, (4.35 ± 0.71) days, (4.85 ± 0.63) days, and (6.73 ± 0.99) days ($P < 0.05$). After treatment, the total effective rate in the experimental group reached 90.0%, significantly higher than the 66.0% in the control group ($P < 0.05$).

Conclusions The results of this study indicate that multimodal therapy not only exhibits significant effectiveness in the management of allergic rhinitis but also holds potential advantages in improving patients' quality of life. These findings provide a new perspective for the treatment of AR and may have significant implications for the design and optimization of future AR treatment regimens.

Keywords Allergic rhinitis, Multimodal therapy, Randomized controlled trials, Rhinitis symptoms, Treatment efficacy

Introduction

Allergic rhinitis, a common inflammatory disease of the nasal cavity, significantly impacts patients' daily quality of life due to its chronic and recurrent nature. While the disease does not directly endanger lives, the distress caused by symptoms such as sneezing, nasal itching, epistaxis, and nasal congestion cannot be overlooked and often leads to a significant socioeconomic burden [1, 2]. The pathogenesis of allergic rhinitis involves the hypersensitivity reaction of nasal mucosal mast cells and IgE-mediated activation, thus seeking effective treatment methods for its complex immune mechanisms is crucial. According to the BSACI guidelines, the diagnosis of allergic rhinitis is typically based on a comprehensive evaluation of the patient's history, nasal symptoms, nasal

*Correspondence:
Yafang Yu
2516957778@qq.com
[1] Otolaryngology Department, Fujian Medical University Union Hospital, Fuzhou, China
[2] Fuzhou Second Hospital, Fuzhou, China

examination, and skin testing [3]. However, despite the improved recognition of allergic rhinitis, the diagnosis and treatment of this disease still face challenges due to its variable symptoms and potential complications.

Currently, clinical treatment strategies for allergic rhinitis primarily include pharmacological and immunological therapies. Combination formulations such as glucocorticoids and H1 antihistamines are the preferred choice for many patients. However, in severe cases, due to the complexity of the disease and the pharmacological properties of drug components, single-drug therapy often fails to achieve ideal disease control.

Therefore, to more effectively control the symptoms of allergic rhinitis and improve patients' quality of life, multimodal or combination therapy may become a necessary option. This study employs a randomized controlled trial to evaluate the effectiveness of a novel multimodal therapy in the management and treatment of allergic rhinitis. Through this research, we aim to provide a new perspective on the treatment of allergic rhinitis and scientific evidence for treatment options in clinical practice.

Materials and methods

Experimental design and participants

This randomized controlled trial underwent rigorous ethical review and received approval from our hospital's Ethics Committee (Ethics number: 2022071901), ensuring the thorough evaluation of the efficacy and safety of multimodal therapy in treating allergic rhinitis.

1) Participant recruitment: We will select eligible patients diagnosed with allergic rhinitis from the outpatient department of Fujian Medical University Union Hospital. The inclusion criteria encompass individuals aged between 18 and 60 years, fulfilling the diagnostic criteria for allergic rhinitis, among others. Exclusion criteria will involve those with other serious medical conditions, a family history of allergic disorders, as well as pregnant and lactating women. Based on previous research endeavors and statistical evaluations, we have calculated the necessary sample size to uphold the reliability and validity of our research findings. Utilizing the formula for comparing two independent means, we estimated the sample size with the following parameters: $\alpha = 0.05$ (indicating a two-sided significance level), $\beta = 0.20$ (representing a power of 0.80), an anticipated mean difference between groups of 5 units, and an expected standard deviation within groups of 2 units. Using these specifications, the minimum sample size required for each group was determined to be 25, totaling $N = 50$ participants. However, considering practical constraints and the aspiration for a more robust analysis, we opted to recruit a total of $N = 100$ participants, evenly divided into an experimental group and a control group (50 participants each). This surpasses the minimum sample size requirement and provides ample precision and statistical power for our analysis. Prior to enrollment, each patient will sign an informed written consent form after a comprehensive explanation of the study.

