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Original Article

A Double-Blind Randomized Controlled Trial to Determine the Preventive Effect of Hangekobokuto on Aspiration Pneumonia in Patients Undergoing Cardiovascular Surgery

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Purpose: This study aimed to assess whether hangekobokuto (HKT) can prevent aspiration pneumonia in patients undergoing cardiovascular surgery.
Methods: We performed a single-center, double-blinded, randomized, placebo-controlled study of HKT in patients undergoing cardiovascular surgery. JPS HKT extract granule (JPS-16) was used as HKT. The primary endpoint was defined as the prevention of post-operative aspiration pneumonia. The secondary endpoints included complete recovery from swallowing and coughing disorders.
Results: Between August 2014 and August 2015, a total of 34 patients were registered in this study. The rate of subjects with postoperative aspiration pneumonia was significantly lower in the HKT group than in the placebo group ($p=0.017$). In high-risk patients for aspiration pneumonia, the rate was significantly lower in the HKT group than in the placebo group ($p=0.015$). The rate of subjects with swallowing disorders tended to be lower in the HKT group than in the placebo group ($p=0.091$), and in high-risk patients, the rate was significantly lower in the HKT group than in the placebo group ($p=0.038$).
Conclusions: HKT can prevent aspiration pneumonia in patients undergoing cardiovascular surgery. In high-risk patients for aspiration pneumonia, HKT can prevent aspiration pneumonia and improve swallowing disorders.

Keywords: hangekobokuto, aspiration pneumonia, dysphagia, Kampo medicine

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Introduction

Aspiration pneumonia is a major complication of cardiovascular surgery. Swallowing dysfunction was reportedly diagnosed in 3%–4% of patients undergoing cardiac operations, and it was found to be associated with pulmonary aspiration in 90% of these patients.[1,2] Daly et al.[3] reported asymptomatic pulmonary aspiration in 70% of patients who were on mechanical ventilation for more than 48 hours after cardiovascular surgery. Several authors have reported that an angiotensin-converting enzyme inhibitor (ACEI) may be useful for preventing aspiration

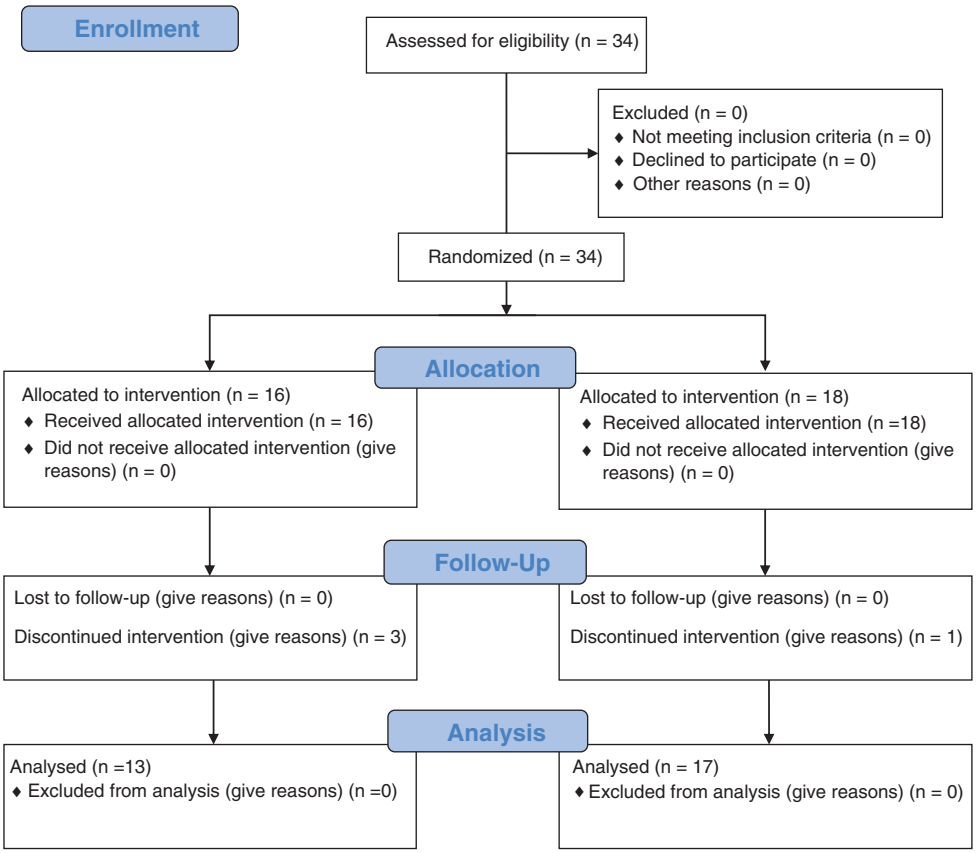

Fig. 1 CONSORT flow diagram of this study.

pneumonia.[4,5] However, dry cough is an unpleasant side effect of ACEI[4,5] and it often causes wound ache in surgical patients.

