Journal of Cardiology 74 (2019) 412–417

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# Effects of Mokuboito, a Japanese Kampo medicine, on symptoms in patients hospitalized for acute decompensated heart failure – A prospective randomized pilot study

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ARTICLE INFO

*Article history:*
Received 14 March 2019
Received in revised form 1 May 2019
Accepted 11 May 2019
Available online 2 July 2019

*Keywords:*
Mokuboito
Acute decompensated heart failure
Visual analog scale

ABSTRACT

*Background:* Although standard treatment for heart failure (HF) has been established, it remains difficult to relieve HF-associated symptoms in some patients. Kampo medicines have been used to treat various diseases; however, it remains unclear whether they are effective in HF patients. We therefore performed a prospective, randomized, controlled trial to investigate whether Mokuboito, a Kampo medicine, affected symptoms and other parameters in hospitalized patients with acute decompensated HF (ADHF), as compared to standard therapy alone.

*Methods:* Forty patients were allocated randomly to Group S (standard therapy alone) or Group M (oral administration of Mokuboito plus standard therapy). The primary outcome was changes in global clinical status based on a visual analog scale (VAS) from baseline at day 10 or discharge if earlier.

*Results:* The decrease in VAS score was significantly greater in Group M than Group S ($p = 0.001$). Although there were no differences between the groups in changes in the secondary endpoints of body weight, peripheral edema, biochemical and echocardiographic parameters, left ventricular end-diastolic diameter, and serum total bilirubin levels were significantly reduced in Group M ($p = 0.038$; 0.002, respectively) but not in Group S, implying that Mokuboito might attenuate organ congestion and cardiac preload.

*Conclusions:* Oral administration of Mokuboito significantly improved ADHF-related symptoms. Our observations might provide the basis for a novel therapeutic strategy in hospitalized patients with ADHF.


## Introduction

Recent progress in treatments for heart failure (HF) has contributed to a better patient prognosis. Standard therapy for HF using medications such as beta-blockers [1–3], angiotensin-converting enzyme inhibitors [4,5] or mineral corticoid receptor antagonists [6,7] has been established based on accumulating evidence obtained in several clinical trials. In addition to these drugs, cardiac resynchronization therapy [8] and adaptive servo ventilation [9,10] reportedly improve symptoms and re-admission rates in patients with HF. However, even if such standard therapies are fully performed, it remains difficult to relieve HF-associated symptoms in some patients. We therefore focused on the use of Kampo medicines (Japanese traditional herbal medicines) in the treatment of HF patients in addition to current standard therapy using Western medicines. Mokuboito is a Japanese Kampo preparation which has a long history as an oral treatment for the symptoms of HF [11]. Our previous retrospective study [12] had suggested that Mokuboito improved symptoms in 12 consecutive patients with severe intractable HF as compared to standard therapy alone.

Although Mokuboito has been used for HF-associated symptoms for a long time, due to a lack of reliable clinical trials, it remains unclear whether Mokuboito is actually beneficial in

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https://doi.org/10.1016/j.jjcc.2019.05.003

treating HF symptoms. We therefore performed a prospective, randomized, controlled trial as a pilot study to investigate whether adding Mokuboito therapy affected symptoms and other parameters in hospitalized patients with acute decompensated HF (ADHF) as compared to standard therapy alone.

## Materials and methods

### *Study population*

Forty consecutive patients admitted to the Tokorozawa Heart Center due to ADHF were prospectively included. They were those who satisfied the inclusion criteria of needing admission for ADHF and giving written informed consent, and did not meet the exclusion criteria. The main exclusion criteria were: (1) younger than 20 years old, (2) communication not possible due to bronchial intubation or shock vital, (3) pregnancy, (4) inability to take oral medicine, (5) inability to undergo examinations (e.g. body weight measurement) due to orthopnea, and (6) having a doctor who did not agree to participate in the study.

### *Study design*

This study was a randomized controlled, open-label study in a single center. To our knowledge, it is the first study to investigate the effect of a Kampo medicine prospectively in patients with ADHF and we therefore planned it as a pilot study. It was realistically possible to enroll the study population of 40 at our institute in a short time. ADHF was diagnosed by each physician according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [13].

