Original Article

Comparing the efficacy and safety of atomization of traditional Chinese medicine Kai Hou Jian and budesonide suspension in adult acute laryngitis: a randomized control trial

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Background: Kai Hou Jian has an outstanding therapeutic effect and clinical use against pharyngeal infection for many years, while a few studies reported it also had an effect in laryngitis. This study aimed to evaluate the efficacy and safety of short-course oral inhalation of traditional Chinese medicine Kai Hou Jian in adults with acute laryngitis.

Methods: A total of 86 patients with acute laryngitis who met the inclusion criteria were randomly assigned according to the random number table method into a Kai Hou Jian treatment group or a budesonide control group. Patients received 2.5 mL of Kai Hou Jian via transoral atomization twice daily for 1 week, while the control group received budesonide nebulization (1 mg, bid) for 1 week. The change of symptoms scores of acute laryngitis and laryngoscopy scores before and after treatment were performed to value the effect of Kai Hou Jian and the safety was assessed by the patient's discomfort and the incidence and self-reported adverse events during treatment.

Results: The symptoms of acute laryngitis were significantly reduced in patients treated with Kai Hou Jian on day-3. Forty-two patients from the Kai Hou Jian and 40 patients from budesonide treated groups both experienced notable clinical improvement after 1 week. There was no difference in the two groups at the baseline. For individual symptoms, Kai Hou Jian could significantly improve sore throat [95% confidence interval (CI): –1.81 to –0.14, P=0.03], while budesonide yielded better improvement in hoarseness (95% CI: 0.67 to 0.20, P=0.001). For laryngoscopic parameters, the scores of laryngeal mucosa were significantly decreased in both groups from baseline, and there were no statistical differences in vocal cord hyperemia, edema, sputum congestion, edema, mucus adhesion, or epiglottic congestion between the groups after 1 week. We also found that the treatment of Kai Hou Jian nebulization could reduce the extent or range of vocal cord leukoplakia after 1 week.

Conclusions: The short-course treatment of Kai Hou Jian atomization had significant effect in improving adult acute laryngitis and it was also possibly exhibiting a positive effect on vocal cord leukoplakia.

Trial Registration: Chinese Clinical Trial Registry identifier: ChiCTR1900026660.

Keywords: Kai Hou Jian; adult acute laryngitis; Chinese medicine; laryngoscope

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Introduction

Acute laryngitis is an acute inflammation of laryngeal mucosa caused by viral or bacterial infections. Local symptoms are mainly hoarseness, throat discomfort or pain, and cough (1). Glucocorticoids are applied in many inflammation induced health problems, and thus becoming a major treatment for acute laryngitis. Owing to its slow onset (2) and the "steroid phobia" of some patients (3), the treatment effect of glucocorticoids is sometimes not satisfactory. In recent years, the understanding of traditional Chinese medicine has broadened, and a growing number of patients are accepting the treatment using Chinese medicine. Currently, Kai Hou Jian spray is used as a common clinical medication and has shown an outstanding therapeutic effect against infection caused by bacteria such as *Candida albicans*, *Staphylococcus aureus*, and *Proteus*, while demonstrating antipyretic and analgesic effects in acute pharyngitis (4-6). Moreover, the ingredients of *Ardisia crenata* Sims (ba zhuajinlong; cultivated in Guizhou Province), *Cicadae periostracum* (chan tui), and *Sophorae tonkinensis* Radix et Rhizom (shan dougen) of Kai Hou Jian induced considerable antipyretic effect and menthol (bo henao) exerted analgesic effect. Thus, it was widely applicated to treat acute pharyngolaryngitis and herpetic angina (7,8), but for laryngitis less studies. Considering the nearby anatomical location, comparable structure, and similar pathophysiological mechanism of infection, we hypothesized that Kai Hou Jian might also have significant therapeutic effects in acute laryngitis. Meng *et al.* found that Kai Hou Jian had better effect in treating acute pharyngitis and tonsillitis than that of acute laryngitis because oral spray drugs can not reach the laryngeal mucosa well (6). In this study, in order to spray the drug fully on the surface of the lesion to maximize the therapeutic effect, we adopted the aerosol inhalation route instead of the conventional oral spray. Subjective symptom scores and laryngoscopy-based scores were used to evaluate the efficacy of Kai Hou Jian inhalation in treating acute laryngitis and. safety was assessed by the patient's discomfort and the incidence and self-reported adverse events during treatment. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4305/rc).

Methods

Patients and study design

This single-center, randomized and open-label study involved 86 patients with acute laryngitis (age 18–60 years) and they were admitted to the Otolaryngology Clinic of Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing, China, from October 2019 to March 2020. The eligible participants were randomized and divided into a Kai Hou Jian treated group and a control group of budesonide treatment. According to the random number table method, 43 patients in the Kai Hou Jian treated group received 2.5 mL of Kai Hou Jian (Guizhou Sanli Pharmaceutical Co., Ltd., Guizhou, China) via transoral aerosol inhalation for about 15 minutes/time, 2 times per day. The other 43 patients in the budesonide treated control group received 2 mL of budesonide suspension (AstraZeneca) via oral aerosol inhalation for about 15 minutes/time, 2 times per day. Patients in these two groups were monitored for 1 week. The individual acute laryngitis symptoms such as sore throat, hoarseness, foreign body sensation, and cough were assessed at baseline, on the third day and the seventh days after treatment initiation using the score scale as displayed in *Table 1*. Similarly, the laryngoscopy scores of acute laryngitis were collected before and after treatment (*Figure 1*). The adverse events of the patients were recorded and evaluated during the treatment period.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the medical ethics committee of Wangjing Hospital of the China Academy of Chinese Medical Sciences (No. WJYY-KT-2018-036-P003) and informed consent was taken from all the patients.

