Self-administered acupressure for allergic rhinitis: Study protocol for a randomized, single blind, non-specific controlled, parallel trial

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Study protocol

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Abstract

Background Allergic rhinitis (AR) is an IgE-mediated inflammatory disease. Current conventional therapies for AR are unsatisfactory. Acupuncture has been recommended as an optional treatment for AR patients who are interested in non-pharmacotherapy in the new clinical practice guidelines for AR. Acupressure is a sub-type of acupuncture which is non-invasive with a low risk and can be self-administered. However, the current limited evidence is compromised by the high risk of bias and heterogeneity of methodology. Therefore, rigorously designed randomized controlled trials (RCTs) are needed. This proposed RCT aims to evaluate the efficacy and safety of self-administered acupressure for the management of AR. Methods/design We have designed a randomized, single blind, non-specific controlled, two-arm, parallel clinical trial involving a 2-week run-in period, a 4-week intervention period and an 8-week follow-up period. The eligible participants will be randomized into either specific or non-specific acupressure group. They will be required to perform self-administered acupressure on either 5 specific acupressure points or 5 non-specific acupressure points, one minute for each point, twice a day for 4 weeks. Participants will be asked to complete self-administered questionnaires for outcome measures including 7-point scale of symptom severity, Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQs), relief medication scores, adverse events and participants' opinion of this study at the different assessment points throughout the trial period. Data will be analyzed by chi-square or t-test using Statistical Package for Social Science (SPSS) software. Discussion The findings from this study will provide scientific evidence for the efficacy and safety of self-administered acupressure for the management of AR. This study may assist to develop a non-cost, non-invasive self-management method for AR sufferers.

Introduction

Allergic rhinitis (AR) is an IgE-mediated immunologic inflammatory response in nasal membrane after exposure to certain allergens which include pollens, dust mites, moulds, smoke, animal dander, air pollutants and occupational agents [1-3]. Patients with AR present with nasal symptoms such as sneezing, nasal itching, nasal congestion and runny nose; which may be combined with non-nasal symptoms such as itchy and watery eyes, as well as itchy and sore throat [2, 4]. AR has a high prevalence worldwide ranging from 10% to 30% of the population affected [5]. In Australia, AR is a common respiratory condition that affects approximately 20% of population and the cost of medication from the pharmacy suppliers increased from $107.8 million to $226.8 million between 2001 and 2010 [6, 7] . The troublesome of AR symptoms have a significant impact on patients' quality of life such as work and school performance, sleep and mental health [2]. Moreover, AR has a high impact on asthma and is associated with rhinosinusitis and other comorbidities such as conjunctivitis and chronic cough [2, 6, 8].

Current management of AR includes allergen avoidance, pharmacotherapies (such as H_1-antihistamine, corticosteroids, chromones, decongestants, anti-cholinergics and anti-leukriences) and allergen-specific immunotherapy [2]. Most of the medications for AR are over-the-counter in Australia [6]. However, these medications are unable to provide full symptomatic relief and some of them are associated with undesirable side effects such as drowsiness and dryness in nasal cavity. Systemic glucocorticosteroids

cannot be used for a long term due to systemic side effects such as suppressed immune system, weakened bones, high blood pressure, diabetes, especially impacts on children's growth [2, 3]. Those could be the major reasons for more and more patients with AR to seek help from complementary and alternative medicine including acupuncture [9].

Acupuncture has a long history for the management of AR. Currently it has been recommended as an optional treatment for AR patients who are interested in non-pharmaceutical therapies in the Clinical Practice Guidelines for AR developed by the American Academy of Otolaryngology – Head and Neck Surgery and endorsed by the American Academy of Family Physicians [10]. Acupressure is a sub-type of acupuncture. It is a non-invasive therapeutic method applying physical pressure to certain acupuncture points by finger, elbow, hand or with various devices to treat diseases [11]. The popularity of acupressure has been increased these years and it was the fourth preferred complementary and alternative therapies in hospitalized patients in Australia [12]. Several clinical studies have validated the effects of acupressure for various health conditions, for instance, nausea, vomiting and pain after caesarean delivery [13], hypertension [14] and constipation [15]. A systematic review of randomized controlled trials (RCTs) in acupressure for respiratory allergic diseases indicated that acupressure is safe for symptomatic relief on AR and asthma. However, no reliable evidence of efficacy could be identified due to the small number of included RCTs, heterogeneity of study design and high/unclear risk of bias [16]. There is a need to perform rigorously-designed RCTs to investigate the efficacy and safety of acupressure for the management of AR.

