Clinical Trial/Experimental Study

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Effect of oral Xiao-xian decoction combined with acupoint application therapy on pediatric adenoid hypertrophy

A randomized trial

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Abstract

Background: This study aimed to observe the clinical effects of Xiao-xian decoction combined with acupoint application therapy (AAT) for treating pediatric adenoid hypertrophy (AH).

Methods: We randomly divided 93 AH children into 3 groups: AAT alone; Xiao-xian decoction + AAT; control: Montelukast oral therapy. All participants were treated for a month. We used the traditional Chinese medicine syndrome score to evaluate the clinical efficacy and the obstructive sleep apnea-18 scale to evaluate the quality of life.

Results: The major symptoms (nasal congestion, open mouth breathing, snoring, and tongue image) and secondary symptoms of patients treated with Xiao-xian decoction + AAT significantly improved compared to before treatment. The pairwise comparison between groups showed that snoring, tongue, secondary symptoms, and total effective rate of the combined treatment group were better than the control and AAT alone. Additionally, the open-mouth breathing, quality of life, and recurrence rate did not differ after treatment.

Conclusion: Oral Xiao-xian decoction combined with AAT significantly improved the symptoms and signs of nasal congestion, open-mouth breathing, snoring, tongue, and quality of life of AH children and may be used as a long-term treatment for AH.

Abbreviations: AAT = acupoint application therapy, AH = adenoid hypertrophy, TCM = traditional Chinese medicine.

Keywords: acupoint application, adenoid hypertrophy, traditional Chinese medicine

1. Introduction

The adenoid is an important immune organ and a part of the pharyngeal lymphatic ring. It is also the upper respiratory tract first line of defense against infectious diseases.[1] Adenoid hypertrophy (AH) is a common childhood disorder often leading to clinical symptoms such as nasal obstruction, snoring, and serious complications, including obstructive sleep apnea and sudden infant death syndrome.[2] Additionally, AH adversely affects jaw development and abnormal occlusal relationship with the front incisor in children.[3,4] Therefore, children should be treated for AH before receiving orthodontic treatment since it affects children growth and development and seriously decreases their quality of life. AH incidence has increased yearly, ranging from 9.9% to 29.9%.[5] Although AH etiology and pathogenesis are uncertain, it might be closely related to infections, allergies, immunity, and other factors.

Currently, AH is mostly treated with surgery or drugs. Although surgery is quick and effective, it often has complications such as bleeding, throat spasms, coughing, restlessness, and even asphyxia. Regarding drug treatments, the clinical efficacy of traditional nasal spray hormone and montelukast sodium has been demonstrated, but it is limited and associated with some side effects.[6–9]

Traditional Chinese medicine (TCM) has provided new ideas and methods for AH treatment.[10–12] Oral Chinese herbal

Written informed consent for publication were obtained from patients.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethic Committee of the Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine (protocol code 2020-74 and date of approval 2020/01/22). Written informed consent was obtained from all individual participants and from the legally authorized representatives or from the guardians for minors in the study.

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medicine combined with external treatment is a unique TCM method. Acupoint application therapy (AAT) is 1 of the most commonly used external treatments for AH. AAT comprises direct acupoint application for treatment through acupoint drug absorption with good safety and without damaging the gastrointestinal tract. In TCM, AH belongs to the "phlegm nucleus "and "snoring sleep" categories. This disease is described in the ancient books "Miraculous Pivot (Ling Shu)" and "General Treatise on Causes and Manifestations of All Diseases (Zhu Bing Yuan Hou Lun)." "Danxi Xinfa Fuyu" believes that phlegm nucleus block is 1 of the main pathogenic factors leading to AH. Our clinical work has also shown that AH is more common with phlegmatic qi stagnation syndrome. AH patients usually present nasal congestion and body fat for a long time. Given these characteristics, we used a prescription with the phlegm, qi, and blood stasis Xiao-xian decoction, in which Fritillaria thunberegii dispels phlegm and reduces blood stasis; wood fragrance benefits the qi and invigorates the spleen, pinellia dryness, and dampness reduces phlegm; tangerine peel dredges stagnation; Aurantii Fructus dissipates the qi and dampness; Poria cocos supplements the spleen and dissipates dampness. Additionally, paeony softens the liver and spleen, and forsythia disperses phlegm and dampness, clearing heat and removing blood stasis. Besides, Trichinus curcuma and Curcuma curcuma regulate blood circulation, and licorice combines many medications to reduce side effects.