Diagnostic of acute laryngitis

Acute laryngitis was diagnosed according to the following criteria from the second edition of *Otolaryngology Head and Neck Surgery* (9): disease course spanning 1 week or

Table 1 Acute laryngitis symptom scoring

Symptoms	0	2	4	6
Hoarseness	None	Slight	Heavy	Completely lost voice
Sore throat	None	Slight	Severe sore throat	Severe sore throat affecting swallowing
Pharyngeal foreign body sensation	None	Slight	Heavy, persistent sensation	Persistent sensation, affecting swallowing
Cough	None	Occasional cough	Frequent cough	Frequent cough, affecting breathing

Scoring for the severity of each symptom: 0, no symptoms; 2, mild symptoms; 4, medium symptoms; and 6, severe symptoms.

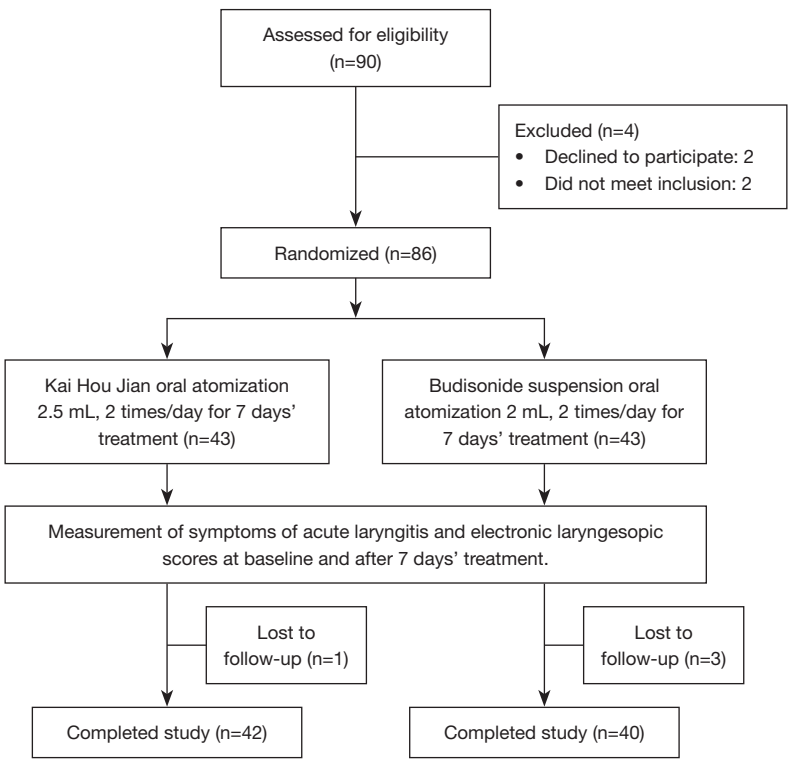

Figure 1 Study flowchart.

less; main symptoms of hoarseness, sore throat, increased pain during vocalization, dry throat and foreign body sensation, and mucopurulent secretions that are not easily expectorated; laryngoscopy showing bilateral symmetric and diffuse, inflammatory changes in the laryngeal mucosa, mucosal redness, and swelling; and glottic insufficiency during vocalization.

Inclusion criteria

Those aged between 18 and 60 years, met the aforementioned diagnostic criteria, had a course of disease of 48 hours or less, and who strictly followed the doctor's advice were included in the study.

Exclusion criteria

The exclusion criteria for patients were the following: a body temperature higher than 37 ℃; with common cold, influenza, acute tonsillitis, or pharyngeal diphtheria; abnormal liver and kidney function and other severe systemic diseases; pregnancy (defined as a positive pregnancy test); lactating or having planned to have children within the past 6 months; having received

traditional Chinese medicine or antibiotic treatment with similar efficacy to the drug in this trial within 48 hours of enrollment; being allergic to the treatment drugs; and being deemed unsuitable by the investigator to participate in the trial like patients with poor adherence, failure to follow up, or severe symptoms requiring oral or intravenous therapy.

Symptom scores

The primary outcome is symptom score. All eligible participants were asked to complete a questionnaire dealing with acute laryngitis symptoms, including throat sore, hoarseness, foreign body sensation, and cough at the baseline, on the third day and the seventh day of treatment. The severity score of each symptom was given as 0, 2, 4, or 6 (0: no symptoms; 2: mild symptoms; 4: medium symptoms and 6: severe symptoms; the specific symptoms are outlined in *Table 1*).

