Acupuncture for allergic rhinitis (Protocol)

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[Intervention Protocol]

Acupuncture for allergic rhinitis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To systematically evaluate the effects of acupuncture for treating allergic rhinitis.

BACKGROUND

Description of the condition

Allergic rhinitis is a highly prevalent condition. The self reported prevalence in the United States ranges between 11.9% and 30.2% of the total population (Nathan 2008). The prevalence of clinically-confirmed allergic rhinitis in Europe is around 22.7% (Bauchau 2004). In Korea, 28% of children who are six years old and over are affected by allergic rhinitis (KCDCP 2008).

Allergic rhinitis is caused by an IgE-mediated hypersensitivity reaction following exposure of the membranes lining the nose to allergens (Bousquet 2001). Symptoms typically consist of sneezing, nasal itching, nasal obstruction and watery nasal discharge (IRMWG 1994). Other symptoms include coughing, wheezing and shortness of breath, eye symptoms (red eyes, itchy eyes and tearing), oral allergy syndrome (manifesting as an itchy, swollen oropharynx on eating stoned fruits) and systemic symptoms, such as tiredness, fever and a sensation of pressure in the head. Allergic rhinitis has a clear impact on a patient's quality of life, interfering with work, sleep and recreational activities (Blaiss 1999). Furthermore, the economic burden is substantial (Bousquet 2008; Meltzer 2011). It is also a major contributor to the cost of lost productivity in the workplace (Lamb 2006). Allergic rhinitis is a chronic condition with substantial economic impacts for the affected persons and their families, for healthcare systems and for society as a whole.

Allergic rhinitis was previously subdivided into seasonal, perennial or occupational, depending on time of exposure. Perennial allergic rhinitis is most frequently caused by indoor allergens, including dust mites, moulds, insects and animal dander. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens, such as pollens or moulds. However, this classification is not entirely satisfactory on multiple levels. A new classification has been developed that is based on the duration of symptoms and distinguishes between 'intermittent' or 'persistent' allergic rhinitis (Bousquet

2008). Intermittent allergic rhinitis means that the symptoms are present for less than four days per week or for less than four consecutive weeks. Persistent allergic rhinitis means that the symptoms are present for more than four days per week or for more than four consecutive weeks. Intermittent allergic rhinitis and persistent allergic rhinitis are not synonymous with seasonal and perennial allergic rhinitis (Bauchau 2004; Demoly 2003; Bachert 2006; Bousquet 2005; Todo-Bom 2007; Van Hoecke 2006)

Management options for allergic rhinitis include allergen avoidance, medication, immunotherapy and education. Medication includes oral and topical H_1-antihistamines, topical and systemic glucocorticosteroids, chromones, decongestants, topical anticholinergics and antileukotrienes. These drugs may provide immediate control of symptoms; however, they have no long-lasting effects when stopped (Bousquet 2008). Most are also associated with adverse effects which can occasionally be serious.

Description of the intervention

Acupuncture is an intervention that stimulates specific points on the body surface, generally using needles. Acupuncture has a long history of use in East Asia. Traditional acupuncture is applied according to the concepts of Yin and Yang, the five elements theory, Qi theory, meridian theory and traditional diagnostic methods of Traditional Eastern Asian Medicine. The overall aim of acupuncture treatment is to restore the body's equilibrium. The westernised medical application of acupuncture involves the use of acupuncture using trigger points, segmental points and commonly-used formula points (Smith 2010). It is an adaptation of Chinese acupuncture using current knowledge of anatomy, physiology and pathology, and the principles of evidence-based medicine (White 2009).

Acupuncture is used in its broad sense to include traditional manual needling, moxibustion, electric acupuncture (electroacupuncture), laser acupuncture (photo-acupuncture), microsystem acupuncture such as ear (auricular), face, hand and scalp acupuncture, and acupressure (the application of pressure at selected sites) (WHO 2003).

Acupuncture is often used in combination with moxibustion; the burning on or over the skin of selected herbs, and it may also involve the application of other kinds of stimulation to certain points.

How the intervention might work

Acupuncture has been used for the treatment of various conditions including osteoarthritis, asthma and other types of chronic pain conditions. It has been hypothesised that acupuncture exerts anti-inflammatory and antinociceptive effects (Cho 2006). Acupuncture has been claimed to influence specific and non-specific cellular influx, the activation of cell proliferation and the regulation of subsequently involved cells that will result in a complex mechanism of transport and further breakdown and clearance of all bioactive mediators (Zijlstra 2003). Acupuncture may activate the cholinergic anti-inflammatory pathway in the treatment of inflammatory diseases (Tracey 2007).