Hangekobokuto (HKT) is a popular prescription used in traditional Japanese medicine; thus, it is called Kampo medicine. HKT has been proven to improve swallowing or coughing reflex, and is expected to prevent aspiration pneumonia.[6–9] Several studies of HKT and aspiration pneumonia in patients with cerebrovascular diseases and Parkinson's disease have demonstrated that HKT could prevent aspiration pneumonia.[6–9] HKT has also no side effects of dry cough. This is the first study to assess whether HKT, a Kampo medicine, can improve swallowing disorder and prevent aspiration pneumonia in patients undergoing cardiovascular surgery.

Materials and Methods

Subjects

The flow of patients in this study is presented in **Fig. 1**. The study protocol was approved by the ethics committee of Tokyo Medical University Hachioji Medical Center before the study began (receipt number: H-20) and was registered in the University Hospital Medical Information Network Clinical Trials Registry (identification number: UMIN000017390).

We performed a single-center, double-blinded, randomized, placebo-controlled study of HKT in patients undergoing cardiovascular surgery. Consecutive patients undergoing cardiovascular surgery at the Department of Cardiovascular Surgery of Tokyo Medical University Hachioji Medical Center between August 2014 and August 2015 were registered. The selection criteria were as follows: (1) patients over 20-years old who can orally ingest HKT and (2) those who received an explanation of the objective and content of this research, and in whom voluntary consent could be obtained. The exclusion criteria were as follows: (1) patients undergoing developing drug administration or patients scheduled for developing drug administration, (2) those who are pregnant or who want to become pregnant during the study observation period, as well as those who are lactating, (3) those who are taking or are scheduled to take other Kampo medicines, and (4) those with Parkinson's disease and cerebral infarction, and those who are prone to develop aspiration pneumonitis. All patients provided written informed consent.

Table 1 Concentration of the aqueous citric acid solutions used in this study

Solution	Concentration (mg/mL)
10	360
9	180
8	90
7	45
6	22.5
5	11.3
4	5.63
3	2.81
2	1.41
1	0.70

Medication

JPS HKT extract granule (JPS-16, JPS Pharmaceutical Co., Ltd., Yokohama, Japan) was used as HKT. It was composed of Pinelliae tuber 6 g, Hoelen 5 g, Magnoliae cortex 3 g, Perillae herba 3 g, and Zingiberis rhizoma 1 g. Lactose powder was used as a placebo. The shape of the lactose powder was similar to HKT, but the taste and smell were different. However, even with these differences, it appears that the patients did not know whether they were taking HKT or the placebo.

Assessment of swallowing reflex, coughing reflex, and Substance P

Swallowing reflex was evaluated according to the method of Iwasaki et al.[6,7] The swallowing reflex was measured by a bolus injection of 1 mL of distilled water into the pharynx through an 8F nasal catheter. The reflex was evaluated by the latency time of response, which was the time from the injection to the onset of swallowing. This test was repeated three times, and the value was averaged. The normal reflex value was determined as 1.4 ± 0.4 seconds, and a reflex value >2.0 seconds was considered as a swallowing disorder.

Coughing reflex was also evaluated according to the method of Iwasaki et al.[8] The coughing reflex was initiated by inhalation of aqueous citric acid. A 10-step density water solution test was constructed (**Table 1**), and the patients were allowed to inhale the solutions in turn, beginning from the most diluted solution. The coughing reflex value was recorded at the density that caused at least five coughs within 30 seconds of inhalation. The normal value was 6.3 ± 1.3 mg/mL and a value >11.3 mg/mL (solution 5) was considered as a coughing disorder.

A sponge was placed into the mouth of the patient for 3 minutes, and was then submitted for the measurement of Substance P (SP). Samples were centrifuged and stored at −30°C until they were processed for the analysis of SP levels using a commercial kit (R&D Systems, Minneapolis, MN, USA), according to the manufacturer's protocols. Samples were taken between 06:00 and 07:00 hours and centrifuged at 3000 rpm for 8 min within 1 h. Within 30 min after centrifugation, plasma was mixed with a stabilizing agent and frozen at −30°C. Saliva SP level was then assayed by the enzyme-linked immunosorbent assay at Kyowa Medex Assay Center.