Laryngoscopy scores

The secondary outcome is laryngoscopy score. The electronic laryngoscopy (CV-260SL processor and CLV-260SL light source, Olympus Optical Co., Ltd., Tokyo, Japan) was performed to observe the degree of vocal cord congestion, vocal cord edema, mucosal congestion, mucosal edema, mucus adhesion, and epiglottic congestion which were scored according to the method described by professor Vaezi *et al.* (10) at the baseline and after 1 week of treatment initiation. The specific method was as follows: the severity of each sign is assessed by a 3-point system (0: normal, 1: mild, 2: severe). When patients were examined at baseline and after 1 week of treatment, 3 experienced laryngoscope operators averaged the score of patients' vocal cord congestion, vocal cord edema, mucosal congestion, mucosal edema, mucus adhesion, and epiglottic congestion according the laryngoscopy individually.

Safety assessment

The safety of treatments was assessed based on the patient's discomfort during treatment and the incidence and self-reported adverse events during treatment.

Statistical analysis

To estimate the sample size, we established the ratio of N1 (budesonide group):N2 (Kai Hou Jian group) =1:1. The pretest indicated that the mean of 2 different treatments were 7.374 and 7.677 with the standard deviation (SD) of 3.600 and 4.177, respectively. According to the following formula: $N=2\times[(u\alpha+ u\beta)^2 \sigma^2]/\delta^2$; when set $\alpha=0.05$, $\beta=0.1$, then $u\alpha=1.96$, $u\beta=1.28$, the formula$\sigma^2=S^2=(S1^2+S2^2)/2=56.656$, $\delta=X1-X2=7.677-5.374=2.303$, The required sample size was $N=N1=N2=30.09$. Additionally, 20% numbers ($30.09\times0.2=6.018$) were added for uncontrollable situations; thus, the sample size of 74 (37 in group 1 + 37 in group 2 =74) participants was needed in this study.

Continuous data are expressed as mean ± SD. The sex ratio of patients was calculated using the chi-square test. Differences between baseline values and post treatment values in the symptom scores of throat sore, hoarseness, foreign body sensation, and cough and laryngoscopy scores of patients' vocal cord congestion, vocal cord edema, mucosal congestion, mucosal edema, mucus adhesion, and epiglottic congestion for the 2 treatment groups were compared by one-way analysis of variance (ANOVA) and Bonferroni's *t* test if $P<0.05$. A value of $P<0.05$ (two-tailed) was considered statistically significant. The data of the patients (42 in Kai Hou Jian group and 40 in budesonide group) who finally completed the experiment were complete. For the missing data of a patient, we will exclude the patient from the experimental group and did not use any data. Statistical analysis was performed using the SPSS version 22.0 (IBM Corp., NY, USA) software.

Results

Patient characteristics

Overall, 86 patients met the inclusion criteria and they were randomized to receive 1 of the 2 treatments for 7 days. Of these, 82 completed the trial and 4 (1 in Kai Hou Jian group and 3 in the budesonide group) were lost to follow-up because of poor adherence (*Figure 1*). There were no statistically significant differences in clinical age, sex distribution, laryngitis symptoms, or laryngoscopy scores at baseline levels between the 2 treatment groups (*Table 2*).

The effect of treatments on symptom scores

Patients in the Kai Hou Jian treatment group showed to have a significant improvement in 4 laryngitis symptoms with the scores of laryngeal symptoms of hoarseness, sore throat, pharyngeal foreign body sensation, and cough significantly reduced ($P<0.0001$; except for cough, $P=0.019$)

Table 2 Baseline clinical features of the patients in the 2 groups

Characteristics	Budesonide group (n=40)	Kai Hou Jian group (n=42)	P value
Gender, male/female	20/20	23/19	0.962
Age (years)	35.90±9.341	36.45±10.825	0.668
Hoarseness	2.512±0.320	2.634±0.308	0.741
Sore throat	3.163±0.334	3.122±0.350	0.965
Pharyngeal foreign body sensation	1.721±0.134	1.634±0.139	0.617
Cough	1.000±0.133	0.951±0.156	0.677
Vocal cord congestion	0.971±0.119	0.697±0.119	0.114
Vocal cord edema	1.171±0.145	1.303±0.102	0.677
Mucosal congestion	0.724±0.114	0.697±0.111	0.875
Mucosal edema	0.952±0.123	0.849±0.108	0.544
Mucus adhesion	0.571±0.125	0.667±0.121	0.515
Epiglottis congestion	0.086±0.048	0.152±0.077	0.587

Data is presented as mean ± standard deviation.