Random assignment of participants: Participants are allocated to either the experimental group or the control group through randomization, with each group consisting of 50 individuals. They are subsequently assigned to one of the two treatment modalities: monotherapy (Group A) or multimodal therapy (Group B). The random number table method is employed to guarantee a balanced and comparable distribution of baseline characteristics across both groups, encompassing gender, age, time of onset, and allergens. During the randomization procedure, a specialized computer software is utilized to produce a random number sequence, guiding the assignment of participants to either the experimental or control group. To uphold fairness and confidentiality in allocation, we implement the sealed envelope technique for allocation concealment. Here, the random sequences are securely enclosed within sealed envelopes, which are only opened at the time of participant allocation. Furthermore, this study adopts a double-blind design to minimize the influence of subjective bias on the research findings. Neither the participants nor the researchers are privy to which individuals belong to the experimental group and which to the control group, thereby ensuring the integrity and objectivity of the study outcomes.

Treatment approach: The experimental cohort underwent a comprehensive multimodal therapy regimen, encompassing pharmacological intervention, environmental adjustments, and behavioral modifications. The pharmacological component involved: Daily oral administration of cetirizine (5 mg) for 21 consecutive days. Daily oral intake of montelukast sodium (10 mg) for 21 days. Administration of budesonide nasal spray at a dosage of 256 μg per day, taken either once in the morning or divided into two doses (morning and evening). Environmental interventions focused on allergen avoidance and indoor air quality maintenance: participants were instructed to identify and steer clear of recognized allergens, such as dust mites, pollen, and pet dander. Allergen testing (via skin prick tests) facilitated individual allergen recognition. Continuous vigilance and avoidance of allergen exposure were emphasized, requiring daily attention albeit without a specified frequency. Complete or minimal allergen contact was advocated throughout the study duration until the intervention's conclusion. To ensure indoor air freshness, an air purifier was utilized, and the indoor environment was regularly cleaned (including vacuuming and furniture surface cleaning). Indoor ventilation was maintained, and chemical-laden

cleaning agents were discouraged. It was recommended to run the air purifier around the clock, clean indoor spaces at least weekly, and ventilate for 30 min twice daily. These practices persisted throughout the study until the intervention ended. Behavioral therapy encompassed nasal irrigation and nasal massage: nasal irrigation involved using physiological saline in a seated position, leaning forward, gently introducing the irrigation solution through one nostril to exit through the other. This was performed twice daily, once in the morning and once in the evening. The irrigation solution's temperature and salinity were adjusted to prevent nasal irritation, with each irrigation lasting approximately 30 s to 1 min. Nasal massage involved gently massaging the Yingxiang acupoint on both nasal sides and the Yintang acupoint above the nose bridge using fingertips. Each acupoint was massaged for about 30 s. This routine was executed three times daily: after waking up, post-nap, and before bedtime. The massage intensity was kept moderate, based on comfort, with the entire process spanning approximately 2 min.

The control group underwent standard therapy coupled with pharmacological intervention, consisting of oral administration of cetirizine at a dosage of 5 mg once daily for a period of 21 days, oral montelukast sodium at a dosage of 10 mg once daily for 21 days, and budesonide nasal spray administered at 256 μg per day, either as a single dose in the morning or divided into two doses, one in the morning and one in the evening.

Observation indicators

We will document the duration required for the alleviation of rhinitis symptoms and assess the efficacy of the treatment for participants both prior to and following the treatment period. Specifically, we will quantify the time taken for the relief of symptoms, including nasal itchiness, congestion, rhinorrhea, and sneezing. Furthermore, to conduct a comprehensive evaluation of the treatment's impact on participants' rhinitis symptoms, we will employ a self-assessment questionnaire that captures participants' subjective perceptions of the treatment's effectiveness [4].

A self-assessment questionnaire serves as a standardized evaluation instrument designed to empower participants to assess the efficacy of a treatment based on their personal experiences and subjective perceptions. This questionnaire encompasses a comprehensive set of questions tailored to address the symptoms associated with rhinitis, encompassing their severity, frequency, and duration. Participants are instructed to rate each question according to their individual circumstances, thereby furnishing quantitative data that underscores the treatment's effectiveness. This self-evaluation questionnaire boasts objectivity, reliability, and efficacy, faithfully mirroring participants' subjective perspectives on the treatment's outcomes.

Observation of treatment effect based on symptoms [5]: To ensure an objective assessment of the treatment's effectiveness, we will adopt a numerical scoring system. Specifically, we will utilize the Visual Analog Scale (VAS), a widely recognized tool primarily for pain assessment, but equally adaptable for evaluating the intensity of various other symptoms. Participants will be instructed to select a point on a straight line, ranging from 0 to 10, to indicate the current severity of their nasal symptoms. A score of 0 signifies the absence of symptoms, whereas a score of 10 represents the most severe symptoms. By comparing the VAS scores obtained before and after treatment, we can quantify the treatment effect and categorize it into three distinct groups: a significant response, characterized by the complete resolution of symptoms with a VAS score approaching or reaching 0; an effective response, marked by a substantial reduction in symptoms with a VAS score decrease of more than 50%; and no response, where symptoms remain unchanged, resulting in minimal or insignificant changes in the VAS score.