Several mechanisms responsible for the effects of acupuncture have been suggested, including the release of neurochemicals, such as β-endorphins, enkephalins and serotonin (Moffet 2006). Another theory suggests that the effects of acupuncture may be the result of the regulation of the autonomic nervous system, by altering sympathetic and parasympathetic nervous system activity (Haker 2000) or by increasing local blood flow and nitric oxide production (Tsuchiya 2007).

In allergic rhinitis, acupuncture could act as a modulator of anti-inflammatory cytokines (Jindal 2008) and by neuroimmunological mechanisms, e.g. lowering plasma levels of vasoactive intestinal peptide and substance P (Li 2007).

A German pragmatic trial suggested that treating patients with allergic rhinitis in routine care with additional acupuncture leads to clinically relevant and persistent benefits (Brinkhaus 2008). Additionally, ear acupressure for allergic rhinitis was shown to be as effective as body acupuncture or antihistamine treatments for producing short-term effects. However, ear acupressure was more effective than antihistamines for long-term effects (Zhang 2010). Acupuncture may help to improve blood rheology indexes by causing an increased volume of blood flow. Additionally, it may regulate the immunological functions of the human body and thus provide therapeutic effects for the treatment of allergic rhinitis.

Why it is important to do this review

There are several reviews and overviews that have evaluated the evidence supporting the use of acupuncture for the treatment of allergic rhinitis (Jindal 2008; Lee 2009; Li 2009; Passalacqua 2006; Resnick 2008; Roberts 2008; Witt 2010; Xiao 2009; Xue 2006). Their conclusions vary, as do the primary studies included in these reviews. Thus, although there is widespread use of acupuncture for the treatment of allergic rhinitis, the evidence supporting its use remains unclear. A rigorous systematic review using Cochrane methodology, and regularly updated in *The Cochrane Library*, is therefore now needed to assess the safety and effectiveness of acupuncture for the treatment of allergic rhinitis.

OBJECTIVES

To systematically evaluate the effects of acupuncture for treating allergic rhinitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Patients of both sexes who have intermittent or persistent allergic rhinitis, regardless of age, race or educational and economic status. The diagnostic criteria for allergic rhinitis for inclusion will be as follows.

- Positive skin prick tests.
- High circulating levels of allergen-specific IgE antibody detected by a specific blood test for allergy called radioallergosorbent test (RAST).
- Clinical history or allergen to have been identified.
- Nasal provocation (test).

Types of interventions

We will define acupuncture as an intervention that stimulates specific points on the body surface, regardless of stimulation methods. We will include all types of acupuncture, including manual acupuncture, electroacupuncture, ear acupuncture or scalp acupuncture, and all styles of acupuncture (Chinese, Japanese, Korean, etc.) that use needles to penetrate the skin at acupuncture points. We will also include acupressure, moxibustion, laser acupuncture, pharmaco-acupuncture and dry needling. We will exclude transcutaneous electrical nerve stimulation (TENS). We will compare acupuncture treatment with placebo, sham acupuncture, waiting list control, usual care and drugs. We will include combination therapy with acupuncture if both the acupuncture and control groups receive the non-acupuncture element of the combination. We will include trials that employ at least four acupuncture sessions, regardless of treatment duration.

Types of outcome measures

Primary outcomes

- Improvement of symptoms, including global symptoms and nasal and non-nasal symptoms (using validated symptom diaries or any validated visual analogue scale).

Secondary outcomes

- Quality of life (using a validated quality of life measure), including the Rhinitis Quality of Life Questionnaire (RQLQ) and general quality of life measures (e.g. SF-36).
- Medication consumption.
- Experimental outcome (skin reactivity (immediate and late phase), levels of specific IgE and IgG antibodies etc. related to allergic rhinitis).
- Adverse effects.
- Health economic data (quality-adjusted life years (QALYs)).
- Compliance.

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear, and we will arrange translations of papers where necessary.

