The Effect of Warm Acupuncture on EOS, IgE, Inflammatory Factors, and T Lymphocyte Subsets in Patients with Allergic Rhinitis of Lung Qi Deficiency and Cold-Type

**Original Research**

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**Abstract**

Objective • The purpose of this study was to investigate the effects of warming needle therapy on eosinophils, specific immunoglobulin E (IgE), inflammatory factors, and T lymphocyte subsets in patients with lung qi deficiency and cold-type allergic rhinitis (AR).

Methods • A total of 155 patients with lung qi deficiency and cold-type AR from May 2021 to December 2022 were randomly divided into a study group of 76 cases and a control group of 79 cases. The control group received medication (chlorpheniramine and fluticasone), and the study group received medication combined with warming needle therapy. The efficacy, TCM syndrome score, eosinophils, IgE, inflammatory factors (interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α)), T lymphocyte subsets (CD3+, CD4+, and CD8+), and rhinoconjunctivitis quality of life questionnaire (RQLQ) scores were evaluated after 2 weeks of treatment.

Results • The total effective rate in the study group was 92.11%, which was higher than that in the control group (77.22%) \( (P < .05) \). The TCM syndrome scores of the study group were lower than those of the control group after 1 and 2 weeks of treatment \( (P < .05) \). The positive rate of eosinophils in the study group was lower than that in the control group after 1 week \( (47.37\% \text{ vs. } 64.56\%, P < .05) \) and after 2 weeks \( (21.05\% \text{ vs. } 37.97\%, P < .05) \) of treatment. The serum levels of specific IgE, IL-6, IL-8, and TNF-α in the study group were lower than those in the control group after 1 and 2 weeks of treatment \( (P < .05) \). The peripheral blood levels of CD3+ and CD4+ were higher and the peripheral blood level of CD8+ was lower in the study group than in the control group after 1 and 2 weeks of treatment \( (P < .05) \). The RQLQ scores of the study group were lower than those of the control group after 1 and 2 weeks of treatment \( (P < .05) \).

Conclusion • Warming needle therapy can effectively improve the clinical symptoms of patients with lung qi deficiency and cold-type AR, reduce inflammation, and enhance immune function. (Altern Ther Health Med. [E-pub ahead of print.])

**Introduction**

Allergic rhinitis (AR) is a global health problem. According to surveys, the incidence of AR is between 11.1% and 17.6%, and it is more common in children and young adults.1 The total number of AR patients worldwide is as high as 500 million.2 The main symptoms of AR include paroxysmal sneezing, watery nasal discharge, nasal congestion, and itching, which can severely affect daily life and sleep, causing great distress.3,4 Although drug treatment for AR has good short-term efficacy, patients may still suffer relapse, since it only treats the symptoms and not the root cause.5

According to Traditional Chinese Medicine (TCM), AR belongs to the category of “nasal congestion,” with lung qi deficiency and coldness being the most common type. The pathogenesis is due to insufficient lung qi in the body, failure to fix the defense system, internal coldness, invasion of wind-cold evil, binding of cold evil in the skin and hair, lack of yang qi to dissipate, failure to ventilate lung qi, sudden stopping of body fluid, and development of nasal congestion.

In recent years, acupuncture has been shown to have unique advantages in treating diseases such as asthma,6 rhinitis,7 and cough,8 with good effects and wide popularity. Compared to conventional acupuncture, warm needle therapy adds moxa cones to the needle tail, with a dual effect of acupuncture and moxibustion, which can warm the...
meridians and collaterals, promote qi circulation and blood circulation, dispel coldness and dredge the meridians, and have remarkable efficacy. However, there is currently limited research on the use of warm needle therapy specifically for lung qi deficiency and cold-type AR. Therefore, this study aims to explore the potential benefits and outcomes of warm needle therapy in treating this particular subtype of AR. The results of this study could contribute to the development of more effective and holistic treatment approaches for AR, providing valuable insights into the efficacy of warm needle therapy and its role in managing this common condition.