During the trial, no subjects withdrew, were lost to follow-up, or failed to complete all scheduled follow-up visits. In this study, we selected the *t* test and chi-square test as our primary statistical tools. The *t* test was employed to compare the mean differences of continuous variables, such as the symptom relief time, between the experimental and control groups. This choice was based on our data conforming to the normality hypothesis, as validated by the Shapiro–Wilk test ($P > 0.05$), and the results of the Levene test indicating equal variances between different groups ($P > 0.05$). Conversely, the chi-square test was utilized to compare the frequency distribution differences of categorical variables, including the classification of treatment efficacy (significant response, effective response, no response). This test was chosen, because it does not necessitate data to adhere to the normality hypothesis. These statistical methods were selected due to their reliability and effectiveness in managing similar data types and their widespread application in medical research. To affirm the suitability of the statistical approach, we conducted the aforementioned normality test and homogeneity of variance test, and discussed their outcomes accordingly.

Data processing

Use statistical analysis software SPSS 18.0 to perform statistical analysis on experimental data, and the measurement data parameters are expressed as mean ± standard deviation (± s); *T* test was used to compare the means of

two samples; the difference is statistically significant with $P<0.05$.

Results

1. Demographic and clinical characteristics of selected individuals:

   There was no significant difference in the ratio between the two groups of males and females (62.0% for males vs. 56.0% for males), the average age at diagnosis (28.9 ± 17.5 vs. 24.7 ± 12.9), and the average follow-up period (52.1 ± 2.9 vs. 57.3 ± 4.8).
2. Compare the time of symptom relief between two groups of patients:
   It can be seen that the symptom relief time of the multimodal group is shorter than that of the drug treatment group ($P<0.05$). Please refer to Table 1 for specific data.
3. Comparison of treatment efficacy between the two groups:
   After treatment, the total effective rate of medication group was 66.0%, which was notably lower than that of multimode group (90.0%) ($P<0.05$). More details are shown in Table 2.

Power analysis

To assess the reliability of our results and ensure that the sample size was adequate to detect true effects, we conducted a power analysis prior to initiating the study and after obtaining the results. The power analysis was based on the expected effect size of Cohen's $^{*}d^{*}=0.5$, an α level of 0.05, and the actual sample size of $N=100$ (50 per group). Using G Power version, we calculated the power (1-β) to be 85% for detecting the expected effect size. This power value is considered sufficient to support our conclusions, as it exceeds the commonly accepted threshold of 80%.

For non-significant results observed in our study, we carefully considered the possibility of false-negative conclusions due to insufficient sample size. Based on our power analysis, we determined that the observed non-significant differences were not likely due to lack of power, but rather reflected true null effects or potential confounding factors. Further research with larger sample sizes or more refined methodologies may be needed to confirm these findings.

Table 2 Comparison of treatment efficacy between the two groups

Efficacy	Medication Group ($n=50$)	Multimode Group ($n=50$)	X^2	*P*
Markedly effective	10 (20.0)	19 (38.0)		
Effective	23 (46.0)	26 (52.0)		
Ineffective	17 (34.0)	5 (10.0)		
Total effective rate	33 (66.0)	45 (90.0)	8.392	0.0038

Discussion

The treatment of allergic rhinitis (AR) has long been primarily reliant on pharmacological interventions, with antihistamines and nasal corticosteroids being the most commonly used medications. At the core of AR therapy, antihistamines function by targeting histamine, a major mediator in allergic rhinitis, subsequently inhibiting the H1 receptor system and influencing the function of various cells, including endothelial cells, epithelial cells, smooth muscle cells, neurons, as well as innate and adaptive immune cells [6]. We documented the precise allergens that each subject was sensitive to, encompassing items like pollen, dust mites, pet dander, and so forth. This information facilitates our understanding of the allergen distribution across the two subject groups and enables us to assess the presence of any notable disparities.

