

Investigation Report by an EBM Work Team of Japanese Association of Oriental  
Psychosomatic Medicine

Evidence of Kampo Therapy for Psychosomatic Diseases and Stress-related Diseases

5) Bronchial Asthma, Hyperventilation Syndrome

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Objectives

In recent years, thanks to the spread of inhalation therapy with steroids and long-acting  $\beta_2$  agonists, the treatment of bronchial asthma has gone through a innovative transformation, significantly improving the QOL of patients. However, there are still refractory patients who are difficult to improve by drug therapy with western medicines alone. In addition, in the current stressful society that has fallen into serious depression there is a high possibility that the pathophysiology of psychosomatic disease whose clinical course is deeply affected by psychosocial factors has an impact on patients with bronchial asthma. Furthermore, there may be an increase in the number of patients who repeatedly develop a hyperventilation attack due to their maladjustment to the social environment.

Receiving such psychosomatic medical needs, this time we investigated the evidence of kampo therapy including the psychosomatic medical aspect with a focus on bronchial asthma.

A. Bronchial asthma

1. Investigation methods

By using the PubMed database, we conducted a search with the following seven drug names: saibokuto, shoseiryuto, bakumondoto, makyokansekito, shinpito, hochuekkito, and hachimijiogan, which are representative Kampo prescriptions for bronchial asthma (hereinafter asthma), and extracted articles on asthma or asthma-related articles. For example, studies with saibokuto were searched for by using the following keywords: Saibokuto, Saiboku-to, and TJ-96. We also conducted a keyword search with the above seven Kampo prescription names and the word “zennsoku (asthma)” at Japan Medical

Abstracts Society website and Tsumura's website Kampo Square. The search period was from 1986 to 2007.

## 2. Search results

### 1) Current situation

1. DB-RCT, placebo controlled	3
2. DB-RCT	2
3. RCT	4
4. Case-series study that involves at least 10 cases	166

### 2) Usefulness

Most of articles whose level of evidence was RCT or higher were reports by Nishizawa et al. The following are the summaries of those reports.

#### (1) DB-RCT, placebo-controlled

[1] Suppressive effect of Kampo medicine, Cai-pu-tang (Japanese name: Saiboku-to, TJ-96) on bronchospasms in aspirin-induced bronchial asthmatic patients and decrease of chronic pain. Especially psychological pain<sup>1)</sup>

Subjects: 32 patients with aspirin-induced asthma. Methods: The patients inhaled lysine-aspirin after inhaling saibokuto or distilled water, and underwent the evaluation of the suppression of airway contraction (forced expiratory volume in one second), physiological active substances in bronchoalveolar lavage fluid (hereinafter, BALF), and QOL scores. Results: Improvements were observed in QOL after inhalation of saibokuto. The inhalation of saibokuto improved respiratory function, and was therefore useful.

[2] Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial<sup>2)</sup>

Subjects: 33 patients with atopic asthma. Methods: The patients was given saibokuto or placebo for 4 weeks, and underwent the evaluation of clinical symptoms, respiratory function testing, methacholine provocation testing, eosinophil counts in blood and sputum, and eosinophilic cationic protein (ECP) in blood and sputum. Results: Subjective symptom score significantly improved. Forced expiratory volume in 1 second improved slightly but not significantly. Significant decreases in eosinophil counts and ECP in blood and sputum were observed. Saibokuto improves symptoms in patients with atopic asthma, and was able to attenuate eosinophilic inflammation.

[3] Clinical effect of chai-po-tang (Japanese name: saiboku-to), a Chinese traditional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: a multicenter, randomized, double-blind, placebo-controlled study<sup>3)</sup>

Subjects: 107 patients with asthma who fulfill one of the following criteria: comprehensive asthma inventory [CAI] score  $\geq 20$ , state trait anxiety inventory [STAI] score  $\geq 41$  in men and  $\geq 42$  in women, or self-rating depression scale [SDS]  $\geq 40$ . Methods: The patients were given saibokuto 7.5 g/day (51 patients) or clonazepam 15-30 mg/day (56 patients) for 3 years, and underwent the evaluation of clinical effects, various types of mental and psychological tests, reactive airway disease, BALF, and improvement in global symptoms. Results: Saibokuto significantly improved inflammation of the airway as compared to clonazepam, and also improved anxiety and depressive symptoms.

## (2) DB-RTC

[1] Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Bronchospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test<sup>4)</sup>

Subjects: 74 patients with aspirin-induced asthma. Methods: The patients inhaled saibokuto (35 patients) or saline (39 patients) for 6 months, and underwent the evaluation of biologically active substances in BALF and the frequency of asthma attacks. Results: The inhalation of saibokuto significantly decreased leukotriene, ECP, eosinophil, and IL-3, 4, 5, and 8 in BALF, and was effective against asthma attacks.

