Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

A multicenter, randomized, controlled trial testing the effects of acupuncture on allergic rhinitis

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To cite this article: Choi S-M, Park J-E, Li S-S, Jung H, Zi M, Kim T-H, Jung S, Kim A, Shin M, Sul J-U, Hong Z, Jiping Z, Lee S, Liyun H, Kang K, Baoyan L. A multicenter, randomized, controlled trial testing the effects of acupuncture on allergic rhinitis. *Allergy* 2013; **68**: 365–374.

Keywords
acupuncture; allergic rhinitis; multicenter trial.

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Trial registration: Current Controlled Trials ISRCTN90807007.

Accepted for publication 20 September 2012

DOI:10.1111/all.12053

Edited by: Wytske Fokkens

Abstract

Background: The aim of this study was to evaluate the efficacy and safety of acupuncture in the treatment for allergic rhinitis.

Methods: This study was a multicenter, randomized, parallel-controlled study. Participants were randomized to either the active acupuncture, sham acupuncture, or waitlist groups. The active and sham acupuncture groups received acupuncture treatment three times per week for 4 weeks. In the sham group, minimal acupuncture at nonacupuncture points was used. The waitlist group did not receive any acupuncture treatment.

Results: Of the 238 participants, 97, 94, and 47 individuals were assigned to the active acupuncture, sham acupuncture, and waitlist group, respectively. After the treatment, the difference in the total nasal symptom score (TNSS) was significantly reduced in the active acupuncture group compared with the sham acupuncture (difference: −1.03, 95% confidence interval [CI]: −1.96, −0.09, $P = 0.03$) and waitlist (difference: −2.49, 95% CI: −3.68, −1.29, $P < 0.0001$). The active acupuncture group exhibited a significant change in the total non-nasal symptom score (TNNSS) compared with the waitlist (difference: −0.78, 95% CI: −1.22, −0.34, $P = 0.0002$), but not the sham acupuncture group (difference; 0.15, 95% CI: −0.21, 0.5, $P = 0.56$). Both active and sham acupuncture treatments resulted in significant improvements in TNSS and TNNSS compared to baseline.

Conclusion: Active acupuncture showed a significantly greater effect on symptoms of allergic rhinitis than either sham acupuncture or no active treatment. The symptoms of allergic rhinitis decreased significantly after treatment in the both acupuncture and sham acupuncture groups. Acupuncture appears to be an effective and safe treatment for allergic rhinitis.

Allergic rhinitis (AR) is a symptomatic disorder of the nose resulting from an IgE-mediated immunological reaction to allergen exposure. Its major symptoms include rhinorrhea, nasal itching, obstruction, and sneezing, all of which are reversible either spontaneously or with treatment (1). These symptoms may cause sleep disturbances and impaired daytime concentration in individuals with AR (2), and AR may also represent a significant economic burden (3, 4).

AR is a highly prevalent chronic respiratory disease that affects between 17–29% of the population of Europe (5, 6) and 7.3% of the population of the United Arab Emirates (7). Allergic rhinitis is associated with asthma, sinusitis, and other comorbidities, such as conjunctivitis (8). The risk factors for allergic rhinitis include indoor and outdoor allergens and occupational agents (8). In children, the risk factors for AR include a diagnosis of atopy, a previous diagnosis of asthma, and the diagnosis of rhinitis in a parent (9).

Current strategies for the management of AR include the avoidance of exposure to allergens, pharmacological treatments, immunotherapy, and patient education (8). Treatments for AR include antihistamines, intranasal glucocorticosteroids, antileukotrienes, and specific immunotherapies. However, these treatments are associated with certain undesirable side-effects, have unclear cost-effectiveness, and frequently do not provide complete symptomatic relief (8, 10, 11). In a nested case–control study on allergies performed in Germany, more than 25% of the population had received complementary and alternative medicine (CAM) for their allergies, and approximately 17% of these rhinitis sufferers had received acupuncture (12).

Acupuncture is a traditional Oriental treatment in which needles are inserted at specific points in the body and then either manipulated or electrically stimulated (13). Acupuncture is currently used around the world to treat a variety of diseases (14, 15) and has shown efficacy in the symptomatic relief of several ailments, including osteoarthritis (16), vomiting (17, 18), and allergy-related itch (19, 20). Although several studies have demonstrated the efficacy of acupuncture treatment on nasal symptoms (21–23), patient quality of life (24), and the cost-effectiveness (25) of acupuncture treatment for AR, others have shown negative or mixed results (26–28). The aim of this study was therefore to evaluate the efficacy and safety of acupuncture for the treatment of persistent allergic rhinitis (PAR).