Additionally, we selected the Tianrong and Lianquan points as sticking acupoints. The Tianrong point regulates throat channels and collars, dredges the liver, regulates the qi, and removes dampness and phlegm. The Lianquan point benefits tongue and throat moistening.

The clinical efficacy of oral Chinese herbal medicine or AAT alone for AH has been reported in China,[13,14] but not their combination. Therefore, we hypothesized that oral Chinese herbal medicine combined with AAT for AH treatment would present better clinical efficacy than each strategy alone. To test this hypothesis, we designed a randomized clinical trial with 93 AH patients divided into 3 groups: AAT alone, oral Chinese medicine combined with AAT, and drug therapy alone.

2. Materials and methods

2.1. Study design and participants

This study was a prospective randomized clinical trial conducted in the pediatric outpatient and inpatient department of the second affiliated Hospital of Shandong University of Traditional Chinese Medicine from March 2020 to January 2021. Before beginning this study, all participants signed the informed consent following the Helsinki Declaration, good clinical practice, and applicable laws and regulations. The Ethics Committee of the second affiliated Hospital of Shandong University of

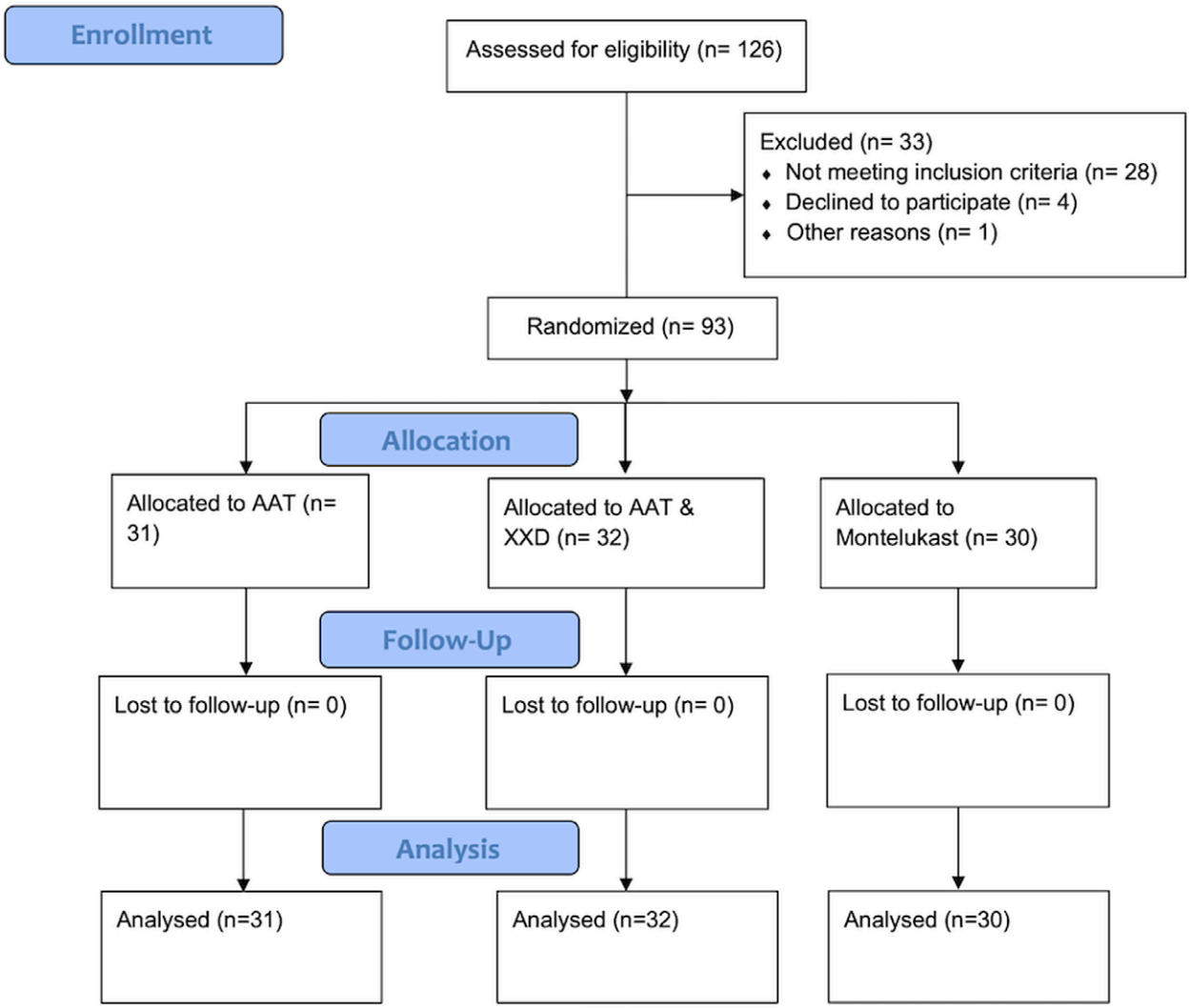

Figure 1. Flow diagram of the study participants. AAT = acupoint application therapy, XXD = xiao-xian decotion.

Traditional Chinese Medicine approved this study. Eligible subjects were randomly divided into 3 groups: AAT once a day for 8 to 10 hours for 1 month. Oral Xiao-xian decoction plus AAT for 1 month (depending on age). The AAT was for the same groups 1 and 2; Control: oral montelukast sodium 4 to 5 mg per day (depending on age) for 1 month. The 3 groups were followed up for the first 2 weeks, then after 1 month, and 6 months after the end of treatment.

The inclusion criteria were: patients who met the AH diagnosis criteria; patients between 2 and 9 years; patients who voluntarily cooperated with the treatment according to the course of treatment; their legal guardian signed the informed consent. The exclusion criteria were: patients who underwent adenoidectomy and/or tonsillectomy; patients with diseases that cause nasal obstruction, such as nasal polyps and deviated nasal septum; patients with blood, endocrine, genetic metabolic, and other diseases; patients who were on hormones or other drugs.