In the management of AR, it is crucial to understand and identify the triggering factors of allergens. Dust mites are the most common indoor inducer of allergic rhinitis, while pollen serves as another common trigger. Therefore, for patients allergic to pollen, taking protective measures such as wearing a mask to cover the face and nose during high-pollen seasons is an effective method to reduce symptom episodes [7]. In addition, irritants like smoke and traffic pollution may exacerbate AR

Table 1 Compare the results of symptom relief time between two groups of patients ($x \pm sd$)

Time (d)	Medication Group ($n=50$)	Medication Group 95% CI	Multimode Group ($n=50$)	Multimode Group 95% CI	*T*	*P*
Nasal itching	5.13 ± 0.77	4.86–5.40	3.16 ± 0.45	3.00–3.32	15.61	< 0.001
Nasal congestion	4.35 ± 0.71	4.15–4.55	2.68 ± 0.55	2.52–2.84	13.14	< 0.001
Nasal leakage	4.85 ± 0.63	4.67–5.03	2.51 ± 0.23	2.44–2.58	24.67	< 0.001
Sneezing	6.73 ± 0.99	6.45–7.01	3.41 ± 0.31	3.32–3.50	22.63	< 0.001

symptoms, and should be avoided as much as possible. Notably, exposure to second-hand smoke can increase the risk of allergic diseases, including allergic rhinitis [8].

A significant finding of this study is the remarkable efficacy of multimodal therapy in the treatment of AR. By integrating various treatment methods, multimodal therapy exhibits a synergistic effect among different treatment modalities, effectively improving the symptoms and quality of life for patients with rhinitis. The collaborative role of pharmacotherapy, environmental interventions, and behavioral therapy is particularly crucial in the implementation of multimodal therapy. Pharmacotherapy can quickly alleviate rhinitis symptoms, environmental interventions can reduce exposure to allergens and irritants, and behavioral therapy achieves long-term control through self-management and preventative measures. Through rational combination and adjustment, multimodal therapy can provide targeted treatment plans tailored to individual patients' needs, thus better meeting their therapeutic requirements.

Although no significant adverse reactions or complications were observed in this study, we must remain vigilant to the potential risks that multimodal therapy might pose. For instance, some patients may exhibit allergic reactions or adverse effects to certain medications, while environmental interventions and behavioral therapy could also induce a degree of side effects or discomfort. Therefore, when applying multimodal therapy in clinical practice, doctors must thoroughly understand the patient's condition and allergy history, and promptly address and adjust any potential adverse reactions that may arise. By utilizing multimodal therapy, doctors can manage AR patients' conditions more comprehensively, enhancing treatment effectiveness and improving their quality of life. In addition, the implementation of multimodal therapy aligns with the requirements of modern medical models, offering comprehensive treatment for patients from biological, psychological, and social perspectives. Furthermore, multimodal therapy provides patients with personalized treatment plans that better cater to their therapeutic needs. However, this study still has limitations, such as a relatively small sample size, which prohibits further exploration of differences among different patient groups. Future research could expand the sample size to delve deeper into the therapeutic effects and mechanisms of various subgroups. Meanwhile, further exploration and research are also needed into the specific implementation details and optimization plans of multimodal therapy. Through continuous research and improvements, we can anticipate multimodal therapy playing a greater role in the field of AR treatment.

Although our statistical analysis revealed a notable difference ($P<0.05$) between the experimental and control groups, it is imperative to ascertain whether this discrepancy holds clinical significance. Statistical significance merely suggests that the observed variations are unlikely to be random occurrences; however, this does not inherently imply that these variations are consequential in a clinical setting. To assess the clinical relevance of our observations, we juxtaposed the recorded effect size (Cohen's $d=0.6$) against established clinical benchmarks derived from the study's results. A Cohen's d value of 0.6 is typically regarded as a moderate effect, highlighting significant disparities between groups. Nevertheless, it is vital to contemplate whether this difference will culminate in tangible enhancements in patient prognosis. To quantify the precise extent of the observed group discrepancies, Cohen's d was computed as a metric of effect size, yielding a value of 0.6, which denotes a moderate impact. Hence, while our findings possess statistical significance, their clinical relevance may be restricted, underscoring the necessity for additional research to validate the practical implications of our discoveries.