Methods

Study design and ethics approval

This study consisted of a multicenter, randomized, parallel, sham acupuncture-controlled, patient assessor-blinded trial. Two centers in Korea and two centers in China participated in the study, including the Kyung-Hee University Medical Center in Seoul, Korea, the Acupuncture and Moxibustion Research Center of the Korea Institute of Oriental Medicine in Daejeon, Korea, and the Acupuncture and Moxibustion Clinic of Guang'anmen Hospital and Dongzhimen Hospital in Beijing, China. This study was approved by the Institutional Review Board at each site. Full details of the trial protocol can be found at www.controlled-trials.com/ISRCTN90807007.

Inclusion/exclusion criteria

The eligible participants were older than 18 years and met the criteria of moderate to severe PAR, according to the criteria listed in 'Allergic Rhinitis and its Impact on Asthma' (ARIA) (8). The inclusion criteria included symptoms that had persisted for more than 4 days per week for more than four consecutive weeks and at least one of the following rhinitis-associated conditions: nasal obstruction, rhinorrhea, sneezing, and nasal itching. All included participants exhibited at least one positive result on an allergy skin prick reaction test at screening. The participants were excluded if they suffered from serious medical conditions, such as uncontrolled hypertension, insulin-dependent diabetes mellitus, a past or current malignant tumor, severe dyslipidemia, liver or kidney dysfunction, anemia, active pulmonary tuberculosis, or other infectious or systemic diseases that would make treatment with acupuncture inappropriate. Participants were deemed ineligible if they suffered from congenital nasal abnormalities including nasal dermoid cysts and congenital midline nasal masses, sinusitis, or asthma, had a history of nose surgery, had received CAM therapy for AR within the previous 6 months, or had received systemically administered corticosteroids, antihistamines, or decongestants within 6 months prior to enrollment.

Recruitment and randomization procedures

The participants were recruited through advertisements in local newspapers, hospital websites, and bulletin boards. Written informed consent was obtained from all eligible candidates, and the participants were randomly assigned to one of the following three groups: active acupuncture, sham acupuncture, or waitlist. Randomization was performed by a statistician using a computerized list with an assignment ratio of 2 : 2 : 1 and a block size of 5. A sealed envelope was used to assign participants to groups at each center, and an acupuncture practitioner performed the interventions according to this assignment. Investigators, including the clinical research coordinators and the analyzing statistician, were blinded to the treatment group assignments with the exception of the Oriental medical doctor (OMD) performing the acupuncture.

Intervention

The active and sham acupuncture group participants received treatments three times weekly for a total of twelve sessions over a period of 4 weeks. Disposable needles of 0.20 mm in diameter × 30 mm in length (Dongbang Acupuncture Inc., Boryung, Korea) were used. For the active acupuncture group, 10 acupuncture points (bilateral LI4, LI20, ST2 and ST36, unilateral EX-1 and GV23) were selected. Each needle was rotated until the participants and the practitioner felt de-qi sensations.

For the sham acupuncture treatment, the needles were inserted at nonacupuncture points that were 1–1.5 cm away from the acupuncture sites. The needles were inserted to a depth of 3–5 mm using a hollow pool and a shallow needling technique to avoid de-qi. Next, the practitioner rotated the needle once for patient blinding. With the exception of the insertion site, depth, and manual stimulation, other factors, such as needle size, retention time, treatment frequency, and the number of treatments, were identical between the acupuncture groups. All active and sham acupuncture treatments were conducted by OMDs with more than 3 years of clinical acupuncture experience.

The participants in the waitlist group did not receive active or sham acupuncture treatments during the study. The treatment period consisted of 1 week of baseline observation, 4 weeks of treatment, and 4 weeks of follow-up for a total study period of 9 weeks.

Medications that could affect the allergic rhinitis symptoms were not permitted. If participants required treatments or medication for their symptoms, they reported the need to the investigators, and a decision was reached through discussion among the OMDs.

Assessment

The primary outcome measured was the change in the weekly average of the participants' total nasal symptom score (TNSS). The secondary outcomes included the total non-nasal symptom score (TNNSS) and the Rhinitis Quality of Life Questionnaire (RQLQ) score.

After screening, the participants who satisfied the entry requirements entered the baseline period. During this period, the participants documented the four nasal symptoms (nasal obstruction, rhinorrhea, sneezing, and itching) involved in assigning the TNSS. The symptoms were graded on a five-point scale (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = very severe symptoms). The weekly TNSS was calculated and compared between the groups, and the TNNSS was assessed and calculated in the same manner as the TNSS. The TNNSS evaluated four non-nasal symptoms, including headache, itching, pain, and eye watering.

The RQLQ measures the influence of AR on quality of life and consists of 28 items in the seven domains of sleep, non-nasal/eye symptoms, emotional function, practical problems, nasal symptoms, eye symptoms, and activities. The patients were asked to assess the impact of AR on these areas during the previous week. The RQLQ score was assessed three times: at baseline, at the end of the treatment period, and at the conclusion of the follow-up period.