Study protocol

All patients undergoing cardiac surgery were preoperatively assessed for the presence or absence of swallowing and coughing disorders, as well as for the SP level in the saliva. The patients were then randomly assigned to the HKT group taking JPS-16 or to the placebo group by an envelope method. The assignment list was opened for us when the assessments of all endpoints were finished in each patient. The participants and care providers as well as those assessing the outcomes were all blinded in this study. The daily dose of JPS-16 or placebo was 7.5 g, and was administered orally three times before and during each meal for 1 to 14 days postoperatively. The patients were reassessed for the presence or absence of the swallowing reflex and cough reflex, and the SP level in the saliva on postoperative day 14.

Primary and secondary endpoints

The primary endpoint was the prevention of postoperative aspiration pneumonia. The secondary endpoint included complete recovery from swallowing and coughing disorders. Aspiration pneumonia was diagnosed according to the Japanese Respiratory Society guidelines for the management of hospital-acquired pneumonia in adults.[10] The diagnosis of aspiration pneumonia is the case that satisfies all of the following: (1) lung alveolar infiltration is detected on chest X-ray or chest computed tomography, (2) any two or more of the following are present: fever (≥37.5°C), high C-reactive protein (CRP) level, high white blood cell level (WBC; ≥9000/μL), and airway symptoms such as hemorrhoids, and (3) suspicion of aspiration. Freedom from swallowing and coughing disorders, the SP level in the saliva, WBC count, CRP level, days of postoperative hospital stay, and days of antibiotic treatment were also evaluated.

Termination, suspension, or interruption of study

This study was terminated when all of the observations and investigations prescribed in this study plan were

Table 2 Background and risk factors of the patients

	JPS-16	Placebo	*p* value
Age (years)	65.2 ± 13.9	69.2 ± 13.0	0.432
Sex			0.712
Male	10	14	
Female	3	3	
Weight (kg)	59.2 ± 11.6	60.1 ± 11.8	0.843
Obesity (BMI ≥ 25)	2	5	0.368
Cigarette smoking			0.469
Never	3	6	
Previous	10	11	
Current	0	0	
Brinkman index	306 ± 361	373 ± 442	0.661
Hypertension	9	7	0.127
Diabetes mellitus	5	6	0.858
COPD	0	1	0.373
Hemodialysis	0	1	0.374
ACEI	2	2	0.772
Restricted ventilation disorder	2	0	0.091
Obstructive ventilation disorder	2	3	0.859
Operation time (min)	333.2 ± 86.3	319.2 ± 67.5	0.622
Off-pump surgery	1	0	0.244
On-pump CABG	5	8	0.637
CPB time (min)	146.0 ± 83.5	121.1 ± 55.6	0.342
Opened pleural cavity	7	13	0.192
Disease			
Valvular disease	5	6	
IHD	6	8	
Valvular disease + IHD	2	2	
ASD	0	1	

p values were calculated using the Pearson χ^2 test for categorical data or the Student's t-test for continuous data. All continuous data were expressed as mean ± SD. The definition of restricted ventilation disorder is %VC < 80%. The definition of obstructive ventilation disorder is FEV1.0% < 70%. ACEI: angiotensin-converting enzyme inhibitor; ASD: atrial septal defect; BMI: body mass index; CPB: cardiopulmonary bypass; COPD: chronic obstructive pulmonary disease; FEV%1: forced expiratory volume % in one second; IHD: ischemic heart disease; JPS-16: JPS hangekobokuto extract granules; %VC: %vital capacity; CABG: coronary artery bypass grafting

completed. A subject was excluded from this study (1) when there was a request from a subject to cancel (participation cooperation refused), (2) when a subject's examination was interrupted owing to the subject's circumstances (e.g., moving, diverting, transferring, busy, and not continuing), (3) when the researcher or the research collaborating doctor judged that it would be difficult for a subject to continue with the study, and that cancellation was more appropriate.

Statistical analysis

All data were expressed as mean ± standard deviation (SD) unless otherwise specified. The Pearson χ^2 test was performed for categorical data, whereas the Student's t-test or a paired t-test was performed for continuous data. All statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered to indicate a statistically significant difference.