[2] Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-qing-long tang (Japanese name: shoseiryu-to) in asthmatics with anxiety and depression due to asthmatic attacks<sup>5)</sup>

Subjects: 139 patients with asthma who fulfill one of the following criteria: CAI score  $\geq 20$ , STAI score  $\geq 41$  in men and  $\geq 42$  in women, or SDS  $\geq 40$ . Methods: The patients were given saibokuto (71 patients) or shoseiryuto (68 patients) for 24 weeks, and underwent the evaluation of various types of mental and psychological tests, subjective symptoms, BALF, hormones (related to HPA-axis), suffering assessment score, and improvement in global symptoms. Results: Saibokuto significantly improved all the items as compared to shoseiryuto, and significantly improved asthma symptoms in asthma patients with anxiety symptoms.

## (3) RCT

[1] Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropionate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation<sup>6)</sup>

Subjects: 94 patients with asthma (patients with stable symptoms whose peak expiratory flow (PEF) rate was maintained at more than 70% of normal for 6 months by the use of inhaled beclomethasone). Methods: Amount of inhaled beclomethasone was reduced by

half at 4 weeks before intervention, and the patients inhaled saibokuto (49 patients) and cromoglycate (45 patients) for 12 months. Evaluation was made by the intensity of subjective symptoms (visual analogue scale), PEF, the frequency of  $\beta_2$  agonist use, cytokine levels in BALF, nitric oxide (NO) concentrations in expired air, and so on. Results: As compared to cromoglycate, saibokuto significantly improved subjective symptoms and respiratory function, and significantly reduced the frequency of  $\beta_2$  agonist use and significantly suppressed NO concentration in expired air.

[2] Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clotiazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial<sup>7)</sup>

Subjects: 107 patients with asthma who fulfill one of the following criteria: CAI score  $\geq$  20, STAI score  $\geq$  41 in men and  $\geq$  42 in women, or SDS  $\geq$  40. Methods: The patients were given saibokuto 7.5 g/day (51 patients) or clotiazepam 15-30 mg/day (56 patients) for 3 years, and underwent the evaluation of clinical effects, various types of mental and psychological tests, reactive airway disease, BALF, and improvement in global symptoms. Results: As compared to clotiazepam, saibokuto significantly improved asthma symptoms in asthma patients with anxiety symptoms.

[3] Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-intolerant bronchial asthmatic patients — a randomized, group-paralleled comparative trial —<sup>8)</sup>

Subjects: 114 patients with aspirin-induced asthma. Methods: The patients inhaled shinpito 500  $\mu$ g/day (53 patients) or cromoglycate 20 mg/day (61 patients), and the effect was evaluated by assessing the levels of leukotrienes in BALF, forced expiratory volume in 1 second after lysine-aspirin inhalation, and the frequency of asthma attacks. Results: As compared to cromoglycate, shinpito significantly improved all the evaluation items, and thus shinpito inhalation therapy is more efficacious than cromoglycate inhalation therapy for the prevention of aspirin-induced asthma.

[4] A randomized, group-parallel comparative trial of the suppressive effect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium cromoglycate inhalation in improving subjective and objective symptoms in bronchial asthmatics<sup>9)</sup>

Subjects: 161 patients with aspirin-induced asthma. Methods: The patients inhaled shinpito 500  $\mu$ g/day (81 patients) or cromoglycate 20 mg/day (80 patients) for 3 years, and underwent the evaluation of the frequency of asthma attacks, improvement in QOL, improvement in chronic pain, and the levels of leukotrienes in BALF. Results: As compared to cromoglycate, shinpito significantly improved all the evaluation items. Shinpito inhalation therapy suppressed the production of leukotrienes, prevented

aspirin-induced asthma, alleviated chronic pain, and improved QOL.

#### (4) Case-series study

There were many articles whose levels of evidence are case-series studies. The following are the numbers of articles classified according to the number of reported cases.

Number of cases	Number of articles
10-20	55
21-30	40
31-40	8
41-50	18
51-100	28
101-200	17
Total	166

#### 3) Effect on QOL

Kondo<sup>10)</sup> evaluated using a QOL questionnaire the Japanese Pediatric Guidelines for the Treatment and Management of Asthma and how Kampo would be positioned. Also, Egashira<sup>11)</sup> discussed the current Kampo formulas in treatment of asthma and new assessment of QOL. Furthermore, Nishizawa<sup>1,9)</sup> evaluated QOL in asthma patients using various QOL rating scales and a global QOL scale, both of which were prepared by himself.

#### 4) Comparison with western medicines

Nishizawa<sup>6-9)</sup> carried out studies of the following titles: Sparing effect of saibokuto inhalation on inhaled beclomethasone dipropionate to halved of reduction of inhaled beclomethasone dipropionate-dose: well-controlled comparative study of saiboku-to-inhalation and sodium cromoglycate-inhalation; Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clonazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial; Suppressive effect of Chinese traditional medicine, she-bi-tang (shinpi to) on bronchospasm in aspirin-intolerant bronchial asthmatic patients — a randomized, group-paralleled comparative trial —; and A randomized, group-parallel comparative trial of the suppressive effect of Chinese traditional medicine, shen-mi-tang (shin-pi-to), compared to sodium cromoglycate inhalation in improving subjective and objective symptoms in bronchial asthmatics. The summaries were as mentioned above.