Finally, we enrolled 93 AH children (Fig. 1). All patients had typical clinical manifestations of nasal congestion, mouth breathing, and nocturnal snoring. Symptoms were also accompanied by sinusitis, rhinitis, and secretory otitis media, often with palatine tonsil hypertrophy, inattention, unresponsiveness, malnutrition, stunting, and adenoid appearance.

2.2. Randomization

Participants were randomly and equally (1:1:1) assigned to groups 1, 2, and 3 using a computerized digital table. The job was saved in a sealed opaque envelope and opened by an independent party participating in the participant selection. Group 1 had 31 children, group 2 had 32, and group 3 had 30.

2.3. Interventions

2.3.1. AAT. The acupoint application formula was composed of the following TCM components: Fritillaria thunberegii (9 g), Aucklandia lappa (6 g), Arisaema cure bile (6 g), Pinellia ternata (6 g), Semen citri peticulatae (6 g), Fructus aurantil (6 g), Radix paeoniae alba (6 g), Poria cocos (9 g), Forsythia suspensa (9 g), Sparganium stoloniferum (9 g), Rhizoma curcumae (9 g), and Licorice (3 g). All herbal medicines come from decompressed granules produced by Guangdong YiFang manufacturers. First, we ground them into a fine powder and sieved them with 100 mesh. Then we added honey, vinegar, liquid paraffin, and azone for application. We applied this preparation in Tianrong (SI17) and Lianquan (RN23) acupoints (Fig. 2) during sleep for 8 to 10 hours once a day for 1 month.

2.3.2. Oral Xiao-xian decoction. The ingredients of the oral Xiao-xian decoction were the same as AAT. All herbal medicines come from decompressed granules produced by Guangdong YiFang manufacturers in China. The dosage varied according to age: 1/3 dose/day at 2 to 3 years old, 1/2 dose/day at 4 to 7 years old, 1 dose/day at 8 to 9 years old, and 1 dose/day at 8 years old. Patients orally received 50 to 100mL in boiled water twice a day for 3 days and stopped for 1 day. The treatment lasted for 1 month.

2.3.3. Oral montelukast sodium. The control group received oral montelukast sodium (Merck Sharp & Dohme Ltd.). The dosage was given according to different ages: 4 mg/day for 2 to 6 years old and 5 mg/day for 7 to 9 years old. The treatment was administered every night before bedtime for 1 month.