Results

Study groups

A total of 34 patients were registered in this study; four patients were dropped out. One patient refused to take medicine because of the bad taste. The family of two patients requested to stop taking medicine because the postoperative course was not smooth owing to congestive heart failure. In the other patient, medicine was

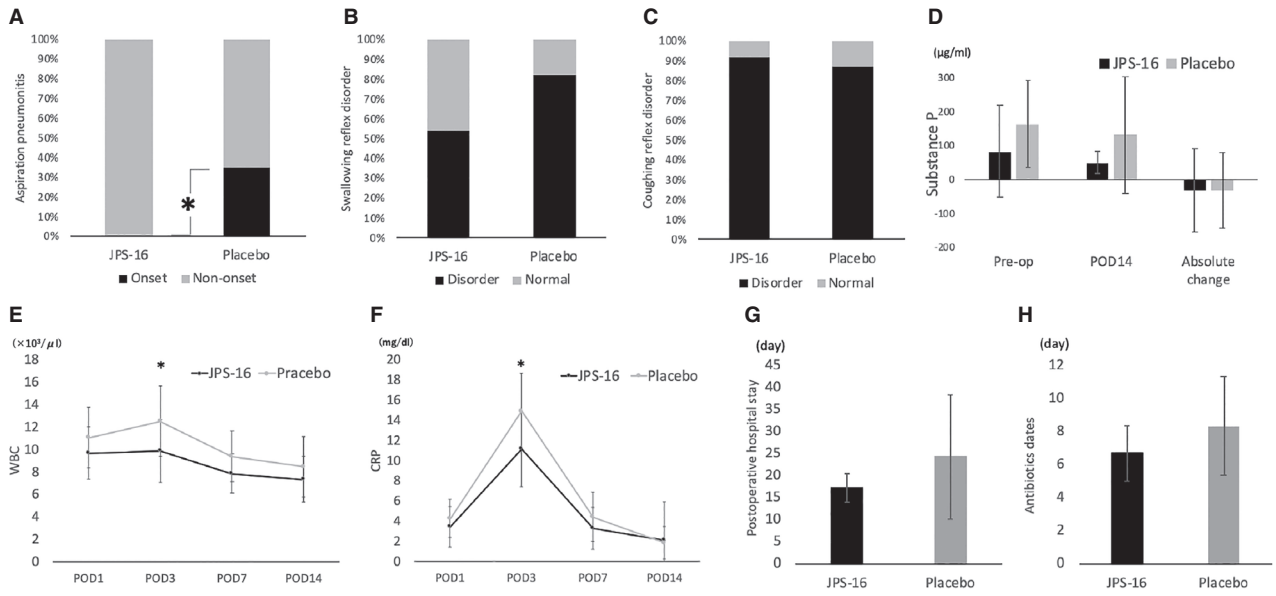

Fig. 2 (**A**) The difference in the rate of subjects with aspiration pneumonia between the JPS-16 and placebo groups. (**B**) The difference in the rate of subjects with swallowing reflex disorder between the JPS-16 and placebo groups. (**C**) The difference in the rate of subjects with coughing reflex disorder between the JPS-16 and placebo groups. (**D**) The difference in SP levels in the saliva between the JPS-16 and placebo groups. (**E**) The difference in WBC counts between the JPS-16 and placebo groups. (**F**) The difference in CRP levels between the JPS-16 and placebo groups. (**G**) The difference in the duration of postoperative hospital stay between the JPS-16 and placebo groups. (**H**) The difference in the duration of antibiotic treatment between the JPS-16 and placebo groups. CRP: C-reactive protein; JPS-16: JPS hangekobokuto extract granules; POD14: postoperative day 14; Pre-op: preoperative; SP: Substance P; WBC: white blood cell

stopped because of an accident unrelated to this study. Therefore, 30 of the 34 patients were forwarded to the analysis. In all, 13 patients were assigned to the HKT group and the other 17 to the placebo group. There were no significant differences in the patient backgrounds between these groups (**Table 2**). All patients were eventually discharged without problems.

Postoperative aspiration pneumonia

The incidence of postoperative aspiration pneumonia was significantly lower in the HKT group than in the placebo group (0% vs. 35%; $p = 0.017$, **Fig. 2A**).

Swallowing and coughing disorders

The rate of swallowing disorder on postoperative day 14 tended to be lower in the HKT group than in the placebo group (53.9% vs. 82.4%; $p = 0.091$, **Fig. 2B**). Coughing disorders were analyzed in 27 of the 30 patients; three patients refused the coughing reflex test because of the smell. There was no significant difference in the rate of coughing disorder on postoperative day 14 between the two groups (91.7% vs. 86.7%, $p = 0.681$, **Fig. 2C**).