This study aims to investigate the efficacy and safety of self-administered acupressure on symptomatic relief and health-related quality of life improvement in adults with AR by conducting a superiority RCT. The study will also explore whether self-administered acupressure is effective in reducing the usage of Western medications in the management of AR.

Materials And Methods

Trial design

This study will be conducted at the Chinese Medicine Clinical Trial Laboratory in Royal Melbourne Institute of Technology (RMIT) University, Bundoora West and City campuses. It has been designed as a randomized, single blind, non-specific controlled (ie. using true acupuncture points without specific indications for AR in the control group), and two-arm parallel clinical trial according to the Guideline of National Statement on Ethical Conduct in Human Research 2007 (Updated May 2018) [17]. The trial will consist of a 2-week run-in period, a 4-week intervention period and an 8-week follow-up period. This study protocol was developed as required by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Additional file 1) [18] and the Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT Statement [19].

The ethics approval has been obtained from RMIT Human Research Ethics Committee (HREC) (project number: 20742). The RMIT HREC will oversee the conduct of this trial. The trial has been registered with

the Australian and New Zealand Clinical Trials Registry (ACTRN12617001106325) (Additional file 2).

Participants

The participants will be based at the general population in Melbourne, Australia and recruited through advertisements on internet, posters, notice boards, leaflets, media release, social media, local newspapers, and newsletters. Participation in this research project is voluntary. The participants will be selected according to the inclusion and exclusion criteria listed in Table 1 below.

Sample size

The sample size was calculated using the program G*Power 3.1.9 [20]. Due to the absence of a similar acupressure study, the sample size estimation was based on an acupuncture study [21] that is closest to our study as we feel using the acupuncture study would produce the best possible estimates of effect size and sample size. The effect size estimate in this acupuncture study was based on the main outcome variable (ie. total nasal symptom score) which is also used in our study. We have also inflated the estimated sample size to cater for a 10% dropout which normally occurs in studies involving acupuncture. The effect size estimate is 0.6505. To achieve 80% power at the significance level 0.05 we need 45 subjects per group taking into consideration of a 10% dropout rate.

Recruitment

People who are interested in taking part in this trial will be provided with Participant Information Sheet with Consent Form (PIS-CF) and asked to complete a general questionnaire and screening questionnaire if they agree with PIS-CF. Written consent will be obtained from each participant by the investigators before an initial interview. The activities in the initial interview will include allergen skin prick test, physical examination and Chinese medicine differential diagnosis [22] to achieve AR diagnosis. The participants meeting the inclusion criteria will enter the 2-week run-in period. During this period, every participant will be asked to conduct two sets of weekly baseline assessment including a 7-point scale symptom severity assessment form [23], a Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQs) [24] and a medication usage form. All baseline assessment forms will be submitted in the first intervention session. The Figure 1 outlines the procedures of the clinical trial.

Randomization and blinding

To minimize bias, eligible participants will be randomized into either the specific-acupressure treatment group or non-specific acupressure control group with an allocation ratio of 1:1. Randomization will be conducted after baseline assessment using a computer program run by an independent researcher who is not directly involved in the trial. The randomization codes will be put into individually sealed opaque envelopes with sequel trial numbers. The sealed opaque envelopes contain the information on the location of specific or non-specific acupressure points for self-administered acupressure. Each participant will be asked to pick one sealed envelope from the pack of all the envelopes and pass it onto the registered acupuncturist. This acupuncturist is the only person who knows the participants' group

allocation in the trial. Neither the participants nor other investigators (such as data entry personnel and data analyst) will know the participants' allocation to receive specific or non-specific acupressure treatment. The randomization codes and the allocation of the participants will be revealed once the RCT is completed. However, in the event of the need of this grouping information (e.g., a participant experiencing severe adverse events), the investigators will access the grouping data on the request of the medical doctor. The relevant information will be documented in the participant's case report form.