2.4. Outcomes

We collected data at the beginning and after the treatment period. We collected the socio-demographic and clinical data at the beginning of the study, including age, sex, scores of major and secondary symptoms before treatment, and quality of life before treatment. During the study, we asked and recorded for each group whether any drug-related adverse reactions had occurred and the corresponding treatment. We followed up with patients for 2 to 6 months after treatment and recorded the scores of major and secondary symptoms, quality of life, and recurrence of the disease, and finally evaluated the clinical efficacy was evaluated finally.

2.4.1. Major and secondary symptoms. We evaluated the changes in symptoms and signs for all patients according to the scoring TCM standard of major syndromes (Table S1, Supplemental Digital Content, http://links.lww.com/MD/I412, which illustrates the scoring criteria of major syndromes). The main symptoms included stuffy nose, open mouth breathing, snoring, and tongue picture, divided into none, mild, moderate, and severe according to severity (0, 1, 2, and 3, respectively). Secondary symptoms included discomfort in the throat, cough, runny nose, teeth grinding, restless sleep, frequent sneezing, slurred speech, occlusive snoring sounds, enlarged tonsils, and purple fingerprints (under 3 years old) or slippery pulse. Each item was scored 1 point, with a maximum of 9.

2.4.2. Quality of life. We applied the obstructive sleep apnea-18 questionnaire to assess the patient quality of life with 5 scoring symptom categories: sleep disturbance, physical condition, emotional symptoms, daytime functioning, and guardian concerns, with a total score range of 1 to 7 and a total score range of 18 to 126.

2.4.3. Clinical efficacy. We evaluated the clinical efficacy based on the sum of the scores of major and secondary symptoms, divided into 4 types: cured, markedly effective, effective, and ineffective. If the symptoms and signs disappeared or the symptom and sign scores decreased by ≥ 95%, the clinical evaluation was cured; if symptoms and signs improved with symptom and sign scores reduced by ≥ 70%, the clinical evaluation was significant; if the symptoms and signs were better than before with a reduction of symptoms and signs scores ≥ 30%, the evaluation was

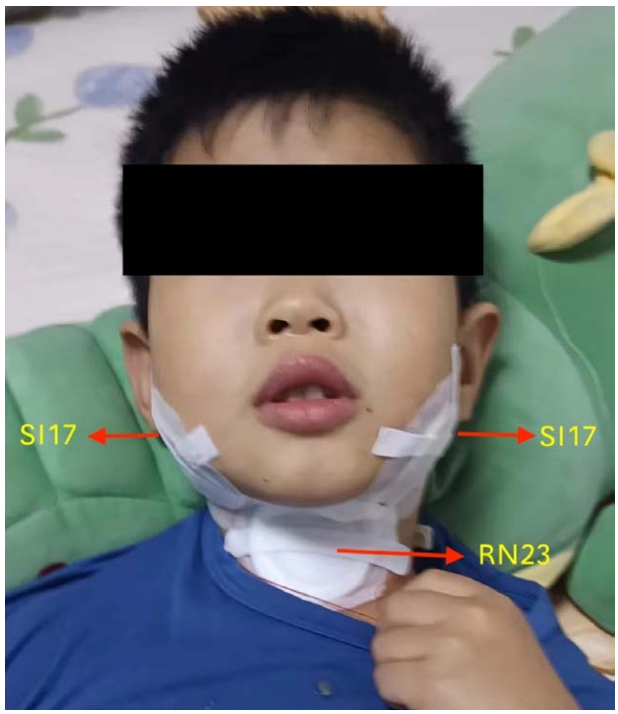

Figure 2. Sample diagram of acupoint application therapy. SI17 = Tianrong acupoint, RN23 = Lianquan acupoint.

effective; if the symptoms and signs did not significantly improve or even worsened with a decrease of < 30%, the evaluation was invalid. We used the Nimodipine method to calculate the formula: Reduction rate of symptom and sign scores = [(total symptom score before treatment - total symptom score after treatment)/total symptom score before treatment] * 100%; Total efficiency = ([total–invalid]/total) * 100%.

2.5. Statistical analysis

Statistical analyses were conducted with SPSS 20.0 (IBM SPSS Inc., Chicago, IL). Measurement data are expressed as means ± standard deviations, and non-parametric tests were used for intra- and inter-group comparisons before and after treatment. The χ^2 test was used for count data. A $P < .05$ was considered statistically significant for intra-group comparisons of measurement data. A $P < .017$ was considered statistically significant for 2-way comparisons between 3 groups for measurement and count data.