After obtaining informed consent, the subjects were assigned to receive standard therapy alone (Group S) or to receive Mokuboito in addition to standard therapy (Group M), within 24 h of admission (Fig. 1), and, except for Mokuboito, the respective physicians in charge of them could independently decide on the medication they would use. The subjects were randomized in a 1:1 fashion to Group S and Group M via a minimization method using a software cloud service.

The primary endpoint was patient-assessed changes in global clinical status based on a visual analog scale (VAS, described in detail below) at day 0 (on admission) and day 10 or discharge if earlier. Secondary endpoints were changes in body weight, plasma brain natriuretic peptide (BNP) concentration, echocardiographic and biochemical parameters, and the degree of peripheral edema, at day 0 and day 10 or discharge if earlier. This study was registered with the University Hospital Medical Information Network-Clinical Trials registry (UMIN-CTR number: UMIN000026621). The Ethics Committee of Tokorozawa Heart Center approved the study protocol (No. H28-3) in accordance with the Declaration of Helsinki, and all patients gave written informed consent to participate.

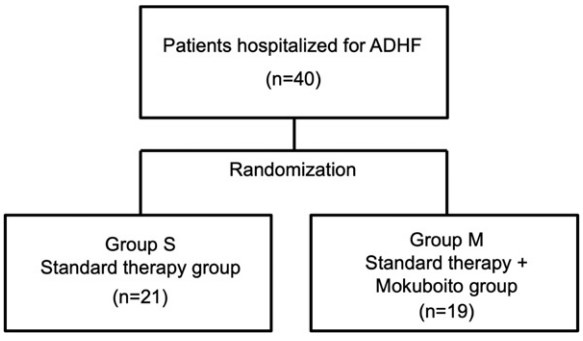


**Fig. 1.** Study design.
ADHF, acute decompensated heart failure.

### *Mokuboito*

We used TSUMURA dried extract of Mokuboito granules, 7.5 g of which contain 1.5 g of the dried extract of the following mixed crude drugs: JP Gypsum 10.0 g, JP Sinomenium Stem 4.0 g, JP Cinnamon Bark 3.0 g, JP Ginseng 3.0 g (JP: The Japanese Pharmacopoeia). Mokuboito was administered orally with lukewarm water before every meal.

### *Visual analog scale and evaluation of peripheral edema*

A VAS was used to evaluate the global clinical status of the symptoms due to HF. We asked the subjects how much they were suffering from HF-associated symptoms such as dyspnea, peripheral edema, general fatigue, and appetite loss. Then we asked them to indicate their suffering by marking the position on the line of the scale printed on the sheet. We used a 100-mm line, where the left edge was 0 mm and right edge 100 mm. Zero mm and 100 mm respectively indicated “the best state you can imagine” and “the worst state you can imagine”. The VAS evaluation was performed at day 0 (on admission) and at day 10 or discharge if earlier. Peripheral edema was checked and quantified, grading it from 0 to 4 every day.

### *Biochemical parameters*

Blood levels of total bilirubin (T-Bil), aspartate amino transferase (AST), alanine amino transferase (ALT), lactate dehydrogenase (LDH), urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K), and BNP were measured at admission and day 10 or discharge if earlier.

### *Echocardiography*

Standard 2D Doppler echocardiography (HD15 High Definition Ultrasound Systems, Royal Philips, Amsterdam, Netherlands; Philips Electronics Japan, Tokyo, Japan) was performed in all subjects. We obtained echocardiographic parameters at day 0 and day 10 or discharge if earlier, which were left ventricular ejection fraction (LVEF) by the Teichholtz method, end-diastolic left ventricular diameter (LVDd), $E/e'$ ($E$: early wave of mitral inflow, $e'$: peak early diastolic mitral annular velocity of the septal wall side), and maximum inferior vena cava diameter (IVCd).

### *Statistical analysis*

We have presented categorical variables as frequency with percentage (%). Quantitative variables are presented as mean with standard deviation. Fisher’s exact test was used to determine any differences in categorical variables between two groups. Differences in quantitative variables between groups were analyzed using Student’s $t$ test for parametric distributed variables and the Mann–Whitney $U$ test for nonparametric distributed variables. Differences in parameters between on admission and day 10 or discharge if earlier were analyzed using the paired $t$ test for parametric distributed variables, and the Wilcoxon signed-rank test for nonparametric distributed variables. Differences between groups in changes in parameters from baseline after each therapy were analyzed using analysis of covariance (ANCOVA). ANCOVA was conducted using baseline parameters as covariates. Positive significance was defined as probability of less than 0.05 for 2-sided tests. The descriptive assessments and analytical statistics were performed with STATA/IC 15.1 (StataCorp LLC, College Station, TX, USA).