Sample size calculation

Based on the pilot study that we conducted, the difference in the TNSS change between active and sham acupuncture after 4 weeks of acupuncture treatment was 2.53 ± 4.74 (mean ± SD). In addition, the TNSS reduction in the active acupuncture group in our pilot study was 4.12. The standard deviation (SD) of the pilot study was adjusted for a more relevant application to the true population.

For the sample size calculation, we established a sample size for an independent *t*-test using the adjusted SD and the difference in TNSS change between the active and the sham acupuncture groups with a power of 80% and an alpha value of 2.5% (two-tailed). Based on this calculation, the estimated sample size was a total of 238 participants, allowing for a 20% withdrawal rate. The details regarding the sample size calculation have been provided by Kim et al. (29).

Statistical analyses

For the primary and secondary outcome measures, an analysis of covariance (ANCOVA) was performed. The objective of this study was to compare the effect of acupuncture between the acupuncture and sham acupuncture groups and between the acupuncture and waitlist groups. Therefore, we analyzed the differences between the acupuncture and sham acupuncture groups as well as between the acupuncture and waitlist groups using ANCOVA. Dunnett's test was used to control the family-wise type I error rate at 0.05 (two-sided). Also, weighted mean difference between two groups was used to calculate the effect size (30).

The change in the TNSS at the end of the four-week treatment period was the primary endpoint. The primary comparison was between the participants who were randomly assigned to the active *vs* the sham acupuncture treatment groups. To compare the effect before and after treatment, a paired *t*-test was used.

All adverse events that arose during the study were reported in the case report forms. Statistical analyses were performed using the SAS statistical package program (v.9.1.3, SAS institute, Inc., Cary, NC, USA), and the level of significance was established at $P = 0.05$.

Data and safety monitoring

Regular monitoring was conducted for quality control at least once every 2 months. Additionally, investigators in China and South Korea exchanged queries to discuss practical issues, adverse events, and any issues raised by participants. During this procedure, information related to group allocation was shared with only OMDs to keep a blinding of other investigators. The data were entered twice and checked according to the standard operating procedure of data management. In the case of an error on the case report form, the data manager sent a data query form to the investigator for review.

Results

Demographic data

Of the 534 participants screened, 238 participants were randomly assigned to the active acupuncture group, the sham acupuncture group, or the waitlist group (97, 94, and 47 participants, respectively). The subjects were recruited between

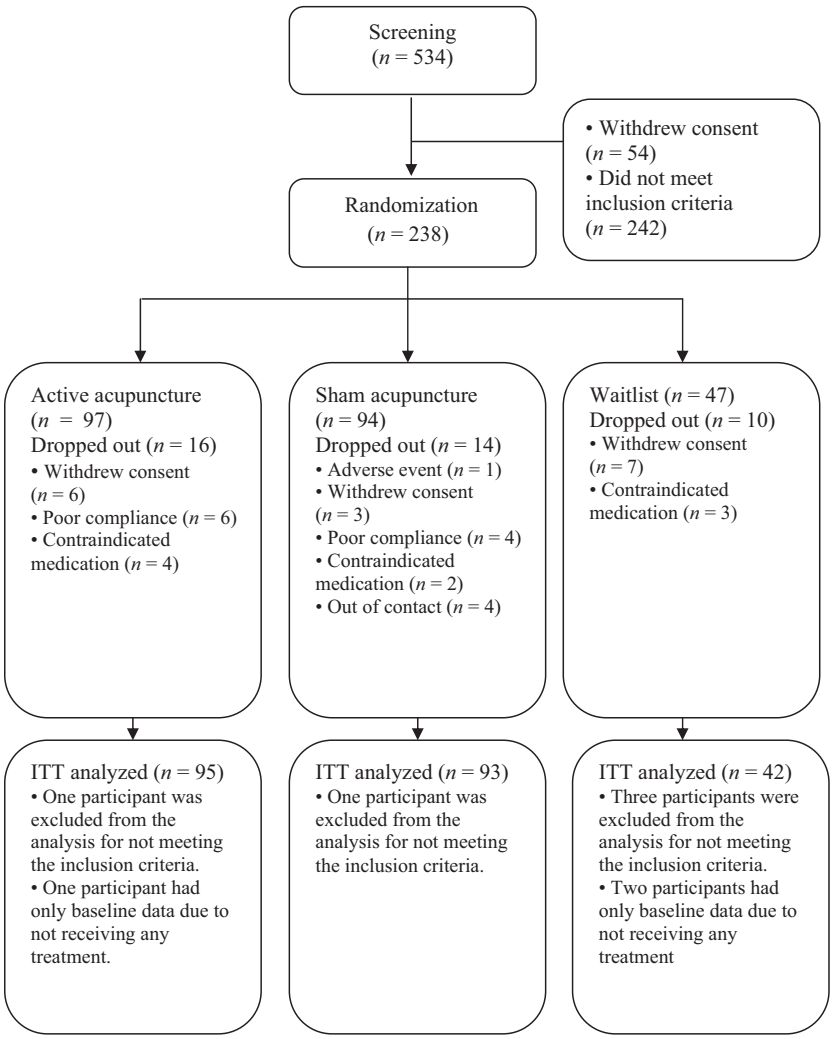

Figure 1 Flowchart.