3. Results

We enrolled 93 patients and randomized them into 3 groups according to the different treatments. The 3 groups did not differ in age, gender, pre-intervention symptom scores, and quality of life scores (Table 1).

3.1. Major and secondary symptoms

After the intervention, the nasal congestion, mouth breathing, snoring, and secondary symptoms significantly improved in the 3 groups compared to before treatment ($P < .05$, Table 2 and Fig. 3). The tongue of groups 1 and 2 was significantly better after intervention than before ($P < .05$), but not in the control group ($P = .058$). After the intervention, the 3 groups differ for open-mouth breathing ($P = .006$), snoring ($P = .008$), tongue ($P < .0001$), and secondary symptoms ($P = .0014$). However, the nasal congestion did not differ among the 3 groups after intervention ($P = .901$).

The inter-group comparisons showed that group 2 was better than group 1 in mouth-opening breathing ($P < .003$), snoring ($P < .013$), tongue ($P < .009$), and secondary symptoms ($P < .010$). The 2 groups presented better snoring ($P = .008$), tongue ($P = .008$), and secondary symptoms ($P = .012$) than the control group but did not differ in open-mouth breathing ($P = .655$). (Table 2 and Fig. 4).

3.2. Quality of life

The quality of life of the 3 groups was significantly better after the intervention than before ($P < .05$). The quality of life score significantly differed among the 3 groups after intervention ($P = .004$). The intergroup comparison showed that the quality of life after intervention in group 2 ($P = .003$) and the control ($P = .004$) was significantly better than in group 1. Meanwhile, group 2 and control did not differ ($P = .655$). (Table 3 and Fig. 5)

3.3. Clinical efficacy

The total effective rate significantly differed between the 3 groups ($P < .05$). The total effective rate of group 2 was significantly higher than group 1 ($P = .009$) and the control group ($P = .014$). Meanwhile, the total effective rate between group 1

Table 1

Comparison of baseline characteristics among 3 groups.

		Group 1 (n = 31)	Group 2 (n = 32)	Group 3 (n = 30)	*P* value
Age (yr)					
2–4.5		11	9	10	.938
4.6–7		14	14	13	
8–9		6	9	7	
Gender					
male		18	19	19	.909
female		13	13	11	
Major symptom score	Nasal congestion	1.65 ± 0.93	1.63 ± 0.65	1.67 ± 0.65	.914
	Open-mouth breathing	1.48 ± 0.80	1.56 ± 0.79	1.57 ± 0.72	.933
	Snoring	1.81 ± 0.96	1.88 ± 0.86	1.87 ± 0.92	.975
	Tongue	1.84 ± 0.81	1.88 ± 0.86	1.83 ± 0.82	.976
Secondary symptom score		3.03 ± 1.05	3.00 ± 0.87	2.87 ± 0.83	.785
OSA-18		68.03 ± 6.32	69.56 ± 6.49	67.43 ± 7.53	.548

OSA = obstructive sleep apnea.

Table 2

Comparison of major and secondary symptom scores among 3 groups.

	Major symptom score								Secondary symptom score	
	Nasal congestion		Open-mouth breathing		Snoring		Tongue			
	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)
Group 1	1.65 ± 0.93	0.61 ± 0.75*	1.48 ± 0.80	1.09 ± 0.86*	1.81 ± 0.96	0.90 ± 0.73*	1.84 ± 0.81	0.94 ± 0.88*,b	3.03 ± 1.05	1.17 ± 0.73*
Group 2	1.63 ± 0.65	0.50 ± 0.61*	1.56 ± 0.79	0.47 ± 0.56*,a	1.88 ± 0.86	0.38 ± 0.60*,a,b	1.88 ± 0.86	0.41 ± 0.61*,a,b	3.00 ± 0.87	0.72 ± 0.62*,a,b
Group 3	1.67 ± 0.65	0.57 ± 0.67*	1.57 ± 0.72	0.57 ± 0.67*,a	1.87 ± 0.92	1.00 ± 0.82*	1.83 ± 0.82	1.57 ± 0.96	2.87 ± 0.83	1.32 ± 0.96*
P value		.901		.006		.008		<.001		.014

SD = standard deviation.

* $P < .017$ versus before intervention.