**Table 1**
Patient characteristics.

| | Group S | Group M | *P* value |
|---|---|---|---|
| Number of patients | 21 | 19 | – |
| Age, years old | 78.2 ± 9.1 | 78.5 ± 7.7 | 0.97* |
| Gender, male, No. (%) | 15 (71.4) | 13 (68.4) | 1.00 |
| BMI, kg/m$^2$ | 23.6 ± 2.2 | 22.4 ± 2.6 | 0.14* |
| Classification of heart failure severity, No. (%) | | | |
| NYHA | | | |
| 1 | 0 (0) | 0 (0) | 0.79 |
| 2 | 5 (23.8) | 5 (26.3) | |
| 3 | 7 (33.3) | 8 (42.1) | |
| 4 | 9 (42.9) | 6 (31.6) | |
| CS | | | |
| 1 | 12 (57.1) | 12 (63.2) | 0.66 |
| 2 | 7 (33.3) | 4 (21.1) | |
| 3 | 2 (9.5) | 3 (15.8) | |
| Nohria | | | |
| A | 0 (0) | 0 (0) | 0.27 |
| B | 8 (38.1) | 10 (52.6) | |
| L | 0 (0) | 1 (5.3) | |
| C | 13 (61.9) | 8 (42.1) | |
| Underlying heart disease, No. (%) | | | |
| IHD | 17 (81.0) | 4 (21.1) | <0.01 |
| Valvular disease | 3 (14.2) | 8 (42.1) | 0.08 |
| Af | 10 (47.6) | 15 (78.9) | 0.06 |
| DCM | 0 (0) | 1 (5.3) | 0.48 |
| Clinical classification of heart failure using left ventricular ejection fraction, No. (%) | | | |
| HFrEF | 14 (66.7) | 10 (52.6) | 0.52 |
| HFmrEF | 3 (14.3) | 4 (21.1) | 0.69 |
| HFpEF | 4 (19.0) | 5 (26.3) | 0.71 |
| Risk factors, No. (%) | | | |
| HTN | 17 (81.0) | 7 (36.8) | <0.01 |
| DM | 13 (61.9) | 5 (26.3) | 0.03 |
| CKD | 13 (61.9) | 8 (42.1) | 0.34 |
| Current smoker | 3 (14.3) | 1 (5.3) | 0.61 |
| Prior medication, No. (%) | | | |
| RAS inhibitor | 13 (61.9) | 12 (63.2) | 1.00 |
| Beta blocker | 14 (66.7) | 13 (68.4) | 1.00 |
| MRA | 2 (10.0) | 5 (26.3) | 0.23 |
| Digitalis | 1 (4.76) | 2 (10.5) | 0.60 |
| Diuretics | 13 (61.9) | 11 (57.9) | 1.00 |
| Pimobendan | 3 (14.3) | 6 (31.6) | 0.26 |
| Tolvaptan | 3 (14.3) | 0 (0) | 0.23 |
| Amiodarone | 2 (9.5) | 4 (21.1) | 0.40 |

*P* value was calculated using Fisher's exact test unless otherwise indicated.
* *P* value was analyzed using Student's *t* test for parametric distributed variables and Mann–Whitney test for nonparametric distributed variables.
*Abbrevations*: BMI, body mass index; NYHA, New York heart Association Functional Classification; CS, clinical scenario of acute decompensated heart failure; Nohria, Nohria–Stevenson classification of acute heart failure syndrome; IHD, ischemic heart disease; Af, atrial fibrilation; DCM, dilated cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; RAS, renin–angiotensin system; MRA, mineralocorticoid receptor antagonist.
Age and BMI are presented as mean ± SD.

## Results

### *Baseline characteristics*

The baseline characteristics of each group (Group S and Group M) are shown in Table 1. There were no differences between the groups in age, gender, body mass index, clinical classification of HF using LVEF, prior medications, or severity of HF as evaluated using the New York Heart Association Functional Classification, Clinical Scenario of acute heart failure syndrome [14], and Nohria–Stevenson classification [15] (Table 1). However, percentages of subjects in Group S were significantly higher than those in Group M for ischemic heart disease (IHD), hypertension, and diabetes mellitus (Table 1).