Interventions

After randomization, the registered acupuncturist will provide detailed instructions and training on self-administered acupressure techniques to each participant individually. A pictorial instruction showing the location of acupressure points will be provided to the participants for further reference. Participants will be asked to perform self-administered acupressure on either five specific or non-specific acupressure points following the sequence from point 1 to point 5. The points will be self-pressed with maximal tolerable pressure but still within the comfortable range for one minute each point, twice a day for four weeks and complete the self-assessment on a weekly basis. During the treatment period, participants are required to have a weekly visit to the Clinical Trial Laboratory and the registered acupuncturist will monitor their skills to ensure the accurate performance of self-administered acupressure techniques. Messages will be sent to each participant to remind them to continue performing acupressure and attend the Clinical Trial Laboratory during each week. The Figure 2 below illustrates the location of five specific acupressure points and five non-specific acupressure points.

Specific self-administered acupressure

Participants in specific acupressure group will apply self-administered acupressure on five specific acupressure points including LI4 Hegu, GV23 Shangxing, BL2 Zanzhu, LI20 Yingxiang and GB20 Fengchi. The acupressure points were selected based on the review of classical and modern literature [11, 16, 22, 25].

Non-specific self-administered acupressure

Participants in non-specific acupressure group will apply self-administered acupressure on another five non-specific acupressure points which are true acupuncture points on the body but not specifically indicated for AR treatment according to literature including Extra Luozhen, GV20 Baihui, GB4 Hanyan, SI18 Quanliao and GB12 Wangu [11, 25].

Symptomatic relief medications

Participants will be allowed to continue their existing management for AR, such as pharmacological therapy. They will be asked to record the details of all medications used in the medication usage form.

Outcome measures

Primary and secondary outcome measures will be included in this clinical trial. The comparison between two groups will be at baseline, at the end of the treatment period and at the end of the follow-up period. The RCT schedule of recruitment, interventions and assessments is shown in Figure 3.

Primary outcome measures

The primary outcome measure will be AR symptomatic relief measured by 7-point scale symptom severity with the score ranging from 1 to 7. It contains four domains including I (nasal symptom severity), II (non-nasal symptom severity) and IV (Quality-of-life assessment of rhinitis severity) where a higher score indicates severer symptoms and better quality of life (QoL) as well as III (Global assessment of nasal and non-nasal symptom severity) where a lower score indicates severer symptoms [23]. The scores of four individual domains will be assessed separately at baseline and during the intervention period on a weekly basis and in the follow-up period on a fortnightly basis. The primary outcome of the intervention will be a combination of the four domains.

Secondary outcome measures

The secondary outcome measures will consist of RQLQs [24], relief medication scores, adverse events and participants' opinion about this clinical trial. RQLQs is used to assess the patient's quality of life and daily activities which contain seven domains with scores from 0 to 6; a higher score indicates a severer impact on QoL [24]. The use of anti-allergic medication is calculated as each daily dose of antihistamines or decongestants nasal spray or eye drop was equivalent to 1 point; oral antihistamines as 2 points and steroid nasal spray or eye drop as 3 points [26]. If the participants use oral corticosteroids or acupuncture for AR during the trial period, they will be asked to discontinue the self-administered acupressure treatment and considered as withdrawal from this study. Adverse events will be self-monitored and recorded in the adverse events form. If there are severe adverse events from the self-administered acupressure, the relevant participants will be asked to terminate the study and contact the researchers immediately. They will be referred to general practitioners or the emergency department for management. All severe adverse events will be investigated and reported in writing to the RMIT HREC immediately. A questionnaire will be used to seek participants' opinion on the expectancy of self-administered acupressure for AR and the credibility of the blinding method used in the study.