[a] $P < .017$ versus Group1.

[b] $P < .017$ versus Group3.

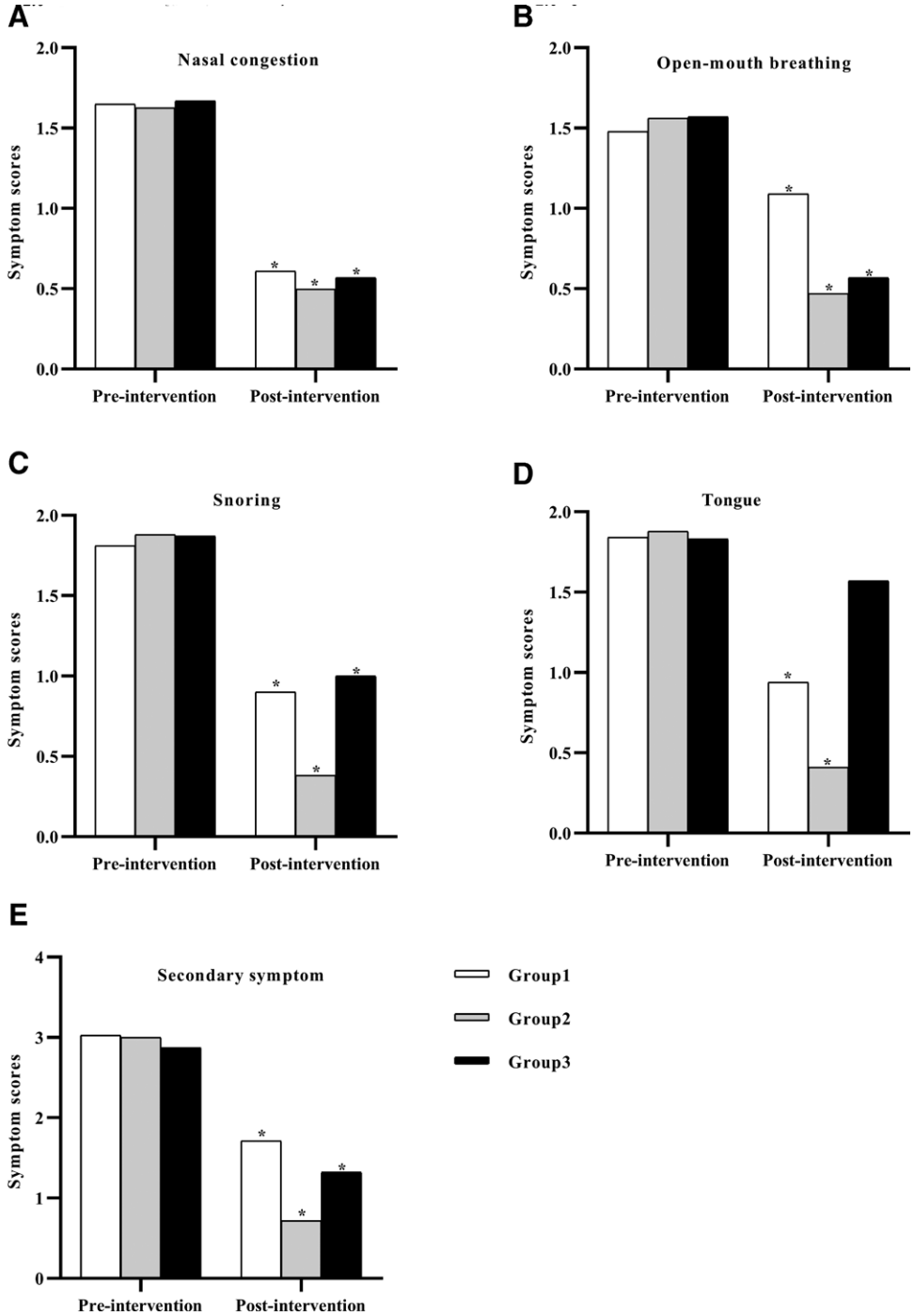

Figure 3. Comparison of symptom scores before and after intervention. A: Nasal congestion; B: Open-mouth breathing; C: Snoring; D: Tongue; E: Secondary symptoms; *: $P < .05$ versus before intervention.

and the control did not differ ($P = .849$). Twenty patients had recurrent diseases in the 3 groups, 7 in group 1, 5 in group 2, and 8 in the control group. The recurrence rate did not differ between the 3 groups ($P > .017$). (Table 4)

3.4. Adverse events

During treatment, among the 93 children, 7 cases in groups 1 and 2 had skin flushing on both sides of the neck after acupoint application, which was relieved after applying snake grease ointment. We did not detect adverse reactions such as vomiting, abdominal pain, and diarrhea in the 2 groups after oral herb medicine intervention.