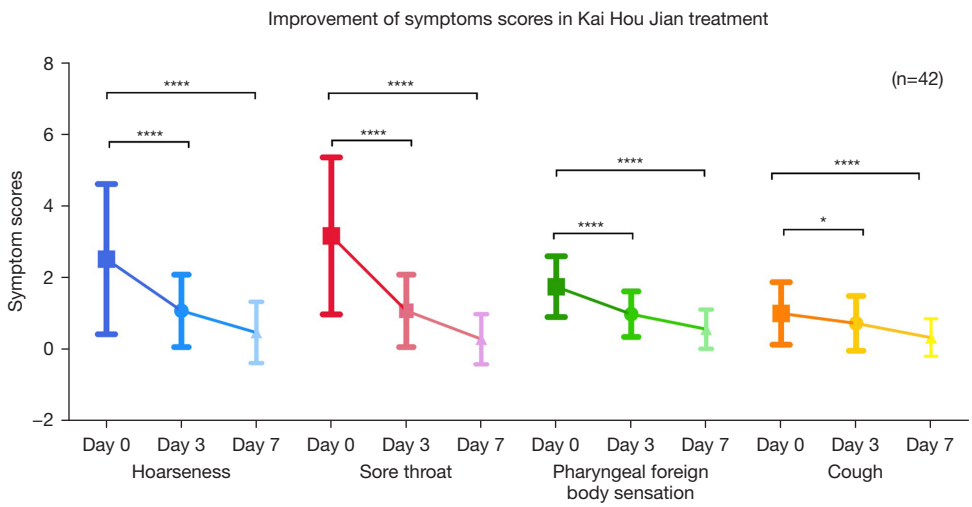

Figure 2 Comparison of the 4 individual acute laryngitis symptoms scores after 3 days and 1 week of treatment with aerosol inhalation of Kai Hou Jian. ****, P<0.0001; *, P<0.05.

after 3 days of treatment. The same trend was evident on the seventh of treatment, as shown in *Figure 2*.

In comparison with the therapeutic effect between Kai Hou Jian group and budesonide suspension group, the mean (SD) baseline values of the scores for the 4 acute laryngitis symptoms in the 82 patients revealed no differences between the 2 treatment groups (*Table 2*). The summed scores of all the symptoms were significantly reduced from baseline to 7 days after treatment initiation in both the groups (P<0.0001; *Table 3* and *Figure 3*), and there was no significant difference between them (P=0.7584; *Figure 3*). A comparison of treatment efficacy on the individual symptoms indicated that Kai Hou Jian could provide greater improvement in sore throat [difference between means: –0.977±0.419; 95% confidence interval (CI): –1.811 to –0.143; *Figure 4A*] but less improvement in hoarseness (difference between means: 1.349±0.373; 95% CI: 0.608–2.090; *Figure 4B*). In addition, there were no significant

Table 3 Symptoms and signs of the 2 groups at the end of the treatment according to laryngoscopy

Characteristics	Budesonide group (n=40)	Kai Hou Jian group (n=42)	P value
Hoarseness	0.500±0.139	0.513±0.160	0.952
Sore throat	0.300±0.114	0.154±0.086	0.313
Pharyngeal foreign body sensation	0.600±0.086	0.641±0.107	0.766
Cough	0.350±0.084	0.256±0.071	0.399
Vocal cord congestion	0.314±0.079	0.242±0.087	0.545
Vocal cord edema	0.314±0.080	0.546±0.107	0.086
Mucosal congestion	0.200±0.069	0.152±0.063	0.607
Mucosal edema	0.314±0.090	0.232±0.073	0.484
Mucus adhesion	0.057±0.057	0.030±0.030	0.685
Epiglottis congestion	0.000±0.000	0.000±0.000	>0.999

Data is presented as mean ± standard deviation.

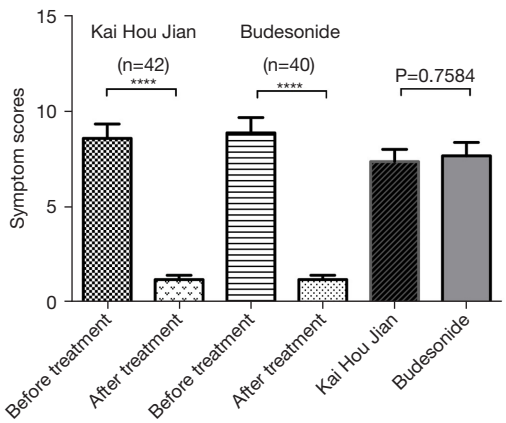

Figure 3 Comparison of the effects of 2 different treatments in the summed scores of the 4 symptoms of acute laryngitis. ****, P<0.0001.

differences in the improvement of pharyngeal foreign body sensation and cough (*Figure 4C,4D*).

The effect of treatments on laryngoscopy scores

Vocal cord congestion, edema, mucosal congestion, edema, mucus secretion, and epiglottic congestion were improved significantly in both treatment groups (P<0.05) after 7 days of treatment. There was a tendency for the Kai Hou Jian treatment group to yield better improvement in mucosal congestion, mucus secretion, and epiglottic congestion. However, the improvement did not show a statistically significant difference (*Figure 5A-5C*) when compared with the budesonide suspension treatment. There were no significant differences between the 2 treatment groups (*Figure 5D-5F*), with P values of 0.2521, 0.6344, and 0.8661, respectively for the vocal cord congestion, edema, and mucosal edema. To better demonstrate the visual changes of signs in the Kai Hou Jian aerosol inhalation treatment group, several pictures of laryngeal signs are provided in *Figure 6* (*Figure 6A-6F* are images taken progressively from baseline to 1 week after treatment).

Side effects

No adverse reactions were reported during the first week of treatment either in the Kai Hou Jian treatment group or in the budesonide treatment group.