**METHODS**

**Study population**

We selected patients diagnosed with lung qi deficiency and cold-dominant type AR who were treated at our hospital from May 2021 to December 2022 as the study population. A total of 160 patients were enrolled, and they were randomly divided into two groups using a random number table: the study group (n = 80) and the control group (n = 80). The study was completed by 155 patients (lost to follow-up: 5), including 76 patients in the study group (lost to follow-up: 4) and 79 patients in the control group (lost to follow-up: 1). The study was approved by the hospital ethics committee, and all participants provided written informed consent. In the study group, there were 44 males and 36 females, with an age range of 18 to 57 years and a mean age of (37.69 ± 6.53) years. The duration of the disease ranged from 3 months to 9 years, with a mean duration of (4.61 ± 1.48) years. The severity of the disease was mild in 23 cases, moderate in 43 cases, and severe in 15 cases. In the control group, there were 42 males and 38 females, with an age range of 20 to 59 years and a mean age of (39.42 ± 6.68) years. The duration of the disease ranged from 4 months to 8 years, with a mean duration of (4.35 ± 1.52) years. The severity of the disease was mild in 20 cases, moderate in 41 cases, and severe in 13 cases. See Table 1. There were no statistically significant differences in the general data between the two groups (P >0.05).

**Diagnostic criteria**

**Western medicine diagnostic criteria.** According to the “Diagnosis and Treatment Guidelines for Allergic Rhinitis,” the typical symptoms of AR, such as paroxysmal sneezing, rhinorrhea, and nasal congestion, occur for more than 1 hour per day. Patients have a clear history of allergies to pollen, dust mites, animal dander, etc. At least one allergen test is positive: positive skin prick test or serum-specific IgE level > 350 U/L.

**TCM diagnostic criteria.** According to the diagnostic criteria for nasal obstruction in “Chinese Medical Diagnosis,” the TCM diagnosis of the study population is lung qi deficiency and cold-dominant type. The clinical manifestations include itchy nose, sneezing, clear and watery nasal discharge, nasal congestion, and easy recurrence of symptoms after exposure to sudden changes in climate or cold weather. The tongue is pale and swollen with a thin white coating, and the pulse is deep and thin.

**Table 1. Comparison of Clinical Baseline Data**

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Females</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Age(years)</td>
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<td></td>
</tr>
<tr>
<td>Range</td>
<td>18-57</td>
<td>20-59</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37.69 ± 6.53</td>
<td>39.42 ± 6.68</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3 months - 9 years</td>
<td>4 months - 8 years</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.61 ± 1.48</td>
<td>4.35 ± 1.52</td>
</tr>
<tr>
<td>Disease Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Moderate</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Severe</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

**Inclusion and Exclusion Criteria**

**Inclusion criteria.** Patients who met the diagnostic criteria for allergic rhinitis, were diagnosed with lung qi deficiency and cold syndrome according to TCM, were aged ≥18 years, and had a disease course of ≥3 months.

**Exclusion criteria.** Patients who had respiratory system diseases such as asthma, bronchitis, or tuberculosis, nasal septal deviation, nasal polyps, nasal trauma, or a history of surgery on the nose, mouth, or throat; patients with cardiovascular and cerebrovascular diseases, liver or kidney dysfunction, or coagulation disorders; patients who had received anti-allergic medication treatment within the past month; patients who had contraindications for warming needle therapy, such as fever, infection, or a history of epilepsy; patients with dementia or a history of mental illness; and pregnant women.

**Methods**

**Control group.** Drug treatment was given, including oral administration of desloratadine dispersible tablets (H20040972, Hainan Puli Pharmaceutical Co., Ltd., 5 mg per dose, once daily) and intranasal administration of fluticasone propionate nasal spray (H20010780, Jiangxi Zhenshiming Pharmaceutical Co., Ltd., 6 ml:6.6 mg per bottle, 2 sprays per nostril, once daily). A course of treatment consisted of 7 days, with 2 courses in total.