March 12, and October 27, 2009, and the trial ended on December 28, 2009.

Sixteen participants in the active acupuncture group, fourteen in the sham acupuncture group, and ten in the waitlist group dropped out (Fig. 1). A total of 230 subjects of the 238 participants were included in the analysis. Of the eight subjects who were excluded, five subjects (one in the active, one in the sham, and three in the waitlist group) did not disclose the taking of prohibited medications at the time of enrollment and therefore did not meet the inclusion criteria. An additional three subjects (one in the active and two in the waitlist group) dropped out of the study before the first assessment.

No significant differences were identified between subjects in each group regarding age, underlying health status, TNSS, or RQLQ score. However, the TNNSS differed significantly between the three groups, and this difference was adjusted using ANCOVA in the analysis (Table 1).

Primary endpoint

For the analysis based on TNSS, the difference between the active and the sham acupuncture groups was not significant until 3 weeks after the start of treatment. The difference in TNSS between the active and the sham acupuncture groups was −0.51 (95% CI: −1.32, 0.29, $P = 0.21$) in week 1, −0.58 (95% CI: −1.48, 0.32, $P = 0.27$) in week 2, and −0.67 (95% CI: −1.63, 0.3, $P = 0.17$) in week 3. After 4 weeks, the difference between the active and sham acupuncture groups was significant, with a difference of −1.03 (95% CI: −1.96, −0.09, $P = 0.03$). This significant difference lasted until 4 weeks after the completion of acupuncture treatment, at which time there was a difference of −1.09 (95% CI: −2.16, −0.03, $P = 0.04$). Compared with the waitlist group, the change in TNSS in the active acupuncture group was significant at 4 weeks after the start of treatment (difference: −2.49, 95% CI: −3.68, −1.29, $P < 0.0001$) (Table 2). Based

Table 1 Demographic data for the participants in each group

	Active acupuncture (n = 95)	Sham acupuncture (n = 93)	Waitlist group (n = 42)	P-value
Age (years)	38.97 ± 11.33	37.04 ± 12.23	38.07 ± 12.40	0.5411
Sex† (males/females)	39/56	30/63	18/24	0.3502
Blood pressure (mmHg)				
Systolic	114.42 ± 9.83	113.49 ± 12.36	116.14 ± 13.12	0.5078
Diastolic	72.35 ± 7.80	71.05 ± 10.44	72.42 ± 10.03	0.5949
Pulse (beats/min)	71.25 ± 5.56	72.77 ± 7.37	73.86 ± 6.68	0.0895
Temperature (°C)	36.43 ± 0.20	36.42 ± 0.22	36.47 ± 0.26	0.5752
Months since the diagnosis of AR	11.43 ± 9.20	12.02 ± 7.40	12.99 ± 8.82	0.6419
TNSS	8.55 ± 3.41	8.59 ± 2.91	7.90 ± 2.55	0.3122
TNNSS	2.52 ± 1.30	2.89 ± 1.30	2.43 ± 1.23	0.0410*
RQLQ				
Activities	3.38 ± 0.96	3.56 ± 0.87	3.46 ± 0.93	0.3947
Sleep	2.49 ± 1.53	2.37 ± 1.46	2.56 ± 1.55	0.7927
Non-nasal/eye	2.72 ± 1.25	2.73 ± 1.31	2.52 ± 1.30	0.5509
Practical problems	3.80 ± 1.36	4.09 ± 1.24	3.83 ± 1.22	0.2709
Nasal problems	3.45 ± 1.20	3.55 ± 1.06	3.33 ± 1.05	0.4830
Eye symptoms	2.27 ± 1.45	2.28 ± 1.40	2.07 ± 1.15	0.5991
Emotional function	2.46 ± 1.27	2.62 ± 1.34	2.59 ± 1.36	0.7072
Overall	2.89 ± 1.03	2.96 ± 0.97	2.83 ± 0.96	0.6632

TNSS, total nasal symptom score; TNNSS, total non-nasal symptom score; RQLQ, rhinitis quality of life questionnaire.
For each variable except sex, the values are expressed as the mean ± SD.
*$P < 0.05$.
†Chi-squared test. The categories without the † mark were analyzed using 'analysis of covariance adjusting group and center.'

on these results, the effect size between the active and sham acupuncture groups was 0.3, and the effect size between the active and waitlist groups was 0.7.