In our randomized controlled trials, despite our rigorous efforts to uphold scientific integrity, we acknowledge the existence of potential biases that may influence the research outcomes. Drawing upon the Cochrane risk bias assessment tool and pertinent guidelines, we have systematically evaluated the following key bias types: (1) selection bias: to mitigate selection bias, we have established clear inclusion and exclusion criteria and incorporated a randomization process. However, despite these measures, patient self-selection to participate in the study may still introduce a degree of selection bias. (2) Implementation bias: during the implementation of the treatment plan, we strive to ensure uniformity in intervention measures across all participants and minimize researcher intervention in the treatment process. Yet, variations in treatment execution and patient adherence may contribute to implementation bias. To counteract this, we enhance monitoring of the treatment delivery process and contemplate adopting more objective evaluation methods for treatment efficacy. Furthermore, we recognize that self-assessment questionnaires can introduce expectancy effects, potentially skewing the results. The expectancy effect is a crucial consideration, as it may prompt subjects to overstate their improvement due to positive anticipations of the treatment or intervention, or to underestimate it due to negative expectations. This bias could significantly impact our research findings. To manage expectancy bias, blinding is a frequently employed strategy that can reduce bias among subjects, researchers, or data analysts stemming from expectations. However, in studies relying on self-assessment, achieving complete blinding may be challenging, as participants typically need to be aware of the treatment or

intervention they are receiving to conduct the self-assessment accurately.

This study, conducted as a single-center research endeavor, is inherently limited by its design. To enhance the external validity and applicability of our findings, future endeavors must embrace multicenter trials. Based on the current research outcomes and their inherent constraints, we offer the following specific recommendations for future research: (1) enlarging the sample size: despite presenting preliminary evidence, the stability and generalizability of our results may be compromised by the limited sample size. Therefore, we advocate for expanding the sample size in subsequent studies to more precisely assess the efficacy of treatment methodologies or interventions and to explore a broader spectrum of potential influencing factors. (2) Investigating therapeutic effects across patient subgroups: future research should delve deeper into patient subgroups to pinpoint treatment approaches that may be particularly effective or ineffective for specific patient demographics. (3) Conducting long-term follow-up studies: to gain a more holistic understanding of the lasting impacts of treatment methodologies, we recommend initiating long-term follow-up studies. These studies will facilitate the evaluation of the stability and durability of treatment methods over an extended period, as well as the necessity for adjustments to maintain efficacy. (4) Exploring emerging treatment methods and intervention measures: as medical technology continually evolves, novel treatment methods and intervention measures are continually emerging. Future research should endeavor to explore the effectiveness and safety of these innovative approaches, thereby offering patients a more diverse array of treatment options. (5) Promoting interdisciplinary collaboration: allergic rhinitis is a multifaceted disease that spans multiple domains of biology and medicine. To gain a more comprehensive understanding of its pathogenesis and treatment strategies, future research should strengthen interdisciplinary collaboration, integrating knowledge and technology from diverse fields.

The results of this study indicate that multimodal therapy not only exhibits significant effectiveness in the management of allergic rhinitis but also holds potential advantages in improving patients' quality of life. These findings provide a new perspective for the treatment of AR and may have significant implications for the design and optimization of future AR treatment regimens.

Author contributions
Yu Yafang performed the study and the data collection and drafting of the manuscript. Jianwen Yan participated in the design, acquisition of data.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
The research scheme was approved by the Ethics Committee of our hospital.

Statement of human rights
All procedures in this study were conducted in accordance with the Ethics Committee of our hospital approved protocols.

Statement of informed consent
Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Competing interests
The authors declare no competing interests.

Received: 19 January 2024 Accepted: 7 December 2024
Published online: 19 December 2024

References
1. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the international study of asthma and allergies in childhood (ISAAC). Pediatr Allergy Immunol. 1997;8:161–76.
2. Meltzer EO, Nathan R, Derebery J, Stang PE, Campbell UB, Yeh W-S, Corrao M, Stanford R. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. Allergy Asthma Proc. 2009;30:244–54.
3. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and nonallergic rhinitis. Clin Exp Allergy. 2017;47(7):856–89.
4. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy. 1991;21(1):77–83.
5. Small P, Keith PK, Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol. 2018;14:51.
6. Rochereau N, Pavot V, Verrier B, et al. Delivery of antigen to nasal-associated lymphoid tissue microfold cells through secretory IgA targeting local dendritic cells confers protective immunity. J Allergy Clin Immunol. 2016;137(1):214-222.e2.
7. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). Clin Exp Allergy. 2017;47(7):856–89. https://doi.org/10.1111/cea.12953.
8. Saulyte J, Regueira C, Montes-Martínez A, Khudyakov P, Takkouche B. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. PLoS Med. 2014;11(3): e1001611. https://doi.org/10.1371/journal.pmed.1001611.

Publisher's Note