**Table 2**
Patient characteristics. Medications used in therapeutic period.

| | Group S | | Group M | | *P* value |
|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | |
| Dobutamin div. | 7 | (33.3) | 7 | (36.8) | 1.00 |
| PDE-3 inhibitor div. | 14 | (66.7) | 13 | (68.4) | 1.00 |
| Vasodilators div. | 9 | (42.9) | 5 | (26.3) | 0.33 |
| Furosemide i.v. | 19 | (90.5) | 16 | (84.2) | 0.65 |
| RAS inhibitor, oral | 18 | (85.7) | 19 | (100) | 0.23 |
| MRA, oral | 9 | (42.9) | 12 | (63.2) | 0.26 |
| Beta blocker, oral | 14 | (66.7) | 16 | (84.2) | 0.28 |
| Diuretics, oral | 21 | (100) | 17 | (89.5) | 0.22 |
| Tolvaptan, oral | 8 | (38.1) | 1 | (5.3) | 0.02 |
| Digitalis, oral | 1 | (4.8) | 2 | (10.5) | 0.60 |
| Pimobendan, oral | 16 | (76.2) | 14 | (73.7) | 1.00 |

*Abbrevations*: PDE-3, phosphodiesterase 3; RAS, renin–angiotensin system; MRA, mineralocorticoid receptor antagonist *P* values were analyzed using Fisher's exact test.

### *Overview of treatments for ADHF*

The medications used to treat ADHF are shown in Table 2. There were no differences between the groups in patient populations treated with the agents administered intravenously. There were also no differences between the groups in the percentage of subjects treated with renin–angiotensin system inhibitors, mineral corticoid receptor antagonists, beta-blockers, diuretics, digitalis, and pimobendan. In contrast, tolvaptan was used significantly more in Group S than Group M (38.1% vs. 5.26%, $p = 0.021$).

In Group M, Mokuboito was well-tolerated in all subjects throughout the study period with no side effects as compared to Group S. Thirty-nine patients were responsive to the treatment, and discharged on foot. Unfortunately, 1 patient in Group S died from multiple organ failure due to progressed ADHF on day 11.

### *Changes in ADHF-related parameters after treatment*

The clinical, biochemical, and echocardiographic parameters at baseline and on day 10 or discharge if earlier are shown in Table 3. There were no differences between the groups in these parameters at baseline.

As a favorable response to the treatment for ADHF at day 10 or discharge, VAS and body weight were significantly reduced but peripheral edema was not affected, in both groups (Table 3). Plasma BNP levels were significantly decreased after the ADHF treatment in both groups (Table 3), also suggesting a favorable effect of treatment. Elevated levels of AST, ALT, and LDH due to ADHF-induced liver congestion were decreased in both groups. In contrast, T-Bil levels were significantly reduced only in Group M.

Levels of serum BUN and Cr were significantly increased after the treatment in both groups, mirroring intravascular dehydration during ADHF treatment, mainly due to administration of diuretics. Serum electrolyte levels were also presumably affected by diuretics: Na and K levels were significantly reduced, respectively, in Group M and S.

Both ADHF therapies significantly increased LVEF, and reduced $E/e'$ and IVCd, indicating improvement of abnormal echocardiographic parameters due to ADHF. LVDd, an indicator of cardiac preload, was significantly decreased after treatment in Group M, but not in Group S.

To assess the effects of Mokuboito, we compared the changes from baseline ($\Delta$) in various parameters between the 2 groups (Table 4). $\Delta$VAS was significantly greater in Group M than in Group S ($-62.2 \pm -25.4$ vs. $-33.0 \pm -30.6$, $p = 0.001$); however,