Discussion

Laryngitis generally refers to inflammation of throat tissue and could be infected by viruses or bacteria (11). Adult acute laryngitis is mainly characterized by changes in vocal sound quality, such as hoarseness, difficulty in speech, and loss of voice, which may be accompanied by mild sore throat and some difficulty in breathing. The main treatments include the general treatment for the infection of bacteria or virus, the prohibition of speech and maintaining vocal cord rest, and corticosteroid inhalation therapy (9,11,12). However, inhaled corticosteroids (ICS) mostly work slower in most cases. One study on the treatment of asthma showed that

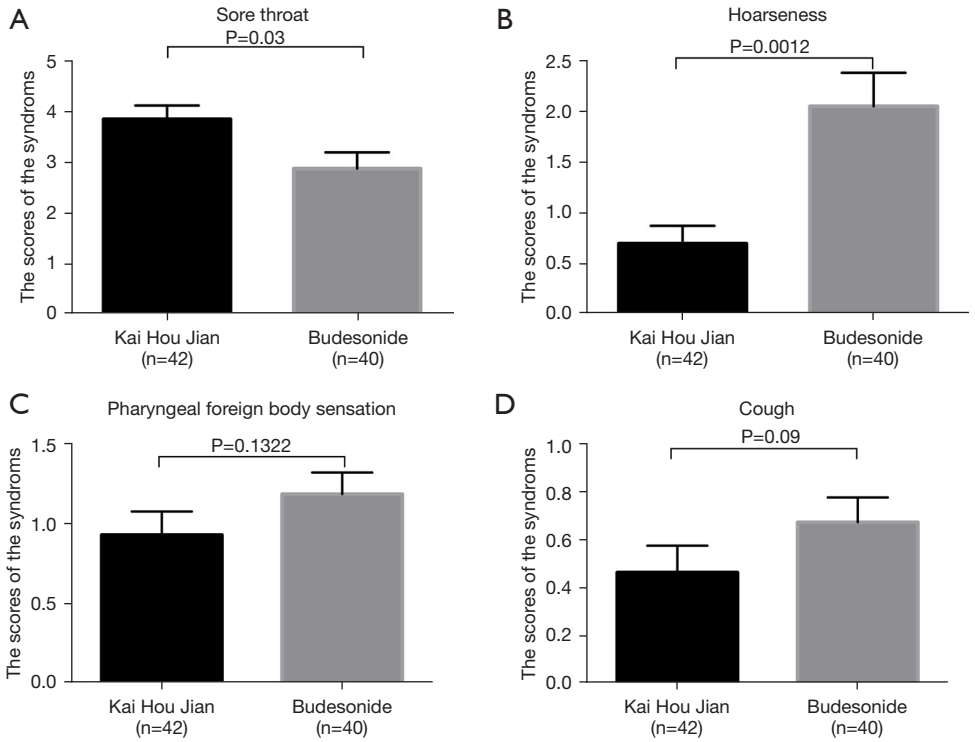

Figure 4 Comparison of the effects of the 2 different treatments in 4 symptoms of acute laryngitis. (A) Sore throat; (B) hoarseness; (C) pharyngeal foreign body sensation; (D) cough.

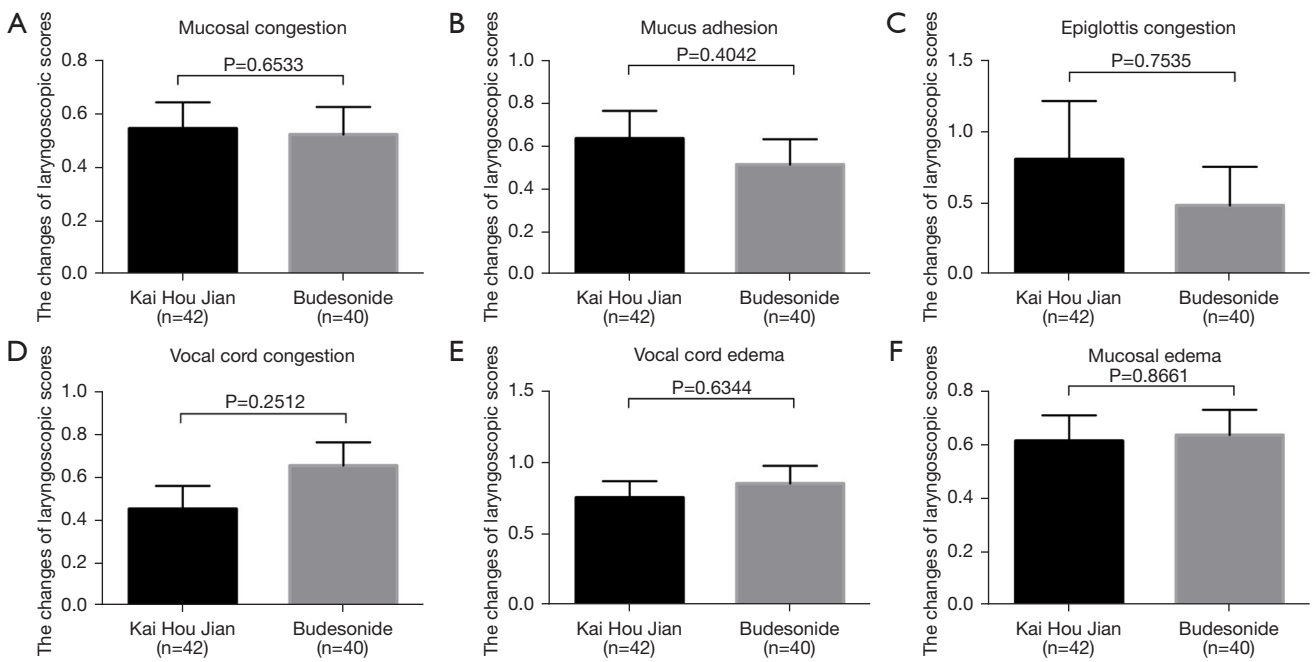

Figure 5 Comparison of the effects of the 2 different treatments according to laryngoscopy scores of acute laryngitis. (A) Mucosal congestion; (B) mucus adhesion; (C) epiglottis congestion; (D) vocal cord congestion; (E) vocal cord edema; (F) mucosal edema.