**Study group.** Acupuncture combined with drug treatment was given. The drug dosage and method were the same as those in the control group. Acupuncture was performed using a 1-inch sterile disposable needle (No. 30). The acupoints included Yintang (between the eyebrows), Baihui (at the vertex), Taiyang (at the temples), Yingxiang (at the junction of the lower edge of the nasal septum and the lateral nasal cartilage), Fengchi (at the midpoint of the outer edge of the nostrils), Shangyingxiang (at the junction of the lower edge of the nasal septum and the lateral nasal cartilage), Fengchi (at the midpoint of the line connecting the upper ends of the sternocleidomastoid and trapezius muscles), and Hegu (at the midpoint of the second metacarpal bone on the radial side). After disinfecting the skin with alcohol, the needle was inserted horizontally to a depth of 0.3 to 0.5 inches and manipulated with reinforcing and reducing techniques until...
the patient felt soreness, distension, and a sense of obtaining qi. A 2 cm long piece of moxa stick was attached to the handle of the needle, ignited, and retained for 20 minutes. Acupuncture plus moxibustion was performed once daily for 7 days, with 2 courses in total.

Evaluation of Therapeutic Efficacy

The efficacy was evaluated after 2 weeks of treatment. The criteria for efficacy assessment were as follows: Marked improvement: the symptoms such as sneezing, runny nose, and nasal congestion basically disappeared, and the TCM syndrome score was reduced by ≥80%. Effective: the related symptoms were significantly reduced, and the TCM syndrome score was reduced by 30%~79%. Ineffective: the related symptoms did not improve or even worsened, and the TCM syndrome score was reduced by <30%. The total effective rate was calculated as \([[(\text{marked improvement} + \text{effective})/\text{total cases}] \times 100\%]\). The TCM syndrome score: (1) Sneezing: 0 points represented no symptoms; 1 point represented mild symptoms, with 1-4 sneezes each time; 2 points represented moderate symptoms, with 5-9 sneezes each time; 3 points represented severe symptoms, with ≥10 sneezes each time. (2) Runny nose: 0 points represented no symptoms; 1 point represented mild symptoms, with less than 4 times of runny nose per day; 2 points represented moderate symptoms, with 5-9 times of runny nose per day; 3 points represented severe symptoms, which affected daily life and sleep with more than 10 times of runny nose per day. (3) Nasal itching: 0 points represented no symptoms; 1 point represented intermittent nasal itching; 2 points represented frequent nasal itching; 3 points represented severe nasal itching, which affected daily life and sleep. (4) Nasal congestion: 0 points represented no symptoms; 1 point represented mild nasal congestion with a feeling of nasal congestion during breathing; 2 points represented moderate nasal congestion, with intermittent nasal congestion; 3 points represented severe nasal congestion, requiring mouth breathing, which affected daily life and sleep. (5) Changes in the nasal cavity: 0 points represented no symptoms; 1 point represented slight swelling of the nasal turbinates and nasal septum; 2 points represented obvious swelling of the nasal turbinates and nasal septum with only a small gap remaining; 3 points represented severe swelling of the nasal turbinates and nasal septum with no gap between them, and the presence of nasal polyps.

Outcome Measures

Eosinophils (EOS). Before treatment, at 1 week, and at 2 weeks after treatment, nasal secretions were collected, slides were made, and the EOS count was observed under a microscope after staining with hematoxylin-eosin.

Serum-specific immunoglobulin E (IgE). Before treatment, at 1 week, and at 2 weeks after treatment, 5 mL of venous blood was collected from patients, the serum was separated by centrifugation, and the specific IgE level was detected using electrochemiluminescence immunoassay. The detection instrument was the 180SE chemiluminescence analyzer (Bayer AG).

Serum inflammatory factors. Before treatment, at 1 week, and at 2 weeks after treatment, 5 mL of venous blood was collected from patients, the serum was separated by centrifugation, and the levels of IL-6, IL-8, and TNF-α were detected using fluorescence immunoassay. The detection instrument was the AFS-1000 fluorescence immunoanalyzer (Beckman Coulter), and the reagent kit was purchased from Xiamen Oude Biotechnology Co., Ltd.

T lymphocyte subsets. Before treatment, at 1 week, and at 2 weeks after treatment, peripheral venous blood was collected from patients with heparin anticoagulation, and the levels of CD3+, CD4+, and CD8+ were detected. The detection instrument was the Attune NxT flow cytometer (Thermo Fisher Scientific), and the reagent kit was purchased from Zhejiang Bioscience Co., Ltd.