RQLQs and relief medication scores will be assessed at baseline, intervention period (weekly) and follow-up period (fortnightly). Acupressure dosage and adverse events will be recorded in a weekly form during the treatment period to monitor participants' compliance and safety, and adverse events will be further assessed fortnightly in follow-up period. Participants' opinion will be assessed at the end of first and final week of intervention period.

Data management

An individual file for each participant will be used to archive the hard copy of case record forms including informed consent, results of allergen skin prick test, results of physical examinations and all completed

questionnaires. The files will be stored in the lock-up cabinet. The electronic submission documents will be kept in a RMIT University password-protected computer. Only the investigators of this study will have the authority to access the data. The results of the study and the grouping information of the participants will be provided to the individual after completion of the trial. Publications will only report aggregated data. Personal identity will not be disclosed.

Data analysis

Statistical analyses will be performed by an independent statistician at RMIT University using IBM SPSS Statistics for Windows Version 25 software (IBM Corp., Armonk, NY, USA). The *chi*-square test will be used to assess differences between the two treatment groups on categorical variables such as characteristic and demographic data at baseline. The *t*-test will be used to assess differences between the two treatment groups on the primary outcomes (nasal and non-nasal symptom scores, QoL, global assessment score as well as the total score of the four domains) and secondary outcome variables (RQLQs and relief medication scores) at the end of treatment and follow-up periods. All analyses will follow the intention-to-treat principle. The Worst-Case Scenario method will be employed to deal with the missing data. That is, we will carry forward the worst possible outcomes for the missing data. Participants enrolled in the study with data from at least one treatment will be included for analysis. No interim analysis will be performed due to the short duration of the trial.

All comparisons will be two-tailed and p values < 0.05 will be considered as statistical significance. Subgroup analysis may be performed according to syndrome differential diagnosis of Chinese medicine, severity of symptoms or age group of participants.

Discussion

Acupuncture has been recommended as an alternative treatment for AR in the new Clinical Practice Guidelines [10] based on existing evidence from high-quality RCTs with positive effects [21, 26, 27]. Acupressure is a subtype of acupuncture which may have similar mechanisms of action to acupuncture, that is, stimulation on acupuncture points could activate the fiber terminals of peripheral nerve, trigger neurological responses [28] and decrease inflammatory cytokine and neuropeptide levels [29]. However, the clinical effects and safety of acupressure have not been fully determined. A recent systematic review has identified the need for rigorously designed RCTs of acupressure for AR due to weaknesses of current limited RCTs (e.g., significant heterogeneity and high/unclear risk of bias) [16]. This proposed RCT aims to fill in this knowledge gap by addressing all the weaknesses identified in this review.

This RCT has been rigorously designed as a randomized, single-blind, non-specific controlled clinical trial to minimize risks of bias. An independent statistician will generate randomization number using computer software and the randomization number will be assigned to participants using sealed opaque envelops. This procedure ensures adequate randomization and allocation concealment of participants. Due to the nature of acupressure, blinding of the acupuncturist is impossible for this trial. However, participants will be blinded during the entire randomization and intervention processes. Selection of

acupressure points in treatment and control groups can be challenging as the size of fingers limits the chance of choosing the non-actual points one to three centimetres next to the real points which is the most popularly used sham control method in acupuncture/acupressure RCTs [30, 31]. This RCT adopts specific and non-specific points which are in the same area but three to four centimetres in between in the treatment and control groups which aims to maximizes the possibility to achieve successful blinding of participants [32]. In addition, all the interventions and the outcome measures will be administered by participants themselves, which avoids involving thirty party assessors to reduce potential performance bias since blinding of assessors is considered more important than blinding practitioners since blinded assessments less likely bring biases to subjective outcomes [33]. When dealing with missing data, we will utilize the worst scenario method and intention-to-treat approach to manage the attrition bias. It is ideal to employ objective measures such as serum allergen specific Immunoglobulin E (IgE) to further investigate the mechanisms of action of acupressure for AR management. However, it is not feasible in this proposed RCT due to limited funding.