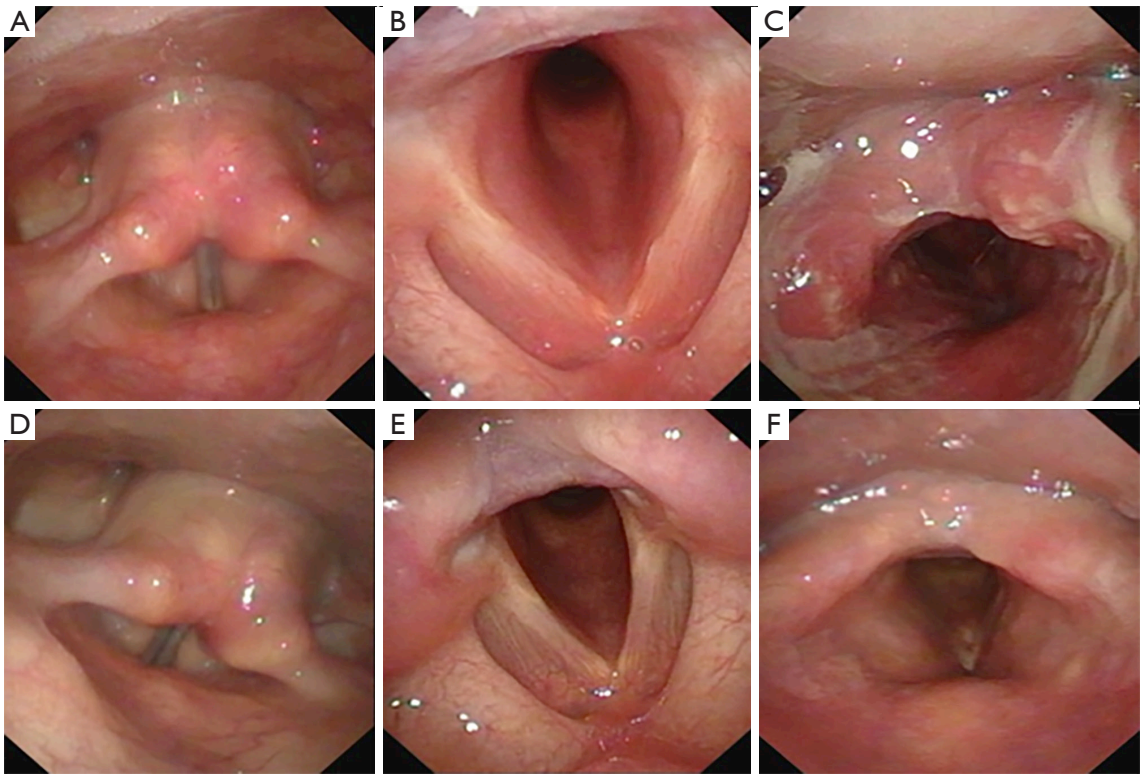

Figure 6 Laryngoscopic images at baselines and 7 days' treatment in the Kai Hou Jian group. (A-C) The laryngeal mucosa at baselines; (D-F) the laryngeal mucosa after 7 days' treatment.

at least 1 week of treatment was needed to have any effect under the assumption of correct usage and dosage, and 1 month was needed to achieve a good therapeutic effect (2). Therefore, ICS for asthma is classified as a controlled drug (a drug that needs to be used for a long time) and not a relieving drug (referred to as an on-demand drug, which relieves asthma symptoms by rapidly releasing bronchospasm) (13,14). It may be thus surmisable that ICS is not suitable for short-term anti-inflammatory treatment of acute airway inflammation. Kong *et al.* believed that budesonide nebulized suspension was a slow-acting drug, and it might be effective after continuous and regular nebulization for at least 2 days. Moreover, its curative effect is an "additive" effect, and the maximum therapeutic benefit will not be manifested until 4-6 weeks, and therefore, the treatment of budesonide suspension atomization to relieve laryngeal edema and reduce the local symptoms of acute laryngitis to be inappropriate (15). In the clinical treatment, it has been observed that some patients are misinformed about corticosteroids, with "steroid phobia" reducing the treatment compliance in these patients (3). Some patients with acute laryngitis might choose non-steroid methods initiatively or stop corticosteroid intake on their own, rendering the dose or administration period of steroid treatment and the symptom control was unsatisfactory.