Electronic searches

We will identify published, unpublished and ongoing studies by searching the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Bone, Joint and Muscle Trauma Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); PubMed; EMBASE; CINAHL; AMED; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; Chinese Medical Database (CNKI and Wangfang); Japan Science and Technology Information Aggregator; ISRCTN; ClinicalTrials.gov; ICTRP; Google; and Korean medical databases (Korean Studies Information, DBPIA, Korea Institute of Science and Technology Information, Research Information Service System, Korean National Assembly Library and Korean Traditional Knowledge Portal).

We will model subject strategies for databases on the search strategy designed for CENTRAL (see Appendix 1). Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, we will search PubMed, TRIPdatabase, NHS Evidence - ENT & Audiology and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

Two review authors (Lee MS and Shin BC) will independently review all identified trials to assess their eligibility for inclusion. Disagreements will be discussed and resolved, if necessary, by the other authors.

Data extraction and management

Three authors will extract data from the selected reports or studies, independently filling in a common data collection form, for which we will conduct a pilot test. We will obtain data for methods, participants, interventions, outcomes, results and miscellaneous items, such as funding sources and ethical approval. Using the GRADEpro software used in Cochrane systematic reviews, we will create a 'Summary of findings' table. Any disagreement will be resolved by discussion. Further disagreements will be arbitrated by another author.

Assessment of risk of bias in included studies

According to the recommendations of The Cochrane Collaboration (Higgins 2011), we will assess the risk of bias for each included study. We will evaluate the following domains for risk of bias: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias (*see* Appendix 2).

It is difficult to develop a perfect placebo control that can blind both the acupuncturist and the participants, therefore double-blind clinical trials are rarely realisable in acupuncture studies (MacPherson 2007). It is therefore necessary that the key outcome assessment should be conducted by blinded participants and blinded outcome assessors for acupuncture research. We will assume a low risk of bias in the blinding domain if participants or outcome assessors were blinded properly. We will try to contact the authors of the included studies if there are any unclear details for assessment of the risk of bias. The review authors will judge the risk of bias for each domain as follows: low risk, high risk and unclear risk, based on the criteria listed in Table 8.5c in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

For continuous data, we will use the mean difference (MD) to measure the treatment effect with 95% confidence intervals (CIs). We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present treatment effects as a risk ratio (RR) with 95% CIs. We will change other binary data into the RR form.

Unit of analysis issues

Principally, we will include data from parallel-group studies for meta-analysis. We will classify data for multiple time point observations as short-term (within eight weeks) and long-term (over eight weeks) follow up, and conduct analysis of these two groups, respectively, for persistent allergic rhinitis. We will classify data for multiple time point observations as short-term (within eight weeks in the 1st year) and long-term (eight weeks in the 2nd year) follow up for intermittent allergic rhinitis.

Dealing with missing data

We will apply the intention-to-treat (ITT) principle for statistical analysis. We will contact the corresponding authors of the included studies if there are any missing or insufficient data from the trials. We will impute both dichotomous and continuous data through the last-observation-carried-forward (LOCF) method.

Assessment of heterogeneity

Clinically, various types of modalities and doses will be included in the acupuncture treatment. We will use the random-effects model for the meta-analysis. If a meta-analysis is possible, we will use the I^2 statistic for quantifying inconsistencies among the included studies. According to the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions*, 50% will be the cut-off point for meaningful heterogeneity. If heterogeneity is observed, we will conduct subgroup analysis to explore the possible causes (Deeks 2011).

Assessment of reporting biases

We will use funnel plots to detect reporting biases and small-study effects. If more than 10 studies are included in the meta-analysis, we will conduct the test for funnel plot asymmetry using Egger's method (Deeks 2011; Egger 1997). We will include all eligible trials, regardless of their methodological quality.

Data synthesis

If a significant number of studies are identified, we will conduct a meta-analysis according to the random-effects model, which may be a reasonable method for the analysis of the variety of included acupuncture modalities.

We will synthesise the data as follows, if sufficient data are available:

1. acupuncture versus conventional medical treatments (antiallergy drugs, immunotherapy or systemic glucocorticosteroids);
2. acupuncture versus no treatment or waiting list control;

3. acupuncture versus sham acupuncture or placebo intervention; and

4. acupuncture plus medical treatment versus medical treatment only.

Subgroup analysis and investigation of heterogeneity

To explore the differences in the effect sizes, we will conduct subgroup analysis based on the following characteristics:

- sex and age of patients;
- the type of allergic rhinitis (seasonal versus perennial or intermittent versus persistent allergic rhinitis);
- the type of acupuncture intervention (manual acupuncture, electroacupuncture, ear acupuncture, scalp acupuncture etc.); and
- the dose of acupuncture (different sessions of acupuncture treatment) or combined treatment (single acupuncture or acupuncture with concomitant medical treatment).

