

Effectiveness of Moxibustion Combined with Conventional Treatment for Moderate-Severe Persistent Allergic Rhinitis: Protocol for a Randomized, Controlled Trial

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Abstract

Introduction: The incidence of allergic rhinitis (AR) has risen dramatically in recent years, and presents with higher symptom frequency, affecting quality of life. Clinical research shows that conventional medical treatment can rapidly relieve AR symptoms; however, there is a high incidence of relapse. Moxibustion treatment reportedly has a good effect in reducing the relapse rate. However, trial-based evidence for the effectiveness of these combined treatments is necessary.

Methods and analysis: This is a protocol for a randomized, controlled trial comparing the effects of combined moxibustion and conventional treatment with conventional treatment alone for patients with moderate-severe persistent AR. After intervention, both groups will be followed-up for 3 months. The primary outcome is frequency of AR symptoms, which will be obtained via a self-recorded AR diary. The secondary outcomes include the Rhinoconjunctivitis Quality of Life Questionnaire score and use of daily medication.

Ethics and dissemination: Ethical approval for the study has been granted by the Institutional Review Board of Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine (ECPJ-BDY-2016-16). Written informed consent will be obtained from all participants. The study findings will be published in open access peer-reviewed journals.

Strengths and limitations of this study

- The trial is designed to address the gap in evidence regarding the effects of combined moxibustion and conventional treatment for patients with moderate-severe persistent AR.
- Experiences with moxibustion treatment in reducing the relapse rate of AR patients will be examined.
- The findings may provide the inter-complementary programme for patients with moderate-severe persistent AR.
- Although numerous of outcomes are assessed, even including some original parts, there may exist different perspectives on what the most suitable outcomes are.
- This RCT is an exploratory study with limited experience. Therefore, there are significant improvements still to be made in the sample size and follow-up pattern.

Trial registration number: ChiCTR-IOR-16008855

Keywords: Allergic rhinitis; Moxibustion; Randomized controlled trial

Introduction

Allergic rhinitis (AR), also called anaphylactic rhinitis, is an immunoglobulin led atopic disorder that affects the nasal mucosa [1], and is mainly manifested by rhinorrhea, sneezing, rhinoboyon and

rhinocnesmus. The incidence of AR has risen dramatically, with AR now affecting an estimated 10-25% of the global population [2]. Besides the nasal symptoms, AR is usually accompanied by other problems. For example, AR is directly responsible for exacerbation of other inflammatory airway diseases in addition to asthma [3], such as rhinosinusitis, chronic otitis media, and other ear, nose, and throat (ENT) disorders [4]. The frequent occurrence and long duration of nasal symptoms also gives rise to mental disorders like depression and anxiety [5]. AR patients reportedly commonly suffer from fatigue, lethargy and somniphathy, which markedly impact on quality of life [6,7].

The first-choice medication for moderate-severe AR in China is glucocorticoids [8]. Pernal nasal glucocorticoid spray is an internationally accepted effective medication for AR that has been recommended by Allergic Rhinitis and its Impact on Asthma (ARIA) as the first-line medication for moderate-severe persistent AR and has been proven safe and effective by multi-center, randomized, controlled trials (RCTs) [9]. However, some clinical research has reported a high relapse rate after application of pernasal glucocorticoid medication [10-12].

AR is one of the 30 diseases for which the World Health Organization has recommended treatment with acupuncture and moxibustion. Moxibustion has a proven therapeutic effect for AR, with a steady long-term effect. One of the causes of AR is imbalanced Th1/Th2 cytokines. Moxibustion can reportedly decrease Th1 cytokine IL-4 and granulocyte-macrophage colony stimulating factor level, and increase Th1 cytokine IFN- γ , thus correcting the imbalance to treat AR [13-15].

We have designed an RCT to test the effectiveness of moxibustion combined with conventional treatment for moderate-severe persistent AR. The aim of this RCT is to determine the optimal combination of Chinese and Western medicine for the treatment of AR.

Methods

Trial design

This will be a double-center RCT investigating the treatment of moderate and severe persistent AR. It has been registered in the Chinese Clinical Trial Register (ChiCTR-IOR-16008855). The study will run simultaneously at Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine and Beijing Gulou Hospital of Traditional Chinese Medicine (TCM). The total study period will be 21 weeks. After a 1-week baseline observation, participants will be randomized to receive either the combination of moxibustion and conventional treatment or conventional treatment alone for 8 weeks, and will then undergo a 12-week follow-up period (Figure 1).