After 2 weeks, all groups exhibited a significant reduction in the TNSS compared with baseline, and these differences were −1.96 (95% CI: −2.63, −1.28, $P < 0.0001$) for the active acupuncture group, −1.40 (95% CI: −2.04, −0.75, $P < 0.0001$) for the sham acupuncture group, and −0.57 (95% CI: −1.08, −0.06, $P = 0.03$) for the waitlist group. However, after 4 weeks, the TNSS decreased significantly compared with the baseline in both the active (difference: −3.11, 95% CI: −3.85, −2.36, $P < 0.0001$) and sham acupuncture groups (difference: −2.11, 95% CI: −2.79, −1.42, $P < 0.0001$), but not in the waitlist group (difference: −0.19, 95% CI: −0.97, 0.59, $P = 0.62$) (Fig. 2).

Secondary endpoints

The TNNSS difference between the active and sham acupuncture groups was not significant after 4 weeks of treatment (difference: 0.15, 95% CI: −0.21, 0.5, $P = 0.56$) or during the follow-up period (difference: −0.18, 95% CI: −0.58, 0.21, $P = 0.36$). However, the TNNSS of the active acupuncture group exhibited a significantly greater change compared with the waitlist group at 4 weeks, with a difference of −0.78 (95% CI: −1.22, −0.34, $P = 0.0002$).

After 2 weeks, the change in the TNNSS was significant in both the active (difference: −0.46, 95% CI: −0.70, −0.22, $P = 0.0002$) and the sham acupuncture groups (difference: −0.54, 95% CI: −0.79, −0.28, $P < 0.0001$) compared with the baseline, and it lasted throughout the 4-week follow-up period in the active (difference: −1.00, 95% CI: −1.27, −0.73, $P < 0.0001$) and the sham acupuncture groups (difference: −0.82, 95% CI: −1.11, −0.53, $P < 0.0001$). However, the waitlist group did not exhibit a significant reduction in TNNSS after 2 weeks (difference: −0.0, 95% CI: −0.36, 0.36, $P = 1.0$) or 4 weeks (difference: −0.10, 95% CI: −0.25, −0.44, $P = 0.58$).

The RQLQ score did not change significantly between the active acupuncture and sham acupuncture groups after 2 weeks (difference: −0.22, 95% CI: −0.45, 0.01, $P = 0.07$) or 4 weeks of treatment (difference: −0.25, 95% CI: −0.53, 0.02, $P = 0.07$). Among the seven domains of the RQLQ, only the 'sleep' domain demonstrated significant differences between the active and sham acupuncture groups ($P = 0.01$ at 2 weeks, $P = 0.01$ at 4 weeks, and $P = 0.02$ at the 4-week follow-up). However, the difference between the active and the waitlist groups was significant after 2 weeks (difference: −0.65, 95% CI: −0.94, −0.36, $P < 0.0001$) and 4 weeks (difference: −0.91, 95% CI: −1.26, −0.56, $P < 0.0001$), and the change in the RQLQ domain score was also significantly different between the active and waitlist groups in all domains (Table 3).

There was a significant improvement in the RQLQ score of the active acupuncture group at the end of 2 weeks (difference: −0.71, 95% CI: −0.89, −0.54, $P < 0.0001$) and 4 weeks of treatment (difference: −1.08, 95% CI: −1.29, −0.88,

Table 2 The change in the TNSS, TNNSS, and RQLQ scores

	Active acupuncture (n = 95)	Sham acupuncture (n = 93)	P-value	Waitlist group (n = 42)	P-value
TNSS					
Baseline	8.55 ± 3.41	8.59 ± 2.91		7.90 ± 2.55	
1 week	−1.63 ± 2.79	−1.12 ± 2.77	0.2079	-	
2 weeks	−1.96 ± 3.32	−1.40 ± 3.13	0.2675	−0.57 ± 1.64	0.0670
3 weeks	−2.44 ± 3.41	−1.77 ± 3.29	0.1736	-	
4 weeks	−3.11 ± 3.68	−2.11 ± 3.32	0.0286*	−0.19 ± 2.49	<0.0001***
f/u 1 week	−3.16 ± 3.90	−2.27 ± 3.45	0.0998	-	-
f/u 4 weeks	−3.61 ± 3.77	−2.52 ± 3.64	0.0442*	-	-
TNNSS					
Baseline	2.52 ± 1.30	2.89 ± 1.30		2.43 ± 1.23	
1 week	−0.20 ± 1.18	−0.30 ± 1.11	0.5466	-	-
2 weeks	−0.46 ± 1.83	−0.54 ± 1.22	0.7254	0.00 ± 1.15	0.0567
3 weeks	−0.62 ± 1.30	−0.60 ± 1.33	0.9215	-	-
4 weeks	−0.75 ± 1.40	−0.83 ± 1.27	0.5631	0.10 ± 1.10	0.0002***
f/u 1 week	−0.74 ± 1.33	−0.68 ± 1.24	0.7514	-	-
f/u 4 weeks	−1.00 ± 1.33	−0.82 ± 1.40	0.3593	-	-
RQLQ					
Baseline	2.89 ± 1.03	2.96 ± 2.97		2.83 ± 0.96	
2 weeks	−0.71 ± 0.84	−0.52 ± 0.80	0.0663	−0.03 ± 0.47	<0.0001***
4 weeks	−1.08 ± 1.01	−0.86 ± 0.94	0.0729	−0.13 ± 0.68	<0.0001***
f/u 4 weeks	−1.18 ± 1.15	−0.99 ± 1.01	0.2353	-	-