**Table 3**
Clinical, biochemical and echocardiographic parameters on admission and day 10 or discharge if earlier.

| | Group S | | | Group M | | | Group S vs. Group M baseline |
|---|---|---|---|---|---|---|---|
| | Baseline | Day 10 or discharge | *P* value | Baseline | Day 10 or discharge | *P* value | |
| VAS, mm | 64.1 ± 26.0 | 31.2 ± 24.9 | <0.01 | 71.8 ± 23.9 | 9.6 ± 11.5 | <0.01 | 0.34 |
| Body weight, kg | 60.0 ± 8.0 | 56.5 ± 8.1 | <0.01 | 57.2 ± 9.8 | 53.2 ± 9.7 | <0.01 | 0.32 |
| Edema, No. (%) | | | | | | | |
| 0 | 4 (19.1) | 12 (57.1) | | 5 (26.3) | 14 (73.7) | | |
| 1 | 1 (4.8) | 3 (14.3) | | 2 (10.5) | 5 (26.3) | | |
| 2 | 12 (57.1) | 4 (19.1) | | 8 (42.1) | 0 (0) | | |
| 3 | 4 (19.1) | 2 (9.5) | | 3 (15.8) | 0 (0) | | |
| 4 | 0 (0) | 0 (0) | 0.44* | 1 (5.3) | 0 (0) | 0.25* | 0.81* |
| Biochemical parameters | | | | | | | |
| BNP, pg/ml | 1082 ± 683 | 656 ± 1182 | <0.01 | 802 ± 417 | 248 ± 250 | <0.01 | 0.25 |
| T-Bil, mg/dl | 0.9 ± 0.4 | 0.71 ± 0.2 | 0.11 | 0.9 ± 0.4 | 0.7 ± 0.19 | <0.01 | 0.76 |
| AST, U/l | 45.1 ± 44.0 | 23.8 ± 13.5 | <0.01 | 34.9 ± 18.6 | 24.4 ± 13.1 | <0.01 | 0.80 |
| ALT, U/l | 35.4 ± 37.3 | 18.2 ± 16.4 | <0.01 | 25.8 ± 21.4 | 16.3 ± 10.1 | <0.01 | 0.66 |
| LDH, U/l | 310 ± 132 | 290 ± 421 | <0.01 | 299 ± 84.1 | 194.8 ± 53 | <0.01 | 0.68 |
| BUN, mg/dl | 27.4 ± 13.1 | 35.4 ± 18.9 | 0.04 | 20.9 ± 8.8 | 31.3 ± 14.7 | <0.01 | 0.06 |
| Cr, mg/dl | 1.3 ± 0.6 | 1.70 ± 1.0 | 0.03 | 1.1 ± 0.5 | 1.3 ± 0.57 | <0.01 | 0.12 |
| Na, mEquiv./l | 142 ± 2.7 | 140 ± 2.8 | 0.11 | 143 ± 2.6 | 141 ± 2.4 | <0.01 | 0.05 |
| K, mEquiv./l | 4.5 ± 0.8 | 4.1 ± 0.7 | 0.04 | 4.3 ± 0.4 | 4.4 ± 0.51 | 0.18 | 0.38 |
| Echocardiographic parameters | | | | | | | |
| LVEF, % | 37.7 ± 14.1 | 44.6 ± 14.5 | 0.01 | 39.3 ± 16.5 | 49.0 ± 16.4 | <0.01 | 0.75 |
| LVDd, mm | 55.1 ± 6.7 | 54.0 ± 7.7 | 0.45 | 53.8 ± 10.0 | 51.8 ± 9.7 | 0.04 | 0.63 |
| *E*/*e*′ | 20.1 ± 7.3 | 15.9 ± 5.5 | 0.04 | 18.8 ± 6.7 | 15.1 ± 4.7 | 0.02 | 0.58 |
| IVCd, mm | 20.7 ± 5.5 | 16.6 ± 5.2 | <0.01 | 19.1 ± 3.4 | 15.7 ± 3.0 | <0.01 | 0.28 |

*Abbrevations*: VAS, visual analog scale; T-Bil, total bilirubin; AST, aspartate amino transferase; ALT, alanine amino transferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; *E*/*e*′, early wave of mitral inflow/peak early diastolic mitral annular velocity of septal wall side; IVCd, maximum diameter of inferior vena cava.
Values are presented as mean ± SD except for edema.
*P* values were analyzed using Student's *t* test for parametric distributed variables and Mann–Whitney test for nonparametric distributed variables unless otherwise indicated.
* *P* value was analyzed using Fisher's exact test.
Logarithmic transformation was conducted before analyzing BNP using Student's *t* test.