Participants

Inclusion criteria

Eligible participants will be those diagnosed with moderate-severe persistent AR according to the ARIA criteria [16] who meet the following requirements:

Persistent symptoms (>4 days/week and >4 weeks/year)

Aged 18–60 years

Mean Visual Analogue Scale (VAS) score for nasal symptoms ≥ 4 for 7 days during the screening period

Provide written, informed consent

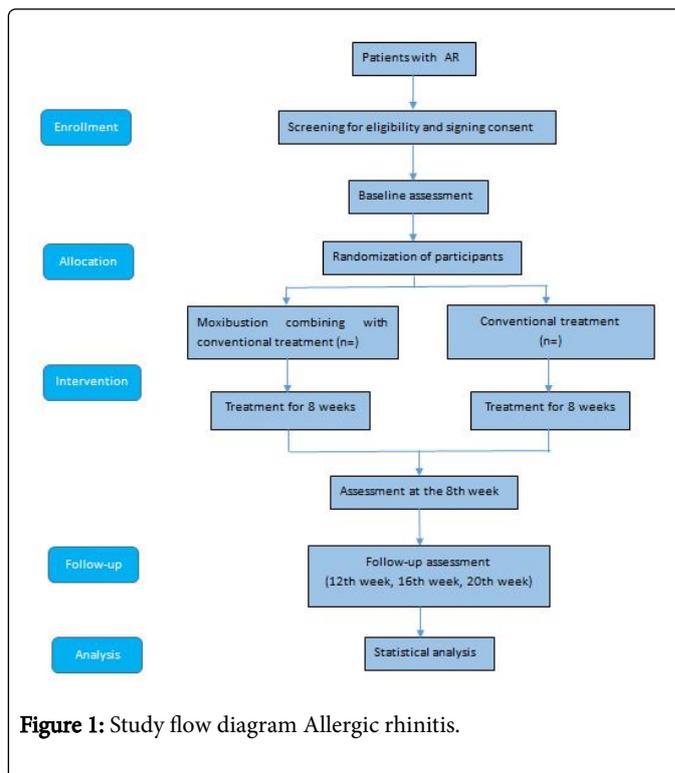


Figure 1: Study flow diagram Allergic rhinitis.

Exclusion criteria

Individuals will be excluded from the study if they meet any of the following criteria:

Individuals with acute respiratory infection, acute paranasal sinusitis, chronic paranasal sinusitis, organic lesions of the nasal cavity, or history of nasal surgery

Individuals with paroxysmal respiratory diseases such as asthma

Consumption of H1-antihistamines, steroids, antihistamine formulation, decongestant (applied to nasal cavity, oral cavity or eyes), corticosteroids, antibiotics and other medicines within 14 days; specific immunotherapy or systemic steroid treatment within 1 year

TCM physiotherapy or other traditional medicine such as acupuncture, moxibustion, cupping and nasal inhalation within 14 days; consumption of Chinese medicine for AR within 14 days

Women who are pregnant, lactating or undergoing preparation for pregnancy

Individuals with infectious diseases such as tuberculosis or hepatitis

Individuals who have smoked 10 cigarettes or more per day for 10 years or more

Individuals with scars at most selected acupoints or individuals who are uncooperative during the treatments

Recruitment

AR volunteers will be recruited through notices posted at Dongzhimen Hospital of Beijing University of Chinese Medicine, the Gulou Hospital of TCM of Beijing, and surrounding community

clinics. Patients who meet the inclusion criteria will sign informed consent and then begin a 1-week screening period, during which all participants will be asked to keep a diary of their VAS scores for nasal symptoms. After 1 week, patients with a mean VAS score ≥ 4 will enter the intervention period and undergo routine testing of blood, and liver and kidney function. Excluded patients will be provided with free 4-week conventional treatment.

Randomization and blinding

SAS 9.3.1 software (SAS Institute Inc., Cary, NC, USA) will be used to generate a random number table to randomize patients in a 1:1 ratio into a treatment group and a control group. The grouping details will be placed in a concealed randomization envelope (a light-proof envelope with a number sequence on the outside and the random number and grouping details inside).

Researchers in charge of data collection, statistical analysis, and outcome evaluation will be blinded to grouping details, but participants and moxibustion physicians will not be blinded because of the nature of the two interventions in this RCT.

Planned interventions

Moxibustion intervention: Individuals in the treatment group will receive moxibustion treatment plus conventional treatment.

1. Acupoint selection: Shenque (CV-8), Zusanli (ST-36), Hegu (LI-4), Yintang (GV-29)

2. Moxa preparation: A mixture of Huangqi and chuanxiong (six parts), Dangshen, Baizhu, and Chenpi (three parts), Ganjiang and Baikouren (two parts), and Gancao (one part) will be ground into a powder and mediated with ginger ale to make a medicinal pastry 2–3 cm in height and 0.8 cm in diameter, with a few holes created in the pastry to permeate heat. Fine moxa tomentum (Beijing Zhongyan Taihe Medicine Co., Ltd., Beijing, China) will be tucked in a mode to make a moxa cone that is 2.5 cm in diameter, 2 cm in height and 2.5 g in weight.