In summary, this protocol offers a standard regime to guide the conduct of RCT. By performing the rigorously designed RCT, this research project will make a significant contribution to the literature on self-administered acupressure. It may lead to the adoption of self-administered acupressure as a low-risk, non-invasive, non-pharmaceutical intervention for AR and could also assist the self-management of AR.

Trial status

This protocol is version 1. The advertisement for the recruitment began in August 2017 after the ethics approval. It is anticipated that the recruitment will be completed by the end of June 2020. The recruitment is currently in progress.

Abbreviations

ANZCTR: Australian and New Zealand Clinical Trials Registry;

AR: Allergic rhinitis;

CONSORT: Consolidated Standards of Reporting Trials;

HREC: Human Research Ethics Committee;

IgE: Immunoglobulin E;

PIS-CF: Participant Information Sheet with Consent Form;

QoL: Quality of life;

RCT: Randomized controlled trial;

RQLQs: Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities;

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials;

SPSS: Statistical Package for Social Science;

STRICTA: STandards for Reporting Interventions in Clinical Trials of Acupuncture.

Declarations

Ethics approval and consent to participate

The ethics approval for this clinical trial was obtained from the Human Research Ethics Committee of RMIT University on 2June 2017 (No. 20742). The trial will be performed according to the National Statement on Ethical Conduct in Human Research 2007 (Update 2018) which is published by the National Health and Medical Research Council of Australia, the Australian Research Council and The Australian Vice-Chancellors' Committee, 2015. A written informed consent will be obtained from each participant (Additional file 3). The participants will be given adequate time to raise questions and to consider whether they participate in this study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. This paper is a protocol for a randomized clinical trial and does not contain any data.

Completing interests

The authors have no conflict of interest.

Sponsor and funding information

RMIT University is the study sponsor for this study. This study is supported by the Transitional Seed Funding provided by the School of Health and Biomedical Sciences, RMIT University, P.O. Box 71, Bundoora 3083.

Author's contributions

AY and GL conceptualized and designed the trial and supervised the preparation of ethics application by YL. YL wrote the first draft of the manuscript. AY and GL reviewed and contributed to subsequent drafts. All authors approved the final version of the manuscript.

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Tables

Table 1: Inclusion and exclusion criteria of participants

Inclusion criteria	Exclusion criteria
· ≥18 years	· Current systemic corticosteroid therapy
· ≥2-year history of AR	· Other current active respiratory disease (e.g., asthma)
· (+) skin prick test	· Have used acupuncture/acupressure for respiratory or allergic diseases within the last month
· Currently not involved in other clinical trials	· Structural defects of the upper respiratory tract
· Agree to make themselves available for the period of the study	· Chinese medicine practitioner, acupuncturist or Chinese medicine student
· Provide written consent for participation	· Pregnancy
· Will not travel overseas or interstates for 14 weeks of the trial period	· Travel overseas or interstates in the 14 weeks of trial period
· Have access to computer and internet	· History of HIV, Hepatitis B or C
	· Nasal polyposis
	· Unable to read and write English