2 weeks, 4 weeks: Analysis of covariance adjusting group and center (active vs. sham: 1 vs. 1, active vs. waitlist: 1 vs. 1).
1 week, 3 weeks, f/u 2 weeks: Two-sample t-test.
For each variable, the values are expressed as the mean ± SD.
f/u, follow-up.
*P < 0.05, ** P < 0.01, *** P < 0.001.

$P < 0.0001$), which continued through the fourth week following treatment (difference: −1.18, 95% CI: −1.42, −0.95, $P < 0.0001$). There was also a remarkable change in the RQLQ score of the sham acupuncture group after treatment compared to baseline (difference: −0.52, 95% CI: −0.38, −0.35, $P < 0.0001$ in 2 weeks; difference: −0.86, 95% CI:

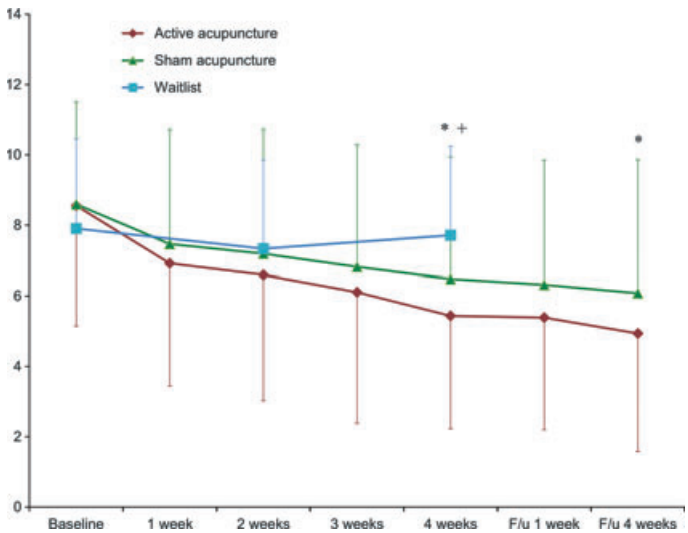

Figure 2 The change in the TNSS mean and standard deviation in the active acupuncture, sham acupuncture, and waitlist groups. The stars indicate the time points with significant differences between the active and sham acupuncture groups; the cross marks indicate the time points with significant differences between the active acupuncture and waitlist groups (*/+: $P < 0.05$). Only the upper or lower standard deviation is shown for clarity.