3. Manipulation: All acupoints will be located according to the People's Republic of China, State Standard Name and Location of Acupoints (GB 12346-2006) [17]. After locating the correct acupoint, the medicinal pastry will be placed on the acupoint, and then the moxa cone will be placed on the pastry. During moxibustion, the length between the moxa cone and the mediator will be adjusted according to each patient's feeling of heat, generating a feeling of diffuse heat on local points. Three zhuang will be burned on each point for 30 min every time. The treatment will be administered every second day, three times per week. One treatment course will last for 8 weeks.

Conventional treatment: Individuals in the control group will receive conventional treatment alone.

According to the guidelines for the treatment of AR recommended by ARIA in 2008 [18], individuals in the control group will receive 2–4 weeks of intranasal corticosteroids, H1-antihistamines or leukotriene receptor antagonists; after this, a specialized ENT examination will be repeated. An otolaryngologist will adjust the dosage or drug schedule according to the ENT findings, and treatments will be continued. One treatment course will last for 8 weeks.

Outcomes

Primary outcome

Average occurrence of symptoms per week: calculate the average occurrence of symptoms per week according to the AR diary (Table 1) in the previous 4 weeks during three follow-up visits. Visit times: V4, V5, and V6 (Figure 2).

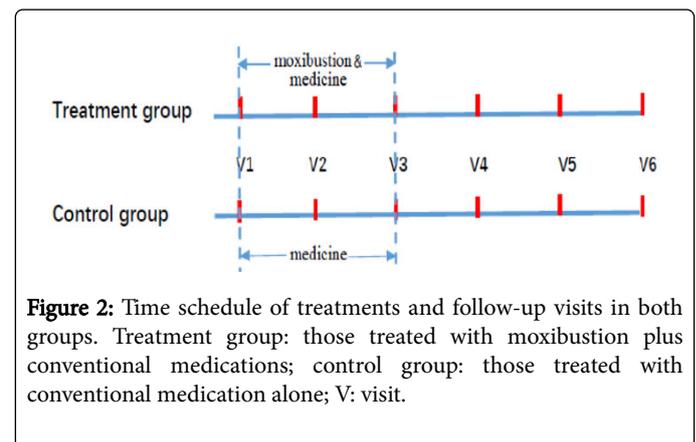


Figure 2: Time schedule of treatments and follow-up visits in both groups. Treatment group: those treated with moxibustion plus conventional medications; control group: those treated with conventional medication alone; V: visit.

Secondary outcome

1. VAS score for nasal symptoms [19]: The VAS score will be used to reflect the overall nasal symptoms over the whole day; this information will be collected from the AR diary. A maximum score of 10 represents the most unbearable discomfort, while 0 indicates no discomfort. The VAS score will be recorded to 1 decimal place. Visit times: V4, V5, and V6 (Figure 2).

2. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [20]: The RQLQ scale includes a total of 24 questions in seven sections: activity, sleeping, symptoms unrelated to nose and eyes, actual problems, nasal symptoms, ocular symptoms, and emotion. The score of each question is divided into seven levels: 0=no influence, 1=almost no influence, 2=some influence, 3=moderate influence, 4=marked influence, 5=worse influence, 6=worst influence. The score is calculated separately in each section, and the total score of these seven sections is considered as the RQLQ score. The maximum RQLQ score is 144. The RQLQ scale will be used to evaluate the influence of AR symptoms on the life quality of patients. Visit times: V1, V2, V3, V4, V5, and V6 (Figure 2).

3. Use of conventional medication: The name, dose and frequency of any drugs used in the follow-up period will be recorded in the AR diary. Visit time: V4, V5, and V6 (Figure 2).

Safety outcome

Laboratory indicators of routine blood tests, alanine aminotransferase, aspartate aminotransferase, creatinine, and blood urea nitrogen will be recorded to monitor the safety of this research. Visit times: baseline and 8 weeks (at the end of treatment).

Adverse events

The occurrence and duration of adverse events will be recorded in detail. Related adverse events may include local burn, vesication, fainting, abscessation, skin ulceration and infection. Other feelings of

discomfort after moxibustion may include fainting, fatigue, lack of appetite, and allergic reaction. Self-feedback will be the major approach to recording adverse events; therefore, participants will be informed of the possible adverse events in advance. If adverse events

occur, a physician will take immediate action to perform the necessary examination and treatment. Participants who experience severe adverse events will be removed from the study, and quick and proper treatment measures will be undertaken and recorded in detail.