4. Discussion

Herein, we explored the efficacy of oral Xiao-xian decoction combined with AAT to treat AH children. We showed that oral Xiao-xian decoction combined with AAT could effectively improve nasal congestion, open mouth breathing, snoring, tongue image, secondary symptoms, and quality of life in AH children with good clinical efficacy.

The AH incidence is high in children.[15] AH causes nasal congestion, snoring, mouth breathing, and incomplete occlusal and maxillofacial development in children, seriously affecting their physical and mental health and quality of life.[16] Surgical removal of adenoids is the most direct treatment for AH. Although surgical resection can quickly eliminate symptoms,

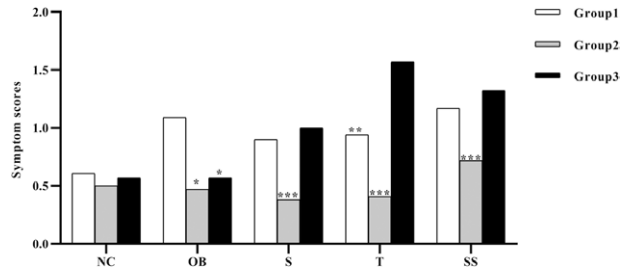

Figure 4. Comparison of symptom scores among the three groups. NC = nasal congestion, OB = open-mouth breathing, S = Snoring, T = Tongue; SS = Secondary symptoms; * $P < .017$ versus Group1; ** $P < .017$ versus Group3; *** $P < .017$ versus Group1 and Group3.

Table 3

Comparison of QoI among 3 groups.

	OSA-18 score	
	Pre-intervention (Mean ± SD)	**Post-intervention (Mean ± SD)**
Group 1	68.03 ± 6.32	59.19 ± 6.57*
Group 2	69.56 ± 6.49	53.47 ± 6.25*,a,b
Group 3	67.43 ± 7.53	58.50 ± 7.47*
P value	.548	.004

SD = standard deviation, OSA = obstructive sleep apnea.

* $P < .017$ versus before treatment.

[a] $P < .017$ versus Group1.

[b] $P < .017$ versus Group3.

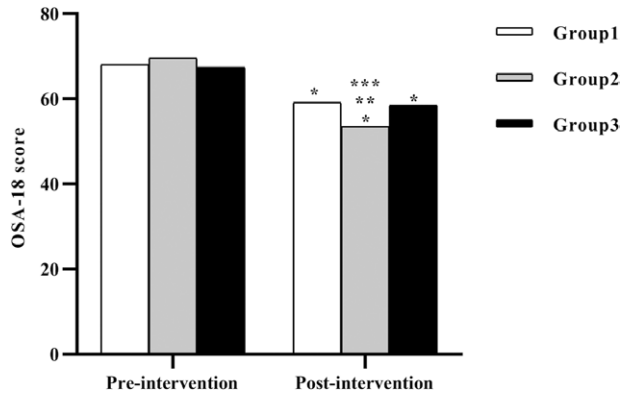

Figure 5. Comparison of OSA-18 score among the three groups. OSA = obstructive sleep apnea. * $P < .05$ versus before intervention; ** $P < .017$ versus Group1; *** $P < .017$ versus Group3.

it still has complications such as anesthesia risk and bleeding, nasopharyngeal stenosis, reduced nasal resistance,[17,18] and even immune suppression.[8,9] Therefore, non-surgical treatments are often the first choice of parents. Montelukast[19,20] and intranasal corticosteroids are important treatment options for AH. However, montelukast is associated with potential risks, including hyperactivity, sleep disorders, and depression.[8,9] At the same time, clinical studies demonstrating that intranasal glucocorticoids have a definite therapeutic effect on adenoid hypertrophy are scarce.[21,22] These shortcomings indicate the need for better treatment options for AH patients.