Quality of life. Before treatment, at 1 week, and at 2 weeks after treatment, the rhinoconjunctivitis quality of life questionnaire (RQLQ) was completed. The RQLQ questionnaire includes 7 dimensions, namely activity (3 items), sleep (3 items), nasal symptoms (7 items), eye symptoms (3 items), non-nasal and non-eye symptoms (4 items), practical problems (4 items), and emotional function (4 items), for a total of 28 items. Each item was scored from 0 to 6, where 0 indicated no bother, 1 indicated almost no bother, 2 indicated some bother, 3 indicated moderate bother, 4 indicated a lot of bother, 5 indicated very much bother, and 6 indicated extreme bother.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Normally distributed continuous data were expressed as mean ± standard deviation (\(\bar{x} \pm s\)), and repeated measures analysis of variance was used with pairwise comparisons which were analyzed using the SNK-t test. Count data were expressed as a percentage (%) and analyzed using the chi-square test. A \(P<.05\) was considered statistically significant.

RESULTS

Comparison of efficacy between two groups

The overall response rate in the study group was 92.11%, higher than 77.22% in the control group, and the difference was statistically significant \((P<.05)\), as shown in Table 2.

Table 2. Comparison of Efficacy Between the Two Groups [Case (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Invalid</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>76</td>
<td>39 (51.32)</td>
<td>31 (40.79)</td>
<td>6 (7.89)</td>
<td>70 (92.11)</td>
</tr>
<tr>
<td>Control group</td>
<td>79</td>
<td>27 (34.18)</td>
<td>34 (43.04)</td>
<td>18 (22.78)</td>
<td>61 (77.22)</td>
</tr>
<tr>
<td>(\chi^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.563</td>
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<tr>
<td>(P) value</td>
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<td>.010</td>
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</tbody>
</table>

Sun—Warm Acupuncture for Allergic Rhinitis
Comparison of TCM syndrome scores between the two groups before and after the treatment

TCM syndrome scores before and after treatment in both groups were statistically significant between groups, time, and interaction action ($P<.05$). Comparison between groups: there was no significant difference in TCM syndrome scores before treatment between the study group and the control group ($P>.05$); the TCM syndrome scores of the study group after 1 week and 2 weeks of treatment were lower than those of the control group ($P<.05$). Time comparison: TCM syndrome scores showed a decreasing trend after 1 and 2 weeks of treatment, which were lower than those before treatment ($P<.05$), as shown in Table 3.

Comparison of the positive rate of EOS in the nasal secretion between the two groups before and after the treatment

Before treatment, the positive rate of EOS in nasal secretion was 89.47% in the study group and 91.14% in the control group, and the difference was not statistically significant ($P>.05$). After 1 week and 2 weeks of treatment, the positive rate of EOS in nasal secretions showed a decreasing trend in both the study group and the control group ($P<0.05$), and the positive rate of EOS in the study group was 47.37% after 1 week of treatment which was lower than 64.56% in the control group ($P<.05$); The positive rate of EOS in the study group 21.05% was lower than that in the control group 37.97% after 2 weeks of treatment ($P<.05$), as shown in Table 4.

Comparison of serum-specific IgE levels between the two groups before and after the treatment

Serum-specific IgE levels before and after treatment in both groups were statistically significant between groups, time, and interaction effect ($P<.05$). Comparison between groups: there was no significant difference in serum-specific IgE level before treatment between the study group and the control group ($P>.05$); serum-specific IgE levels were lower in the study group than in the control group after both 1 week and 2 weeks of treatment ($P<.05$). Time comparison: Serum-specific IgE levels showed a tendency to decrease after 1 and 2 weeks of treatment, and the levels were lower than those before treatment ($P<.05$), as shown in Table 5.
the study group and the control group (P > .05); levels of CD3+ and CD4+ in peripheral blood after 1 week and 2 weeks of treatment were higher in the study group than in the control group while the CD8+ levels in peripheral blood of study group were lower than in controls (P < .05). Time comparison: After 1 and 2 weeks of treatment, the levels of CD3+ and CD4+ in peripheral blood showed a tendency to increase, and the levels were higher than those before treatment (P < .05); CD8+ levels in peripheral blood tended to decrease and the levels were lower than the pre-treatment levels (P < .05), as shown in Table 7.

