Effect of a traditional herbal medicine, hangekobokuto, on the sensation of a lump in the throat in patients with respiratory diseases

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Abstract. The sensation of a lump in the throat (SLT) is not a rarely encountered symptom. The etiology of SLT appears to be multifactorial, and the psychological characteristics, stress and pressure of a psychiatric disorder may be significant factors in SLT. Hangekobokuto, one of the traditional herbal medicines, is a known drug that has an effect on SLT. The efficacy of a short-term hangekobokuto treatment on SLT was evaluated. To assess whether a 2-week prescription of hangekobokuto improves SLT mainly in patients with respiratory diseases, a retrospective study was performed between April 2013 and August 2015. During the study period, a total of 43 patients were treated with hangekobokuto. Twelve (27.9%) of the 43 patients were reported to experience completely effective treatment (SLT completely disappeared), and 14 (32.6%) experienced moderately effective treatment (25-99% SLT disappeared). Patients with bronchial asthma and those without a medical history of respiratory disease exhibited a good response to hangekobokuto. No specific predictive factor of the response to hangekobokuto on SLT was identified in the multivariate regression analysis. Therefore, the present results suggested that hangekobokuto could be one of the treatment choices for uncontrolled SLT.

Introduction

The sensation of a lump in the throat (SLT), also known as globus hystericus, is not a rarely encountered symptom. It has been reported in 7-14% of the population worldwide (1-4). The etiology of SLT appears to be multifactorial, and the psychological characteristics, stress and pressure of a psychiatric disorder may be significant factors in SLT (5). In addition, certain studies suggested that bronchial asthma (6), and gastroesophageal reflux disease (GERD) may be major factors of SLT (7,8). Hangekobokuto (Tsumura Co., Tokyo, Japan), one of the traditional herbal medicines that has been developed by Zhang Zhongjing, a well-known physician of traditional Chinese medicine in the third century, is known as an effective drug on SLT in North-East Asia (9). Treating SLT by hangekobokuto has been previous studied, for example in Jin Gui Yao Lue (a classic clinical book of essential prescriptions of traditional Chinese medicine written by Zhang Zhongjing in the third century). A number of Kampo doctors are experienced in this regard, and the effects of hangekobokuto on SLT have been reported by certain Japanese otolaryngologists, as published in Japanese (10-12). However, to the best of our knowledge, there have been no studies published in English. English publications are required to introduce the usefulness of this traditional herbal medicine to numerous 'non-Kampo doctors' in areas other than North-East Asia.

SLT appears to not be a serious symptom, but it is difficult to completely treat in patients with respiratory diseases, particularly in those with bronchial asthma who have even undergone treatment with inhaled corticosteroid/long acting β2-agonist (ICS/LABA) or oral corticosteroids. As aforementioned, treating SLT by hangekobokuto is not a new area of research; however, whether the effect could be achieved in the short-term has not been established. The present study evaluated the effect of a short-term, 2-week prescription of hangekobokuto on SLT in patients with respiratory diseases.

Patients and methods

Patients. The retrospective study was performed at Mito Medical Center, University of Tsukuba, Mito Kyodo General Hospital (Mito, Japan), by evaluating medical charts of patients with respiratory diseases between April 2013 and August 2015. All the consecutive patients with SLT as their primary complaint who underwent a 2-week prescription of hangekobokuto were evaluated in this study. All were outpatient clinic patients, and none were admitted. Patients with laryngeal, pharyngeal diseases and connective tissue diseases were excluded, but those with SLT with a medical history of GERD were included in this study.

Prescription of hangekobokuto. The indication and contraindication of hangekobokuto was explained and the study obtained an agreement for administering hangekobokuto for SLT, and prescribed the drug (2.5 g three times a day) for

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Table I. Characteristics of the 39 patients treated with hangekobokuto.

Characteristics	Patients
Median age, years (range)	72 (17-90)
Gender, no.	
Male	9
Female	34
Medical history of respiratory disease, no.	
None	7
Bronchial asthma	29
Other respiratory diseases	7
Chronic obstructive pulmonary disease	2
Idiopathic pulmonary fibrosis	2
Bronchiectasis	2
Lung cancer	1

Table II. Patient responses to hangekobokuto.

Response	Patients, no. (%)
Overall	43
Completely effective	12 (27.9)
Moderately effective	14 (32.6)
No change	17 (39.5)
Worsened symptom	0 (0.0)
Patients with BA	29
Completely effective	8 (27.6)
Moderately effective	12 (41.4)
No change	9 (31.0)
Worsened symptom	0 (0.0)
Patients with respiratory diseases other than BA	7
Completely effective	0 (0.0)
Moderately effective	2 (28.6)
No change	5 (71.4)
Worsened symptom	0 (0.0)
Patients with no history of respiratory disease	7
Completely effective	4 (57.1)
Moderately effective	0 (0.0)
No change	3 (42.9)
Worsened symptom	0 (0.0)

BA, bronchial asthma; ICS/LABA, inhaled corticosteroid/long acting β2-agonist.

2 weeks. Other drugs, which were already prescribed, were continued with hangekobokuto.

Evaluation of the effect of hangekobokuto. After a 2-week administration of hangekobokuto, changes in SLT were evaluated. The verbal rating scale was used to determine the change of SLT: Completely effective (CE), SLT had completely disappeared; moderately effective (ME), 25-99% of SLT had disappeared; not effective (NE), 0-24% of SLT had disappeared; and worsened symptom (WS), SLT was worse than prior to the prescription.

Ethics. The study was conducted in accordance with the Declaration of Helsinki Good Clinical Practice and was approved by the Institutional Review Board at Mito Medical Center, University of Tsukuba for human studies (no. 15-13).