Table 3 The effect of treatment on the RQLQ score

	Active acupuncture	Sham acupuncture	*P*-value	Waitlist group	*P*-value
Activities					
Baseline	3.38 ± 0.96	3.56 ± 0.87		3.46 ± 0.93	
2 weeks	−0.51 ± 1.04	−0.37 ± 0.95	0.1517	−0.17 ± 0.86	0.0478*
4 weeks	−0.84 ± 1.18	−0.73 ± 1.11	0.2345	−0.25 ± 0.88	0.0013**
f/u 4 weeks	−0.91 ± 1.16	−0.96 ± 1.24	0.7676	-	
Sleep					
Baseline	2.49 ± 1.53	2.37 ± 1.46		2.56 ± 1.55	
2 weeks	−0.79 ± 1.35	−0.30 ± 1.18	0.0079**	0.02 ± 0.88	<0.0001***
4 weeks	−0.19 ± 1.54	−0.69 ± 1.20	0.0075**	−0.02 ± 0.95	<0.0001***
f/u 4 weeks	−1.22 ± 1.62	−0.69 ± 1.35	0.0153*	-	
Non-nasal/eye					
Baseline	2.72 ± 1.25	2.73 ± 1.31		2.52 ± 1.30	
2 weeks	−0.73 ± 1.02	−0.49 ± 0.92	0.0926	0.05 ± 0.67	<0.0001***
4 weeks	−1.10 ± 1.19	−0.87 ± 1.08	0.1857	−0.04 ± 0.83	<0.0001***
f/u 4 weeks	−1.19 ± 1.28	−0.99 ± 1.10	0.2634	-	
Practical problems					
Baseline	3.80 ± 1.36	4.09 ± 1.24		3.83 ± 1.22	
2 weeks	−0.84 ± 1.26	−0.76 ± 1.13	0.3912	−0.18 ± 0.92	0.0017**
4 weeks	−1.35 ± 1.43	−1.18 ± 1.34	0.1284	−0.30 ± 1.30	<0.0001***
f/u 4 weeks	−1.48 ± 1.56	−1.36 ± 1.44	0.5668	-	
Nasal problems					
Baseline	3.45 ± 1.20	3.55 ± 1.06		3.33 ± 1.05	
2 weeks	−0.82 ± 1.13	−0.59 ± 1.04	0.0830	−0.12 ± 0.68	0.0005***
4 weeks	−1.18 ± 1.28	−0.95 ± 1.21	0.1131	−0.23 ± 0.73	<0.0001***
f/u 4 weeks	−1.33 ± 1.44	−1.14 ± 1.34	0.3594	-	
Eye symptoms					
Baseline	2.27 ± 1.44	2.28 ± 1.40		2.07 ± 1.15	
2 weeks	−0.56 ± 1.06	−0.52 ± 1.12	0.9206	0.10 ± 0.68	0.0013**
4 weeks	−0.87 ± 1.17	−0.66 ± 1.16	0.2124	−0.006 ± 0.78	<0.0001***
f/u 4 weeks	−1.05 ± 1.32	−0.81 ± 1.22	0.2048	-	
Emotional function					
Baseline	2.46 ± 1.27	2.62 ± 1.34		2.59 ± 1.36	
2 weeks	−0.72 ± 1.05	−0.58 ± 0.98	0.2002	−0.01 ± 0.69	<0.0001***
4 weeks	−1.06 ± 1.21	−0.93 ± 1.08	0.3017	−0.20 ± 0.79	<0.0001***
f/u 4 weeks	−1.11 ± 1.31	−1.01 ± 1.17	0.5923	-	

Analysis of covariance adjusting group and center (active vs. sham: 1 vs. 1, active vs. waiting: 1 vs. 1).
For each variable, the values are expressed as the mean ± SD.
f/u 2 weeks: Two-sample *t*-test.
*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

−1.05, −0.67, $P < 0.0001$ in 4 weeks; and difference: −0.99, 95% CI: −1.20, −0.79, $P < 0.0001$ at the 4-week follow-up).

Blinding

Twenty-five participants in the active acupuncture group and twenty-two participants in the sham acupuncture group thought they had received the active acupuncture treatment. Forty-seven and forty-six participants in the active and sham acupuncture groups, respectively, stated that they were unsure of which treatment they received. All participants in the acupuncture groups were blinded to the type of acupuncture that they received ($P = 0.50$) (Table 4).

Table 4 The results of the test for blinding

	Active	Sham	Not known	Total
Active *N* (%)	25 (31.25)	8 (10.00)	47 (58.75)	80 (100)
Sham *N* (%)	22 (27.16)	13 (16.05)	46 (56.79)	81 (100)

Chi-squared test, *P*-value: 0.4999.

Safety

One subject in the sham acupuncture group reported hospitalization as a serious adverse event during the trial, but the

hospitalization was due to enteritis and was not believed to have been related to the acupuncture treatment.

One of two subjects reporting adverse events in the active group complained of papules, pruritus, and ocular pruritus, whereas the other subject reported subcutaneous bleeding. The subject in the sham group reported headache and vertigo. The only dropout resulting from an adverse event was the participant who was hospitalized for enteritis.

Discussion

This study was the first multination acupuncture trial to evaluate the efficacy of acupuncture for PAR. Allergic rhinitis can be classified as either seasonal allergic rhinitis (SAR) or persistent allergic rhinitis (PAR). The Allergic Rhinitis and its Impact on Asthma (ARIA) classification separates these diagnoses based on the duration and severity of symptoms (8). Despite the differences in the duration and symptoms of rhinitis cases, many previous trials evaluating the effect of acupuncture have examined AR without considering the differences between SAR and PAR (23, 24, 27). Moreover, other studies have compared the efficacy of acupuncture without using control group for sham acupuncture (31), and studies examining PAR have used a sample size that was too small to allow for generalized conclusions of the findings (21, 22). This multicenter, randomized, sham-controlled study enabled the unbiased evaluation of the efficacy of acupuncture in PAR.