Comparison of quality of life between the two groups before and after the treatment

The RQLQ scores before and after treatment in both groups were statistically significant between groups, time, and interaction effect (P < .05). Comparison between groups: there was no significant difference in RQLQ score between the study group and the control group before treatment (P > .05); after 1 week and 2 weeks of treatment, the RQLQ scores of the study group were lower than those of the control group (P < .05). Time comparison: The RQLQ scores showed a tendency to decrease after 1 and 2 weeks of treatment, both scores were lower than the pre-treatment score (P < .05), as shown in Table 8.

Adverse Reactions

During treatment, the study group recorded the experience of nausea in 2 patients, dry mouth in 1 patient, somnolence and drowsiness in 1 patient, and dizziness and headache in 1 patient, with the total adverse reactions in 5 patients (6.58%). In the control group, nausea occurred in 1 patient, and dizziness and headache in 1 patient, and somnolence and drowsiness in 1 patient, with the total adverse reactions in 3 patients (4.01%). There was no significant difference in the overall adverse reaction rate between the two groups (P > .05).

DISCUSSION

In TCM, the most common mechanism of AR is lung qi deficiency and coldness. The lung is the “huagai” and the water passage is connected to the nose, when dampness and pathogenic factors stagnate in the lung, the nasal orifice is obstructed and the protective function of the lung is compromised. Therefore, the treatment of lung qi deficiency and coldness type AR should focus on promoting lung ventilation and opening the nasal passage, as well as dispelling wind and resolving the surface. In this study, warm needling was combined with the drug therapy of...
loratadine and fluticasone propionate to treat lung qi deficiency and cold-type AR. The results showed that the total effective rate of the treatment group was higher than that of the control group. Moreover, the TCM syndrome scores and quality of life scores of the treatment group were lower than those of the control group at both 1 and 2 weeks after treatment. These findings suggest that warm needling significantly improves the therapeutic effect, reduces clinical symptoms, and enhances the quality of life in patients with lung qi deficiency and cold-type AR when used in conjunction with drug therapy.

The warming needle technique is a TCM technique that was first mentioned in the “Treatise on Cold Damage Disorders.” A circular cake made of fragrant white atractylodes is placed on the needle and burned with moxibustion. After the fine needle is inserted, the moxa stick is placed on the end of the needle, and the heat is conducted to the acupoint through the needle, producing the dual effects of acupuncture and moxibustion.

From a pharmacological perspective, the acupoints selected for warming needle therapy include the Yintang, Baihui, Taiyang, Yingxiang, Shangyangxiang, Fengchi, and Hegu acupoints. Yintang is an extraordinary acupoint outside of the meridian, and needling Yintang has the functions of improving vision, clearing the nose, calming the wind, and calming the mind. Baihui and Taiyang belong to the Du Meridian. Needling Baihui can open the orifices, tonify the lungs, solidify the exterior, and warm the yang to prevent leakage. It can treat nasal congestion. Yingxiang and Shangyangxiang belong to the Hand Yangming Large Intestine Meridian and are used to treat nasal congestion, epistaxis, and nasal obstruction. They have the functions of dispelling wind-heat and unblocking the nose. Since Yingxiang and Shangyangxiang are located beside the nose, needling these acupoints can directly stimulate the nose, making them particularly effective for promoting the flow of channels and collaterals and unblocking the nose. Fengchi belongs to the Foot Shaoyang Gallbladder Meridian and is used to treat cold, nasal discharge, and epistaxis. It has the functions of tonifying yang, benefiting qi, and unblocking the orifices. The Hegu acupoint belongs to the Hand Yangming Large Intestine Meridian and has the effects of promoting clear ascending and descending turbidity, dispersing wind and releasing the surface, and promoting the flow of qi and blood. When combined with the Yingxiang acupoint, needling can treat nasal congestion and rhinorrhea, promote the opening of the lung, and tonify the skin. Additionally, after needling with filiform needles, moxibustion can be applied to produce a warming effect that stimulates the acupoint, promoting the dispersal of cold, enhancing the circulation of blood in blood vessels, and regulating the flow of qi and blood. This method is particularly effective in treating conditions characterized by sluggish blood circulation and lung qi deficiency with cold. Mugwort is warm and dispersing, aromatic and penetrating, and able to relieve surface obstruction and nasal congestion, expel wind and alleviate pain, promote the clear qi of the Yangming meridian, and treat heavy nasal obstruction and rhinorrhea. It can also expel pathogenic factors and promote the opening of the lung and the clearing of the mind.