SP levels in the saliva

SP levels in the saliva were analyzed in 22 of the 30 patients; eight patients did not have sufficient amounts of collected saliva. There were no significant differences in the change in SP levels in the saliva between the two groups (-32.7 ± 121.9 vs. -31.5 ± 111.4, $p = 0.981$, **Fig. 2D**).

Blood analysis

Blood analysis was carried out in 29 of the 30 patients on postoperative day 14. WBC counts on postoperative day 3 and the CRP levels on postoperative day 3 were significantly lower in the HKT group than in the placebo group ($p = 0.004$ and $p = 0.006$, respectively, **Fig. 2E** and **2F**).

Postoperative hospital stay and duration of antibiotic treatment

Three patients who had received an antibiotic for the preoperative treatment of infective endocarditis were excluded. The postoperative hospital stay (17.3 ± 3.2 vs. 24.4 ± 14.2, $p = 0.138$) and the duration of antibiotic treatment (6.7 ± 1.7 vs. 8.4 ± 3.0 days, $p = 0.124$) tended to be shorter in the HKT group than in the placebo group

(**Fig. 2G** and **2H**). As antibiotic, sulbactam/ampicillin was basically administrated. After the results of sputum culture were obtained, the antibiotic was changed to appropriate one. The administration period of the antibiotic was left to the judgment of the infection control team based on the laboratory findings and clinical findings.

Subgroup analysis of high-risk patients for aspiration pneumonia

The patients who were judged preoperatively as having both swallowing and coughing disorders were categorized as high-risk patients for aspiration pneumonia. In all, 21 (70%) of the 30 patients were categorized as high-risk patients for aspiration pneumonia, and subgroup analysis was carried out with these high-risk patients. Ten patients were assigned to the HKT group, whereas the other 11 were assigned to the placebo group. In the high-risk patients, the rate of subjects with postoperative aspiration pneumonia was significantly lower in the HKT group than in the placebo group (0% vs. 45%; $p = 0.015$, **Fig. 3A**). The rate of subjects with swallowing disorders on postoperative day 14 was significantly lower in the HKT group than in the placebo group (50% vs. 91%; $p = 0.038$, **Fig. 3B**). However, there was no significant difference in the rate of subjects with coughing disorders between the two groups. There were also no significant differences in changes in SP levels in the saliva between the two groups (-36.8 ± 129.6 vs. -3.2 ± 102.7, $p = 0.560$). WBC counts on postoperative days 3 and 7 were significantly lower in the HKT group than in the placebo group ($p = 0.006$ and $p = 0.032$, respectively). CRP levels on postoperative day 3 were also significantly lower in the HKT group than in the placebo group ($p = 0.028$). The duration of postoperative hospital stay (17.9 ± 2.8 vs. 26.3 ± 17.1 days, $p = 0.165$) and the duration of antibiotic treatment (6.7 ± 1.8 vs. 9.1 ± 3.5 days, $p = 0.075$) also tended to be shorter in the HKT group than in the placebo group.

Discussion

HKT is written in a classic clinical book on traditional Chinese medicine called "Kinkiyoryaku (Essential Prescriptions from the Golden Cabinet)," by Zhang Zhongjing (150–219) at the end of the Eastern Han dynasty. HKT contains five types of herbal ingredients: Pinelliae tuber (hange), Magnoliae cortex (koboku), Hoelen (bukuryo), Zingiberis rhizoma (shokyo), and Perillae herba (soyo). The quantity of the herbal ingredients can be differed by pharmaceutical company.

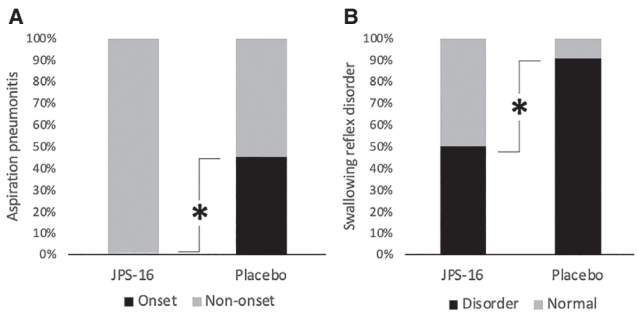

Fig. 3 (**A**) The difference in the rate of high-risk subjects with aspiration pneumonitis between the JPS-16 and placebo groups. (**B**) The difference in the rate of high-risk subjects with swallowing reflex disorder between the JPS-16 and placebo groups. JPS-16: JPS hangekobokuto extract granules