In this study, active acupuncture treatment was associated with an improvement in patient symptoms and quality of life. Furthermore, the results of this study suggest that active acupuncture can alleviate the nasal symptoms of PAR more effectively than sham acupuncture or observation alone. The effect size between the active and sham acupuncture groups was 0.3 in this study. The difference between active and sham acupuncture groups was not large, and this difference could have occurred through chance. In addition, if the blinding is not maintained, the effects of acupuncture could be merely those of a placebo. However, in this study, the participants were blinded, and the difference between active and sham acupuncture was greater after 4 weeks of follow-up than after the completion of acupuncture treatment. This evidence suggests that the treatment effect was real, as the placebo effect would be expected to wear off or remain the same in prolonged trials. This study demonstrates the positive effect of acupuncture treatment for patients with PAR. Compared to sham acupuncture, acupuncture showed a greater improvement on the symptoms of allergic rhinitis than sublingual immunotherapy (32). Also, acupuncture showed a larger effect than Chinese herbal medicine when compared to the waitlist group (33).

The sham acupuncture group exhibited a significant reduction in AR symptoms compared with baseline, and this was true even when the acupuncture was applied to nonacupuncture points without manual stimulation. The observed reduction in symptoms in the sham acupuncture group may have been caused either by the effect of sham acupuncture itself or through a placebo effect. Sham acupuncture has been reported to potentially evoke a physiological response, which may have had some therapeutic effect. This effect of sham acupuncture could lead to a false-negative result in clinical trials when evaluating the effect of acupuncture (34, 35). In this study, sham acupuncture treatment possessed several factors that could evoke a physiological response, such as the minimal puncture, the chosen acupuncture points, and the pressure on the skin. In addition, the effect of sham acupuncture might be caused by nonspecific effects of the procedure, including the contact with doctors, patient expectations, and the Hawthorne effect. These factors could positively affect participant symptoms. Thus, further studies are required to investigate which factors are responsible for positive outcomes.

The period of acupuncture treatment required for therapeutic improvement may differ based on the treatment frequency, the number of prior treatments, the presence of disease, and the patient lifestyle. However, estimating the treatment period required for a therapeutic effect is important (even if only a rough estimate can be made) to maximize symptom improvement in the clinic or to assess the effect of acupuncture in clinical trials. In many clinical trials of AR, the duration of acupuncture treatment was 4 weeks or more (21, 22, 24, 36). In this study, the acupuncture group exhibited greater nasal and non-nasal symptom improvements compared with the sham acupuncture and waitlist groups after 4 weeks of acupuncture treatment. Thus, it appears that acupuncture treatment should be conducted for at least 4 weeks in order to improve the symptoms of PAR. However, more rigorous trials are needed to determine the appropriate treatment duration for the greatest efficacy of acupuncture for PAR.

The finding that the effect of acupuncture on PAR persisted for more than 4 weeks after the final acupuncture treatment is meaningful to clinicians and investigators, as a clinical practitioner could use these results to more accurately determine the optimal frequency of acupuncture sessions for PAR treatment. In addition, the results of this study could be useful for determining the washout period in acupuncture clinical trials. However, additional studies with longer follow-up periods are needed to evaluate the duration of the effect of acupuncture treatment.

Five participants enrolled in the current study were found to have been taking prohibited medications. All participants were asked to report all medication use; however, some participants may have not properly reported their medication use due to a misunderstanding or unfamiliarity with the name of a medication. Therefore, investigators should ask participants about medication use with easy-to-understand questions. In addition, investigators could verify medication use by contacting another source, such as a family member or the local hospital that dispensed the medication, if a participant is unable to provide adequate information.

In this trial, serious adverse events were limited to one case, and the symptoms appeared to be unrelated to the acupuncture treatment. All other adverse events reported in this study were mild and transient. Because these adverse events

were limited and mild, acupuncture treatment for allergy rhinitis appears to be safe.

Conclusions

This study showed a significant reduction in the symptoms of persistent allergic rhinitis after acupuncture treatment compared to sham acupuncture or no treatment. The results suggest that acupuncture might be an effective and safe treatment for controlling the symptoms of allergic rhinitis.

Acknowledgments

This study was supported by the Korea Institute of Oriental Medicine (K09020). We thank Kwon-Eui Hong of Daejeon University and all of the staff of the Korea Institute of Oriental Medicine, Kyung-Hee University, Guang'anmen Hospital, and Dongzhimen Hospital for their valuable help and advice. We also thank China Academy of Chinese Medical Science for giving support to design and monitor the clinical trial during the study.

Author contributions

SMC and LB designed the study. HL participated in the study design, and JEP drafted the manuscript. SSL, HJJ, and MZ participated in the study as clinical research associates. THK, JUS, ZH, ZJ, and SHL participated as OMDs, and SYJ, ARK, and MSS participated as clinical research coordinators. KYK conducted the statistical analyses. All authors read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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