#### 5) Effect on refractory cases

Although there are some reports on the effect of Kampo prescriptions on refractory

cases of asthma, their levels of evidence are merely of case-series studies.

#### 6) Study of concomitant use with western medicines

There is no article with a high level of evidence that investigated combinations of Kampo prescriptions and western drugs in treatment of asthma.

#### 7) Study of Sho

There is no article with a high level of evidence that investigated Sho in Kampo therapy of asthma.

#### 8) Psychosomatic study

As psychosomatic studies of bronchial asthma treated with saibokuto, Nishizawa<sup>3,5,7)</sup> conducted studies of the following titles: Clinical effect of chai-po-tang (Japanese name: saiboku-to), a Chinese traditional herbal medicine, in patients with bronchial asthma and autonomic nerve dysfunction: a multicenter, randomized, double-blind, placebo-controlled study; Clinical effect of a Kampo medicine, chai-po-tang (Japanese name: saiboku-to) compared with xiao-qing-long tang (Japanese name: shoseiryu-to) in asthmatics with anxiety and depression due to asthmatic attacks; and Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clonazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial. The summaries were as mentioned above.

#### 9) Grades of recommendation

The following are articles on Kampo prescriptions referenced in asthma guidelines in recent years.

An article in which Egashira<sup>14)</sup> reports the usefulness of saibokuto and an article in which Egashira<sup>15)</sup> reports the usefulness of saibokuto, makyokansekito, shoseiryuto, bakumondoto, shosaikoto, hochuekkito, and hachimijiogan are referenced in the Allergic Diseases Treatment Guidelines 1995<sup>12)</sup> and the Asthma Prevention and Management Guidelines 2003<sup>13)</sup> prepared by the Japanese Society of Allergology.

The EBM-Based Asthma Treatment Guidelines 2004<sup>16)</sup> refers to an article in which Watanabe<sup>17)</sup> reports the effect of bakumondoto on bronchial asthma with increased cough sensitivity and articles in which Nishizawa reports the results of the following studies: Suppressive Effect of Japanese Herbal Medicine, Saiboku-to (Cai-Pu-Tang) on Bronchospasms in Aspirin-induced Bronchial Asthmatic Patients. A Randomized, Double-blind Test<sup>4)</sup> and Clinical effect of a Chinese traditional herbal medicine, chai-po-tang (Japanese name: saiboku-to) compared with clonazepam in patients with bronchial asthmatics and anxiety disorder in multicenter randomized, comparative trial.<sup>7)</sup>

In the Guidelines for the Diagnosis and Management of Asthma, third edition (National

Asthma Education and Prevention Program) 2006,<sup>18)</sup> foreign articles by Dorsch<sup>19)</sup> and Ziment<sup>20)</sup> are referenced, though the data are as old as the early 1990s.

#### 10) Future problems and consideration

[1] Since most of reports are those of Kampo formulas indicated in the chronic stable phase, reports on Kampo prescriptions used in the acute exacerbation phase are desirable.

[2] High levels of evidence are desirable for reports on concomitant use with western medicines and reports on refractory cases.

[3] Although the comprehensive asthma inventory (CAI) is used as a questionnaire for the psychosomatic evaluation of asthma, studies are desired to include evaluation by new guidelines for psychosomatic disease.<sup>21)</sup>

### B. Hyperventilation syndrome

#### 1. Investigation methods

A search was performed with keywords “kakannki OR kakokyyu” and “kannpou OR Kannpouyaku” at Japan Medical Abstracts Society website, and “kakannkishoukougunn,” “rinnshou,” and “chiryuu” at Tsumura’s website Kampo Square. The search period was from 1986 to 2007.

#### 2. Search results

##### 1) Current situation

1. DB-RCT, placebo controlled	0
2. DB-RCT	0
3. RCT	0
4. Case-series study that involves at least 11 cases	14

There was no article whose level of evidence was RCT or higher.

The number of patients subject to a case report was mostly 10 or less. The following are the numbers of articles classified according to the number of cases.

Number of cases	Number of articles
1-10	55
11-30	4
31-50	6
51-100	3
101-200	1
Total	69

##### 2) Future problems and consideration

This time, there was no article with a high level of evidence regarding Kampo therapy of hyperventilation syndrome.

As for hyperventilation syndrome, there are problems even in making a diagnosis such as a difference between panic attack and hyperventilation attack, and confusion is currently happening in clinical setting. In addition, since there are differences in diagnosis and treatment among medical institutions, it seems difficult to obtain uniform evidence even in the future.

As a related pathophysiology, there is panic disorder, but it has been discussed in another category, and thus is omitted in this article.