Statistical analysis. Comparisons between two groups were evaluated using χ^2 test and multiple logistic regression analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. During the study period, a total of 43 patients were treated with hangekobokuto. The patient characteristics are summarized in Table I. The median age of the patients was 72 years (range, 17-90 years). Nine (26.5%) of the patients were male. A total of 29 patients (67.4%) had bronchial asthma. All had initiated ICS/LABA therapy.

Change of SLT following hangekobokuto therapy. Table II shows the response to hangekobokuto. Twelve (27.9%) of the 43 patients had CE, and 14 (32.6%) exhibited ME. However, 17 (39.5%) had NE, but none exhibited WS. In particular, 20 (69.0%) of the 29 patients with bronchial asthma and 4 (57.1%) of the 7 patients with no medical history of respiratory diseases were effective, and tended to exhibit a higher response (CE and ME) rate than that in 7 patients with other respiratory diseases than bronchial asthma (28.6%), but the difference was not statistically significant (P=0.1149 and P=0.8679, respectively).

Predictive factors of the response to hangekobokuto on SLT. Table III shows the results of the prediction of the SLT response to hangekobokuto using multiple logistic regression

Table III. Predictive factors of the response to hangekobokuto on the sensation of a lump of the throat using multiple regression analysis.

Factors	Hazard ratio	95% CI	P-value
Age	1.916	0.449-8.176	0.3800
Gender	1.079	0.176-6.625	0.9348
History of respiratory disease	1.677	0.066-42.539	0.7539
Drug prescription			
ICS/LABA	0.333	0.018-6.045	0.4570
Antitussive drug	0.510	0.104-2.505	0.4071
Expectorant	1.344	0.264-6.836	0.7214
PPI and H2	1.326	0.202-8.719	0.7692

ICS/LABA, inhaled corticosteroid/long acting β2-agonist; PPI, proton pump inhibitor; H2, H2 antagonist; CI, confidence interval.

analysis. Female, elderly (>65 years) patients with a medical history of respiratory disease, and simultaneous prescription of other drugs including ICS/BALA were not evaluated as predictive factors of the response to hangekobokuto on SLT.

Adverse events of hangekobokuto therapy. There was no severe (grade 3-4, common toxicity criteria) event in the hangekobokuto therapy. Only 1 patient experienced tentative nausea (grade 1), but this disappeared quickly following the termination of the hangekobokuto treatment.

Discussion

SLT is a nonspecific symptom of throat discomfort. The etiology of SLT appears to be multifactorial, and the psychological characteristics, stress and pressure of a psychiatric disorder may be significant factors in SLT (5). Bronchial asthma may also be a major factor of SLT (6). In the present study, three points were focused on as follows; however, a strong conclusion could not be derived. First, 20 of the 29 patients with bronchial asthma, who were treated with inhaled ICS/LABA, reported CE and ME. These results suggested that prescription of hangekobokuto could be considered for the bronchial asthma patients with SLT. However, the effectiveness of hangekobokuto in patients who were prescribed ICS/LABA simultaneously to hangekobokuto could not be estimated due to the small number of patients, although ICS/LABA was not a predictive factor of the response to hangekobokuto on SLT in the multiple regression analysis (Table III). Second, certain previous studies have suggested that GERD may be a major factor of SLT (7,8). By contrast, other studies did not support GERD as an etiology of SLT (9). In the present study, there was efficacy of hangekobokuto in 4 of the 7 patients who had been prescribed a proton pump inhibitor or H2 antagonist. Third, the majority of patients were female and they exhibit a higher response compared to male patients. However, there was no statistical difference in the response between them. Larger prospective studies are required to confirm these results and explain their mechanisms.

Hangekobokuto (Banxia-Houpo-Tang) is a traditional herbal medicine (formula of magnolia and pinelliae), which has been administered to patients with airway obstructions (by Zhang Zhongjing, a well-known physician of traditional Chinese medicine in the third century). Hangekobokuto modulates cerebral levels of 5-hydroxytryptamine, noradrenaline, dopamine and substance-P (9,11). Improvement of the swallowing function may be associated with their increased cerebral levels (9,11). Hangekobokuto is well-known in North-East Asia for its effective treatment of psychological characteristics, stress and pressure of psychiatric disorder as well as bronchial asthma and impairment of swallowing reflex (9,12). Our previous study reported the successful treatment of an elderly patient with bronchial asthma (6). The patient complained of SLT, which was not controlled by ICS/LABA and oral prednisolone, and was treated by the addition of a 2-week hangekobokuto treatment to these drugs. In the present study, a retrospective study was performed and showed the effect of hangekobokuto on SLT in patients with respiratory diseases, including those with bronchial asthma.

In Kampo traditional herbal medicine, 'Sho' is the important concept (13,14). The physical and psychological conditions of the patients are evaluated as having 'Jitsu-sho' and 'Kyo-sho'. Hangekobokuto has been evaluated as more effective in patients with 'Kyo-sho', low body mass index and a depressive mood disorder (13,14). In the present study, however, it did not appear that the efficacy of hangekobokuto was obtained in such patients. This may be due to the small sample size of the study.

There were several limitations of the present study. First, it was a small-sized retrospective study. Second, it was not a placebo-controlled study. Third, the study included patients with or without bronchial asthma and GERD, and several drugs for these diseases. Despite these limitations, the results provide important information regarding the treatment of SLT.

The etiology of SLT is likely multifocal. In a patient with SLT, several factors may be associated with SLT. Bronchial asthma and GERD may be two of the etiology associated with SLT. Therefore, therapy for such diseases must be indicated at first; however, if SLT is uncontrolled by such therapies, prescription of hangekobokuto may be considered.

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