Our study clearly demonstrated that the administration of HKT significantly prevented the onset of aspiration pneumonia in patients undergoing cardiovascular surgery who were at high risk of aspiration pneumonia. HKT significantly improved swallowing disorder, which is closely associated with aspiration pneumonia, in the high-risk patients. This significantly suppressed the inflammatory reaction during the early postoperative period. Postoperative hospital stay and duration of antibiotic treatment also tended to be decreased. These results suggest that HKT should be useful in preventing aspiration pneumonia in high-risk patients undergoing cardiovascular surgery. Clinically, the high risk of aspiration pneumonia after cardiovascular surgery includes a history of cerebrovascular disease, neurological deficit after surgery, and chronic obstructive pulmonary disease.[11,12]

The incidence of postoperative aspiration pneumonia after cardiovascular surgery was reported to be 9.8% in a Japanese university hospital,[11] whereas it was as high as 35% in the placebo group of our study. The ratio of on-pump coronary artery bypass grafting (CABG) in this study (43%) is higher than in Miyata et al (9.7%). Our study also included as many as 70.0% of high-risk patients who had disorders of both swallowing and coughing reflexes. These factors may underlie the predisposition to develop aspiration pneumonia.

The relationship between aspiration pneumonia and SP has been elucidated in patients with cerebral infarction or Parkinson's disease. SP is a neuropeptide acting as a neurotransmitter and neuromodulator, and is an important trigger of swallowing and coughing reflexes.[13,14] SP levels in the saliva are known to be low in patients with swallowing or coughing disorder.[15,16] SP is released from sensory nerve terminals to the mucous membrane

of the pharynx, larynx, or trachea.[13,14,17] The amount of SP is closely related to the amount of dopamine, which is produced by the substantia nigra striatum in the basal nuclei.[16,18] The dopamine level is decreased when the basal nuclei suffer from cerebral infarction or Parkinson's disease.[19] Patients with cerebral infarction or Parkinson's disease are more likely to develop aspiration pneumonia.[19,20]

ACE is known to be involved in SP catabolism; SP is degraded by ACEs, and its action is potentiated by ACEI.[5] HKT also modulates the cerebral levels of 5-hydroxytryptamine, noradrenaline, dopamine, and SP.[21] Therefore, ACEI and HKT have been used for preventing aspiration pneumonia in patients with cerebral, respiratory, and other diseases.[4,5] In the present study, the relationship between HKT and SP was investigated in patients undergoing cardiovascular surgery, but there was no significant difference in the changes in SP levels in the saliva between the HKT and placebo groups. This result suggests that HKT may have a different mechanism from SP on swallowing disorders.

In addition, HKT appeared to be safe for patients undergoing cardiovascular surgery. Two patients dropped out from this study because of congestive heart failure, which was less likely to occur with HKT; heart failure is not described in the information on the side effects of HKT and each of its herbal ingredients.

In terms of the cost and benefit, inexpensive Kampo medicines, such as HKT, can reduce the overall medical expenditure.[22] The financial management of the insurance system has shown severe development in recent years due to the increase in the national medical expenses. The balance of the country of debt was ¥ 1,503,357.2 billion in the end of March 2015, and the debt per capita based on population was calculated as approximately ¥ 830,000.[23]

Study limitations

This study has some limitations. *First*, although this was a prospective, randomized study, the series was relatively small being a single-center study. *Second*, the SP level was not measurable in 27% of the patients; the amount of SP was not sufficient for measuring SP level because of dehydration after cardiovascular surgery. This may affect the SP results. *Third*, the use of ACEI was not stopped because it was necessary to maintain the patients' condition.

Conclusions

Aspiration pneumonia can be prevented by HKT in patients after cardiovascular surgery, and it is expected to reduce the duration of postoperative hospital stay as well as antibiotic treatment. In high-risk patients for aspiration pneumonia, HKT significantly prevented aspiration pneumonia and improved swallowing disorders. A larger cohort study is required to fully establish the efficacy and safety of HKT in patients undergoing cardiovascular surgery.

Acknowledgments

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Disclosure Statement

The authors declare that they have no conflicts of interest associated with this research. Part of this study was presented at the 68th Annual Scientific Meeting of the Japanese Association for Thoracic Surgery.

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