Sensitivity analysis

For the sensitivity analysis, we will repeat the meta-analysis, substituting decisions alternatively to test the robustness of the primary decisions of the review process (Deeks 2011). The principal decision nodes are as follows:

1. methodological quality (sequence generation, allocation concealment or blinding in the assessment of outcomes and symptom severity);

2. sample size (small sample size studies, e.g. below 40 in each group, and large sample size studies, e.g. over 40 in each group); and

3. the option of missing data (using the LOCF method) for perennial allergic rhinitis only.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Rhinitis explode all trees
#2 (rhiniti* OR rhinopath* OR rhinosinusit* OR rhinoconjunctivitis OR ozena* OR hayfever OR hay NEXT fever OR pollinosis OR pollenosis OR pollonosis OR SAR OR PAR)
#3 ((nose :ti OR nasal :ti) AND allerg :ti)
#4 ((allerg*:ti OR hypersen*:ti) AND (cat*:ti OR dander:ti OR mite*:ti OR dust*:ti OR dog*:ti OR ragweed:ti OR pollen:ti OR grass*:ti OR cedar:ti OR alder:ti OR willow:ti OR birch:ti OR mugwort:ti OR tree*:ti OR weed*:ti OR rapeseed*:ti OR perennial*:ti OR season*:ti OR spring:ti OR summer:ti OR respiratory:ti))
#5 #1 OR #2 OR #3 OR #4
#6 (acupuncture or akupuncture or acupoint* or auriculoacupuncture or acupressure or eletroacupuncture or meridians or needling or needle*)
#7 (trigger and point*)
#8 ((jing adj luo) or jingluo or (ching adj lo))
#9 MeSH descriptor Acupuncture explode all trees
#10 MeSH descriptor Acupuncture Therapy explode all trees
#11 #6 OR #7 OR #8 OR #9 OR #10
#12 #5 AND #11

Appendix 2. The 'Risk of bias' assessment tool

Domain	Description	Judgement question	Note
Sequence generation	The process of sequence generation should be described sufficiently	Was the allocation sequence adequately generated?	
Allocation concealment	Investigators and participants should not predict the assignment before the allocation process	Was allocation adequately concealed?	
Blinding of participants, personnel and outcome assessors	Participants or outcome assessors should not know about the allocation result during the study period	Was knowledge of the allocated interventions adequately prevented from participants or outcome assessors during the study?	Blinding of participants or outcome assessors is a key factor for judging the risk of bias in this domain
Incomplete outcome data	Any missing data with reasons or imputation of the data with a reasonable statistical method should be described properly	Were incomplete outcome data adequately addressed?	
Selective outcome reporting	The outcomes of the trial should be described completely according to the protocol in a pre-defined way	Are reports of the study free of suggestion of selective outcome reporting?	The study will be regarded as high risk if there is no available protocol
Other sources of bias	The trial should be free of other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias?	
We will classify every domain into one of the three categories: low risk of bias, high risk of bias or unclear risk of bias			

CONTRIBUTIONS OF AUTHORS

MS Lee, DH Lee, JI Kim, BC Shin and E Ernst drafted the protocol.

The search strategy will be developed and run by Gemma Sandberg in the Cochrane ENT group.

MS Lee and BC Shin will run the search in the Korean, Japanese and Chinese databases when it is needed.

JI Kim and DH Lee will obtain copies of studies.

MS Lee and BC Shin will carry out selection of the studies to include and E Ernst will act as an arbiter at the study selection stage.

MS Lee and DH Lee will conduct data extraction from studies and E Ernst will act as an arbiter at the data extraction stage.

JI Kim and BC Shin will enter data into RevMan 5.1 (RevMan 2011).

MS Lee and E Ernst will carry out the analysis.

MS Lee, DH Lee, JI Kim, BC Shin and E Ernst will carry out interpretation of the analysis.

MS Lee, DH Lee, JI Kim, BC Shin and E Ernst will draft the final review.

MS Lee and DH Lee will update the review.

DECLARATIONS OF INTEREST

There are no conflicts of interest.

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- Korea Institute of Oriental Medicine, Korea, South.

External sources

- No sources of support supplied