**Table 4**
Changes from baseline in various parameters after treatments.

| | Group S | Group M | *P* value |
|---|---|---|---|
| ΔVAS, mm | −33.0 ± 30.6 | −62.2 ± 25.4 | <0.01 |
| ΔBody weight, kg | −3.0 ± 3.0 | −3.97 ± 2.8 | 0.24 |
| Edema | – | – | 0.82* |
| Biochemical parameters | | | |
| ΔBNP, pg/ml | −426 ± 1356 | −554 ± 431 | 0.18 |
| ΔT-Bil, mg/dl | −0.2 ± 0.5 | −0.3 ± 0.4 | 0.58 |
| ΔAST, U/l | −21.3 ± 45.2 | −10.5 ± 14.5 | 0.74 |
| ΔALT, U/l | −17.2 ± 31.1 | −9.5 ± 15.8 | 0.86 |
| ΔLDH, U/l | −20.5 ± 431 | −104 ± 63.2 | 0.36 |
| ΔBUN (mg/dl) | 7.9 ± 17.8 | 10.4 ± 10.9 | 0.85 |
| ΔCr, mg/dl | 0.4 ± 0.9 | 0.2 ± 0.2 | 0.27 |
| ΔNa, mEquiv./l | −1.3 ± 3.6 | −2.5 ± 1.9 | 0.86 |
| ΔK, mEquiv./l | −0.4 ± 0.9 | 0.1 ± 0.4 | 0.08 |
| Echocardiographic parameters | | | |
| ΔLVEF, % | 6.9 ± 11.1 | 9.7 ± 10.6 | 0.77 |
| ΔLVDd, mm | −1.1 ± 6.2 | −2.0 ± 3.9 | 0.32 |
| Δ*E*/*e*′ | −3.4 ± 6.6 | −3.7 ± 6.5 | 0.62 |
| ΔIVCd, mm | −4.4 ± 3.7 | −3.4 ± 3.9 | 0.43 |

*Abbrevations*: VAS, visual analog scale; T-Bil, total bilirubin; AST, aspartate amino transferase; ALT, alanine amino transferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; *E*/*e*′, early wave of mitral inflow/peak early diastolic mitral annular velocity of septal wall side; IVCd, maximum diameter of inferior vena cava; Δ means change from baseline; ANCOVA, analysis of covariance.
Values are presented as mean ± SD except for edema.
*P* values were analyzed using ANCOVA unless otherwise indicated.
Logarithmic transformation was conducted before analyzing BNP using ANCOVA.
* *P* value was analyzed using Fisher's exact test.

there were no significant differences between the groups in body weight, degree of peripheral edema, or biochemical and echocardiographic parameters. As shown in Fig. 2, the differences in ΔVAS between the groups were not dependent on the baseline levels.

## Discussion

We investigated the additive effects of Mokuboito in hospitalized patients with ADHF in the present pilot study. This revealed a greater improvement in ADHF-related symptoms evaluated using

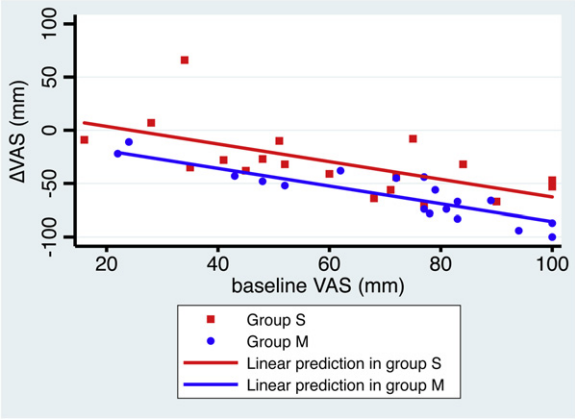


**Fig. 2.** ΔVAS vs. baseline VAS in two groups was analyzed with ANCOVA. ΔVAS, change in visual analog scale from baseline; ANCOVA, analysis of covariance; M, standard therapy plus Mokuboito; S, standard therapy alone.

VAS in subjects treated with Mokuboito than those with standard therapy alone. Although there were no differences between the two groups in changes from before to after the study period, only for subjects treated with Mokuboito, there was a significant reduction in serum T-Bil levels and the echocardiographic parameter LVDd after treatment, implying that Mokuboito might attenuate organ congestion and cardiac preload.