This study found that warm needle therapy significantly reduced the positive rate of eosinophils in nasal secretions, specific IgE levels in serum, and levels of inflammatory factors IL-6, IL-8, and TNF-α in serum, as well as regulated T lymphocyte subgroups by increasing peripheral blood CD3+ and CD4+ levels while decreasing CD8+ levels in peripheral blood in patients with lung qi deficiency-cold-type allergic rhinitis. The mechanism analysis showed that in susceptible individuals, after exposure to allergens, immune-active cells such as mast cells and eosinophils are activated through IgE mediation, which releases a large amount of inflammatory mediators such as histamine and leukotrienes, causing nasal mucosal inflammatory reactions, stimulating sensory nerve endings and blood vessels, and inducing an immediate allergic reaction.10-12 In addition, inflammatory mediators can induce the secretion of adhesion molecules and chemotactic factors, unbalance Th1/Th2 immune responses, increase the dominance of Th2 immunity, aggravate the inflammatory response, cause nasal mucosal tissue swelling, and induce nasal hyper-reactivity.13 This study utilized a combination therapy of loratadine and fluticasone propionate with a warm needling technique. Loratadine is an antihistamine drug that selectively antagonizes peripheral histamine H1 receptors, thereby reducing IgE and eosinophils levels. Fluticasone propionate is a glucocorticoid with anti-inflammatory, anti-allergic, and vasoconstrictive effects, which can lower serum levels of inflammatory cytokines IL-6, IL-8, and TNF-α, regulate T lymphocyte subgroups, and alleviate immune inflammatory responses.14 Modern acupuncture research has also found that thermal stimulation through warm needling can enhance local blood and lymphatic circulation, reduce inflammatory exudate, and promote the immune cell re-circulation by improving lymphatic circulation, thus enhancing the immune response of Th1 cells, regulating Th1/Th2 immune balance, and reducing allergic reactions.15,16

It is important to acknowledge the limitations of this study. Firstly, the study duration was relatively short, with a treatment period of only 2 weeks. The long-term effects and sustainability of the observed benefits are yet to be determined. Additionally, the study did not include a follow-up assessment to evaluate the long-term outcomes. Moreover, the study lacked a placebo control group, which could have provided a better comparison for the effectiveness of warming needle therapy. Thus, further research with larger sample sizes, longer follow-up periods, and rigorous control groups is needed to validate and generalize the findings of this study.

CONCLUSION

In summary, warm needle therapy can effectively improve the clinical symptoms of patients with lung qi deficiency and cold-type allergic rhinitis, reduce inflammatory reactions, enhance immune function, and achieve good
therapeutic outcomes with rapid effect. This study also has some limitations, such as a small sample size and a lack of long-term follow-up and recurrence data. Future large-scale, prospective, and multicenter trials can help to verify the long-term efficacy of moxibustion therapy.

FUNDING
This study was supported by the Science and Technology Development Program of Traditional Chinese Medicine Administration of Jiangsu Province, No.YB2020073.

AUTHOR DISCLOSURE STATEMENT
The authors have no potential conflicts of interest to report relevant to this article.

ACKNOWLEDGEMENT
DS and MJ contributed equally to this work. DS, MJ, and YW designed the study and performed the experiments; ML and XM collected the data; ML, XM, and GS analyzed the data; and DS, MJ, and YW prepared the manuscript. All authors read and approved the final manuscript.

REFERENCES