The traditional Chinese medicine Kai Hou Jian (adult dosage form) spray, which mainly consists of *Ardisia crenata* Sims (ba zhuajinlong), *Cicadae periostracum* (chan tui), *Sophorae tonkinensis* Radix et Rhizom (shan dougen), and menthol (bo henao), has demonstrated an outstanding therapeutic effect on the infection caused by bacteria such as *Candida albicans*, *Staphylococcus aureus*, and *Proteus*. These 4 ingredients are based on the principle of the concept of traditional Chinese medicinal, "monarch" and "minister", with *Ardisia crenata* Sims (ba zhuajinlong; cultivated in Guizhou Province) exerting considerable antiviral effects. Moreover, Kai Hou Jian induced antipyretic and analgesic effects, and thus it was widely used to treat acute pharyngolaryngitis (6,16-18). It is also useful for outpatients due to its advantages of convenient administration, direct absorption, rapid onset, high efficacy, and short course of treatment (19,20). In their study, Meng *et al.* (6) reported

that the effective rates of treatment of Kai Hou Jian in acute pharyngitis, tonsillitis, and laryngitis were 100.0%, 95.8%, and 50.0%, respectively. They speculated that the anatomical location of throat might contribute to the lower therapeutic efficacy of laryngitis treatment compared to other pharyngeal diseases, with the determining factor being the concentration of drug reaching the lesion mucosa. We thus changed the way the drug was used and adopted oral nebulization, which would enable Kai Hou Jian to reach the mucosa of the larynx more effectively.

Aerosol inhalation is a direct method of administration for target organs like the respiratory tract and the lungs, possessing the advantages of fast onset, high local drug concentration, low use dosage, convenient application, and fewer systemic adverse reactions. As a consequence, it has become an important treatment method for respiratory diseases. In recent years, a growing number of traditional Chinese medicines or spray-type drugs have been modified for use with different atomization devices, allowing them atomizing to the lesions and thus yielding a better treatment effect (21,22). In the present study, we evaluated the clinical effect of a Kai Hou Jian atomization inhalation treatment for acute laryngitis by comparing its therapeutic effect to that of budesonide suspension aerosolization.

In this study, the recommended dose of 8 sprays/day of Kai Hou Jian for adult acute laryngitis was changed to 2.5 mL of atomization in 2 times/day, which was half of the recommended dose. The study found that the Kai Hou Jian atomization treatment could better alleviate the patients' sore throat symptoms, which might be related to the overlay of antipyretic and analgesic effects of different drug components in Kai Hou Jian (23-25). To further study the drug effects, we also observed the changes of the laryngeal mucosa through an electronic laryngoscopy display. We found that Kai Hou Jian was better in reducing local edema, congestion of the throat mucosa, and mucus production than the treatment with budesonide suspension. No clinical adverse events were observed in the Kai Hou Jian inhalation group or the budesonide inhalation group throughout the first week of treatment, and none of the 82 enrolled patients was reported for any adverse effects.

To our surprise, we found that some patients with laryngitis showed an improvement to the extent of vocal cord leukoplakia after the treatment with Kai Hou Jian atomization. Vocal cord leukoplakia is a histomorphological descriptive diagnostic term that is used to denote a white plaque-like or verrucous raised lesion attached to the surface or margins of the vocal cords, either limited to the front of vocal cords or spread over the entire length of vocal cords and deep in the mucosal layer or invading the submucosa (26). Presently, the etiology of vocal cord leukoplakia is complex, complicated, and unclear. According to the recent literature, it is relatively clear that irritation, chronic inflammation, laryngitis reflux, and other factors can cause excessive proliferation and dysplasia of squamous epithelial cells in the vocal cord mucosa, which may constitute a precancerous lesion with malignant potential. In contrast, benign lesions are mostly arising from voice abuse and acute infection. According to our specialist consensus, biopsy is emphasized as the gold standard to determine the pathological nature of vocal cord leukoplakia, but it remains controversial whether or not patients should undergo this procedure (27). In some patients with vocal cord leukoplakia, conservative treatment was able to achieve significant reduction in symptoms or even symptom disappearance. At our study, Kai Hou Jian also had the effect in improving vocal cord leukoplakia, which was shown in *Figure* 7. Instead of undergoing biopsies, electronic laryngoscopy was taken for the narrow mode to get further information of the character of vocal cord leukoplakia, and the images of three patients with vocal cord leukoplakia in Kai Hou Jian group were shown in *Figure* 7*A1*, 7*B1*, 7*C1* and 7*A1N*, 7*B1N*, and 7*C1N* in the narrow band image (NBI) mode, respectively. It was found that the extent or range of vocal cord leukoplakia had decreased or even disappeared after 1 week of Kai Hou Jian atomization treatment (*Figure* 7*A2*, 7*B2*, 7*C27* and 7*A2N*, 7*B2N*, and 7*C2N*, respectively), which was in line with the findings of previous studies related to traditional Chinese medicine (28-32). It is worth noting that patients in these studies were administered these drugs orally in systematic fashion. In contrast, our study adopted the local atomization, which is more targeted and better avoiding any possible systematic side effects.

Some limitations to this study should be mentioned. Kai Hou Jian nebulization was observed only by the changes of lesion extent under electronic laryngoscopy, no further detailed information regarding medical history was recorded, and no classification of leukoplakia was performed. Hence, we will include collection of a wider array of information and relevant experimental data to clarify the effect and mechanism of Kai Hou Jian on vocal cord leukoplakia in the future.