Formulas for Mokuboito first appear in "Jin Gui Yao Lue", a classic clinical text of traditional Chinese medicine written about 1800 years ago. It states, "Mokuboito is effective for patients suffering from dyspnea with wheeze, hardness in the epigastric region and upper abdomen, and cyanosis." These symptoms are considered to be those of congestive heart failure. Although the precise mechanisms for the cardioprotective effects remains unclear, Sinomenine, one of the crude drugs in Mokuboito, is believed to be the main contributor to its favorable properties [16]. In this regard, several basic researches observed that Mokuboito had vasodilative [17] and protective effects against myocardial injury [18]. We therefore previously performed a retrospective observational study to investigate the effects of Mokuboito in 12 consecutive patients with intractable heart failure [12]. The symptoms due to heart failure were improved in all patients and plasma BNP levels were decreased significantly after the treatment with Mokuboito. Such observations lead us to perform a prospective, randomized, controlled trial to investigate the effects of Mokuboito in patients with ADHF.

The present study revealed that Mokuboito significantly improved symptoms due to ADHF as evaluated using the VAS (Table 4, Fig. 2). To explore mechanisms for this favorable effect, we focused on echocardiographic and biochemical parameters. LVDd and serum T-Bil levels are known to be independent indicators of cardiac preload and body congestion due to right HF [19]. Although there were no differences between the two groups in the changes from baseline after therapy, LVDd and T-Bil levels were significantly reduced only in Group M, but not Group S (Table 3). These results suggest that the beneficial effects of Mokuboito might be due to reducing cardiac preload and attenuating congestion. In addition to body congestion, low cardiac output also causes ADHF-related symptoms, such as fatigue. Before and after the study period, we measured LVEF as an inotropic parameter, which significantly increased in both groups. However, there was no difference between two groups in ΔLVEF.

As shown in Table 2, there was no difference between the groups in numbers of subjects treated with intravenous and oral diuretics. In contrast, torvaptan was less used in Group M than Group S, whereas there was no difference between the two groups in changes in body weight and edema. These observations indicate that physicians in charge of particular patients treated more in Group S than in Group M to achieve the goals for the ADHF-related factors of body weight and edema. Unfortunately, we did not count urine output; therefore, it remains unclear whether Mokuboito has diuretic effects. Future studies will need to include urine output as a secondary endpoint. The present study also revealed that Mokuboito attenuated hypokalemia (Table 3) due to treatment for ADHF, presumably with loop-diuretics, despite the fact that there was no difference between the groups in numbers of subjects treated with loop-diuretics. In Kampo medicine, Mokuboito has been called a "water utilization agent" meaning that it achieves an appropriate distribution of water throughout the body depending on water needs [20]. This property of Mokuboito might have beneficial effects in patients with ADHF with respect to body congestion and hypokalemia induced by loop-diuretics. However, it remains unclear how Mokuboito exerts such effects and therefore further investigation will be needed to explore the underlying mechanisms.

Regarding the safety of Mokuboito, we had been concerned that, in subjects with reduced LVEF or hypotension, Mokuboito might exert a harmful effect, because Lim et al. [21] noted that ADHF patients with a low EF and hypotension had a poor prognosis within 30 days. However, as mentioned above, there were no subjects with persistent hypotension or shock during the study. We also observed no difference in ΔVAS between with or without low LVEF/hypotension, both at baseline and after the treatment.

## Study limitations

The present study has several limitations. First, it was a single center, open-label, pilot study. As the number of participants was small, a large-scale multi-center study will be needed in the future to further investigate not only HF-related symptoms or biochemical/echocardiographic parameters, but also hard end-points such as mortality. Second, it should have used a placebo to obtain a more robust conclusion; however, it is difficult to prepare a placebo since Kampo preparations have a unique smell and flavor. Third, in the present study, we observed short-term effects and therefore, further studies investigating the long-term effects and safety of Mokuboito should be performed. Finally, Group S included more subjects with ischemic heart disease, hypertension, and diabetes mellitus and such bias might have affected the results of this study.

## Conclusions

Oral administration of Mokuboito significantly improved ADHF-related symptoms, presumably due to reduction of congestion and cardiac preload. The observations of this study provide the basis for a novel therapeutic strategy using Mokuboito in hospitalized patients with ADHF.

## Funding

This research received no grant from any public, commercial or non-profit funding organization.

## Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

## Acknowledgment

We appreciate Mr. Alexander Cox for the English proofreading of our manuscript.

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