Figures

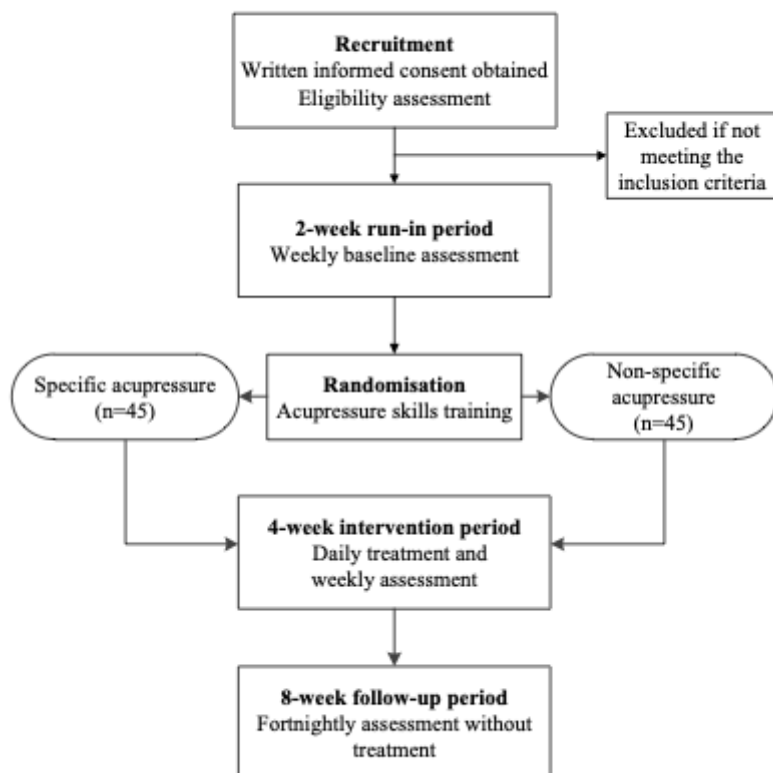



Figure 1

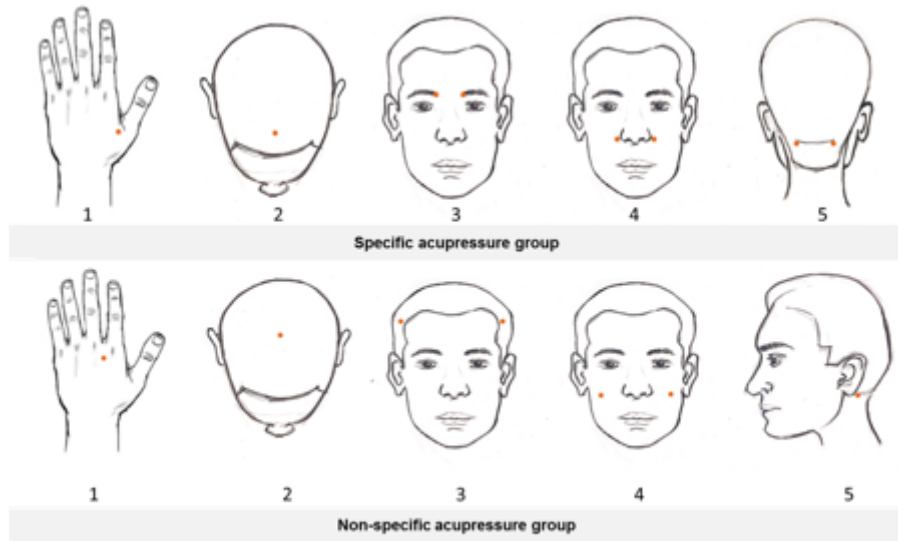
Flow chart of the clinical trial procedures

(Artwork by GX Fang)

Figure 2

The location of five specific and five non-specific acupressure points

			Study period													
TIMEPOINT:	Interview	Baseline		Treatment				Follow-up								
Week		-2	-1	1	2	3	4	5	6	7	8	9	10	11	12
RECRUITMENT:																
Informed consent	×															
Eligibility screen	×															
Allergen skin prick test	×															
Physical examination	×															
Chinese medicine diagnosis	×															
Randomization				×												
INTERVENTIONS:																
Specific acupressure				♦———————♦												
Non-specific acupressure				♦———————♦												
ASSESSMENTS:																
7-point scale symptom severity		×	×	×	×	×	×		×		×		×		×	
Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities		×	×	×	×	×	×		×		×		×		×	
Medication usage		×	×	×	×	×	×		×		×		×		×	
Adverse events				×	×	×	×		×		×		×		×	
Participants' opinion				×			×									

Figure 3

The schedule of recruitment, interventions and assessments