Please fill in at 21:00 o'clock everyday							
From (d/m/y) to (d/m/y)							
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Catch cold	Yes	yes	yes	yes	yes	yes	yes
	No	no	no	no	no	no	no
Rhinitis attack	yes	yes	yes	yes	yes	yes	yes
	no	no	no	no	no	no	no
Syndrome	Block	Block	Block	Block	Block	Block	Block
	Itching	Itching	Itching	Itching	Itching	Itching	Itching
	Sneeze	Sneeze	Sneeze	Sneeze	Sneeze	Sneeze	Sneeze
	Running	Running	Running	Running	Running	Running	Running
Duration	hour	hour	hour	hour	hour	hour	hour
VAS of overall nasal symptoms of whole day	score	score	score	score	score	score	score
Usage of drugs							
Name							
Dose (pill/spray)							
Frequency							
Attack criterion: to meet at least one of four main symptoms, and the duration \geq 1 h							

Table 1: The diary that will be used by allergic rhinitis patients.

Sample size

This study is an exploratory research designed to investigate a new technique in clinical practice. Consulting the “Administration of drug registration” [21] issued by year 2005 in China, the minimum sample size of clinical trial is 20 cases. Considering the condition and ability of our research unit, 60 cases can reach the information saturation; taking into account a 20% drop-out rate, a total of 72 cases will be recruited. Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine and Beijing Gulou Hospital of TCM will take each recruit 50% of cases.

Statistical analysis

Data processing will be done using SPSS version 21.0 software (IBM Corp. Released 2012. Armonk, NY, USA). Demographic data (including age, sex, course, and family history) and baseline clinical data (VAS score) will be evaluated to test for comparability between groups. The mean \pm standard deviation will be used to describe measurement data of the primary and secondary outcomes. The paired sample t-test will be used to compare outcome data before and after treatment, the independent sample t-test will be used for between-group comparisons [22,23]. The enumeration data comparison will be conducted by the Chi-squared test or non-parametric test. A P value of less than 0.05 will be taken to indicate statistical significance.

Ethics and dissemination

Ethical approval for this RCT has been granted by the Institutional Review Board of Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine. Any adjustment of the study protocol will be reported to and approved by the ethics committee and the study participants. Written informed consent will be obtained from all participants. The findings of the RCT will be published in open access, peer-reviewed journals.

Discussion

AR has recently become one of the most common and refractory diseases in the world; it not only lowers quality of life, but also gives rise to many diseases that prevent the normal living and working capability of patients. AR is treated using many kinds of locally and orally applied drugs in modern clinical practice; although these medications relieve symptoms rapidly, they cannot change the frequent susceptible state of patients, and thus fail to maintain a long-term effect. Specific immunotherapy can vary the course of the allergic reaction, but patient compliance rate is low due to the long course of treatment [24].

TCM is rooted in the Chinese medical environment. Recently, many in-depth and extensive studies have been carried out on moxibustion. Moxibustion has proved to have a satisfactory effect for an increasing number of complicated cases [25,26]. Moxibustion has a positive dual-side regulatory effect on the immune system, which can promote the

normalization of disorderly immune function, and also facilitate the resistance capability of the body [27]. For the treatment of allergic diseases, moxibustion is convenient, produces a stable long-term effect, and decreases the severity of relapse. In TCM theory, moxibustion can warm the channels and stimulate the self-repairing capability of the meridian systems, thus facilitating vital qi and regulating zangfu function to improve constitution for the prevention and treatment of AR [28].

Recently, an increasing number of studies have evaluated the effects of moxibustion [29,30], including clinical studies on either the human body or experimental animals. One mechanism study [31] on asthma in rats revealed that moxibustion can cause the inhibition of IL-4 secretion, suppress the inflammatory response of IgE, and enhance the ratio of IFN- γ /IL-4. The universally accepted theory is that moxibustion can affect the release, combination and interaction of neurotransmitters, hormones and immuno-reactive substances through the nerve-endocrine-immune network to regulate the human body.

During this RCT, attention will be paid to patient compliance. The follow-up period in this study is extensive. Therefore, researchers must keep in close contact with participants and provide prompt daily life, hygiene and healthcare guidance. To guarantee timely, intact and accurate information collection, researchers will send out and collect diaries and questionnaires in paper and electronic version in accordance with the preference of each participant. This RCT is an exploratory study with limited experience. Therefore, the sample size, outcome evaluation items and follow-up pattern should be improved in the future.

Contributors

SC and S-NG conceived the study and wrote the protocol. X-SH, Z-HW, YX and W-MZ helped searching the literatures and critically revised the manuscript. FM, S-HQ and Y-FJ wrote the introduction of this protocol. J-PZ and D-ML advised on the protocol design and revised the manuscript. All authors read and approved the final manuscript.

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Competing Interests

None declared.

Consent for Publication

Not applicable.

Data Sharing Statement

On completion, anonymised data obtained in the trial will be available from the corresponding author, on reasonable request.

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