Conclusions

Kai Hou Jian inhalation treatment could improve the symptoms of hoarseness, sore throat, cough, and pharyngeal

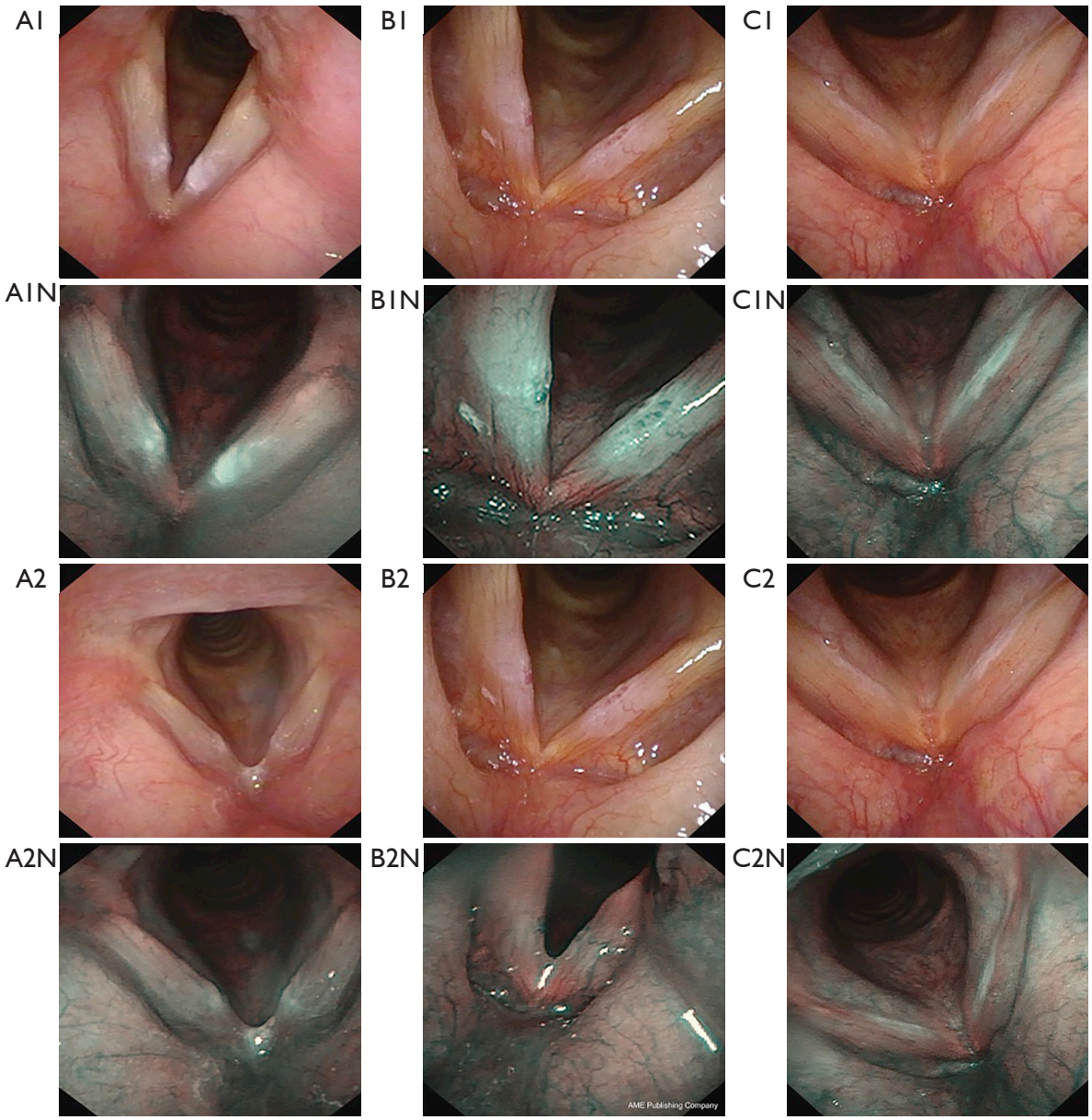

Figure 7 Laryngoscopic pictures at baselines and 7 days' treatment in the Kai Hou Jian group. A1, B1, and C1 show vocal cord leukoplakia at baseline of three patients in Kai Hou Jian treatment group; A1N, B1N, and C1N show vocal cord leukoplakia of the three patients at NBI mode, respectively; A2, B2, and C2 show vocal cord leukoplakia after 7 days' treatment of the three patients and A2N, B2N, and C2N are the images at NBI mode, respectively. (N: images taken in narrow band image mode). NBI, narrow band image.

foreign body sensation of adult acute laryngitis by reducing congestion, edema, and mucus production of the throat mucosa. It could be a potential clinical treatment option for adults with acute laryngitis, especially for those with "steroid phobia". We adopted the aerosol inhalation method instead of traditional oral spray, which could directly reach the lesions and the advantage of enabling dose reduction, and conferring the same therapeutic effect as that of the oral spray method.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4305/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4305/tp

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the medical ethics committee of Wangjing Hospital of the China Academy of Chinese Medical Sciences (No. WJYY-KT-2018-036-P003) and informed consent was taken from all the patients. The study has been registered with the Chinese Clinical Trial Registry (ChiCTR1900026660; http://www.chictr.org.cn).

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