Internal and external treatments are important strategies in China, often combined. Many Chinese studies have also proven oral Chinese herbal medicine treatment of AH effective and safe.[10,11] AAT is a unique external TCM treatment with good immunomodulatory effects on children with asthma [23] However, there is no relevant research on TCM treatment of AH outside China. Additionally, there is still no evidence supporting the therapeutic effects of oral Chinese medicine combined with AAT.

We demonstrated that the combined treatment group was superior to AAT alone and oral montelukast sodium to improve nasal congestion, snoring tongue coating, and secondary symptoms. The combined treatment presented a total effective rate of 93.75%, significantly superior to ATT alone (67.74%) and the montelukast sodium control (70%), consistent with previous studies. For example, Wang et al[13] conducted combined therapy and oral Chinese medicine alone in 78 AH children and found that combined therapy was superior in total effective rate, symptom disappearance time, and satisfaction. Moreover, Liu et al[14] conducted a randomized controlled trial with 60 patients and found that the oral Chinese medicine group had significantly better symptom relief and total effective rate than the control nasal hormone group.

The clinical effects of combination therapy might be related to the following points: First, many TCM components in the Xiao-xian decoction have certain therapeutic effects on AH. For example, Fritillaria Thunbergii can regulate immunity through molecular targets such as ADIPOQ and related chemical pathways and have anti-inflammatory and antioxidant mechanisms to treat AH.[24] Forsythiin concentrates have anti-allergic effects.[25] Poria polysaccharide promotes lymphocyte proliferation and activation, inhibits inflammatory factors, and enhances immunity.[26] Pinellia pinellia has cough suppressant, expectorant, anti-inflammatory, and broad-spectrum antifungal effects and can stimulate the adrenal gland to release glucocorticoid and produce glucocorticoid effects.[27] Second, the direct administration effects of AAT also affect the combined treatment. Compared to Western medicine, AAT has fewer side effects and better efficacy. Previous studies have shown that AAT has good immunomodulatory effects on childhood asthma. Moreover, in vivo studies have also shown that AAT can reduce allergic inflammation by inhibiting the expression of NGF and its downstream pathways.[28] Here, we used Tianrong and Lianquan points, both empirical points for treating throat diseases, with a close anatomical location to adenoids, facilitating the drug to reach the disease site. Based on the results of this study, we recommended that oral Xiaoxian decoction combined with AAT may be a long-term treatment for AH in children.

However, our current study also has some limitations. First, we applied a short follow-up time, which might lead to some data bias. Second, due to the limitation of the outpatient imaging data, we could not compare the A/N values of each group

Table 4

Comparison of clinical efficacy and recurrence.

	Recovery (n[%])	**Marked effect (n[%])**	**Effectiveness (n[%])**	**Invalidation (n[%])**	**Total effective rate (%)**	**Recurrence (n [%])**
Group 1 (n = 31)	4 (12.90%)*	4 (12.90%)*	13 (41.94%)	10 (32.26%)*	67.74%*	7 (25.00%)
Group 2 (n = 32)	7 (21.88%)	13 (40.63%)	10 (31.25%)	2 (6.25%)	93.75%	5 (17.24%)
Group 3 (n = 30)	3 (10.00%)*	10 (33.33%)*	8 (26.67%)	9 (30.00%)*	70.00%*	8 (29.63%)

* $P < .05$ versus Group 2.

before and after treatment, lacking good imaging data support. Additionally, due to the limited sample size, we could not set an oral Chinese medicine alone group, limiting the credibility of the combined treatment efficacy.

5. Conclusion

In summary, we demonstrated that oral Xiao-xian decoction combined with AAT could effectively improve the clinical symptoms and quality of life of AH children, with good clinical efficacy, and might be a suitable long-term treatment. In the future, more large-scale prospective studies are needed to confirm the efficacy and safety of this combined therapy.

Author contributions

Conceptualization: Xue Zhao, Ming-Yue Wang, Xiao-Xia Zhang.
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Data curation: Xue Zhao, Hui-Shan Shi.
Investigation: Xue Zhao, Jie Xu.
Software: Xue Zhao, Zi-Wei Hou.
Resources: Ming-Yue Wang.
Visualization: Xue Zhao.
Writing – original draft: Xue Zhao.
Writing – review & editing: Xue Zhao, Ming-Yue Wang, Zi-Wei Hou, Xiao-Xia Zhang.

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