Clinical evaluation of Moku-boi-to (Mu-Fang-Yi-Tang) : A Japanese and Chinese traditional medicine for heart failure

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Abstract

As for Japanese and Chinese traditional Kampo medicine for treatment of heart failure, Moku-boi-to (Mu-Fang-Yi-Tang) is the most widely known; however, the efficacy of traditional medicines has been assessed only qualitatively, based on the improvement of symptoms and it is difficult to estimate it accurately based on clinical examinations. The plasma concentration of brain natriuretic peptide (BNP) is an indicator of the degree of heart failure or cardiac function. Thus, we tried to investigate the effect of Moku-boi-to in patients with heart failure based on a qualitative assessment of symptoms and on the changes in the plasma concentration of BNP. We studied 12 patients with moderate chronic heart failure [New York Heart Association (NYHA) class 2 or 3]. We assessed the effect of Moku-boi-to using Moku-boi-to extract granules (Tsumura Co.,Ltd., Tokyo, Japan) (TJ-36). Before and after treatment with TJ-36 for more than 12 weeks, we investigated heart failure symptoms, NYHA class, plasma BNP concentration, as well as several other parameters. In this study we observed cardiac arrhythmia in 2 patients (16.7%). Of the 12 patients, nine showed improvement of the symptoms (75.0%). In the 10 patients in whom we measured all parameters, the decrease of plasma BNP concentration and the improvement of NYHA class were significant ($p<0.01$). Thus we think that Moku-boi-to may serve as an adjuvant to other therapies for heart failure.

Key words Moku-boi-to (Mu-Fang-Yi-Tang), heart failure, brain natriuretic peptide (BNP), NYHA classification.

Abbreviations Moku-boi-to (Mu-Fang-Yi-Tang, 木防已湯) ; BNP, brain natriuretic peptide ; Gypsum fibrosum, 石膏 ; Sinomeni caulis rhizoma, 防已 ; Cinnamomi cortex, 桂皮; Ginseng radix, 人参.

Introduction

Among Japanese and Chinese traditional Kampo medicines for heart failure, Moku-boi-to (Mu-Fang-Yi-Tang) is quite well known.[1-3)] Otsuka recommended oral administration of Moku-boi-to for patients with cardiac dysfunction due to cardiac valvular disease accompanied by cyanosis, edema, cough, dyspnea, oliguria, and hardness of the epigastric region in the physical examination.[4)] He frequently encountered patients with serious heart failure who were saved by orally administered Moku-boi-to. On the other hand, Kikutani thought that Moku-boi-to was indicated for patients with mild impaired cardiac function, such as those with ischemic heart disease who complained of a feeling of abdominal fullness and their epigastric region was as hard as a board.[5)] He inferred that the effects of Moku-boi-to on cardiac dysfunction were not so strong. While Terasawa described that the target group for Moku-boi-to consisted of relatively weak patients with excess reaction of organism against disease, showing hard resistance in the epigastrium, edema, tachycardia, thirst and oliguria.[6)] Moreover, he described that Moku-boi-to was indicated in patients with anemia, cough, dyspnea, hard resistance not tender on pressure of the epigastric region, dysfunction of kidneys, edema, asthma or cor pulmonale.

As mentioned above, Moku-boi-to is supposed to be effective in patients with heart failure; however, its efficacy has been inferred only from the improvement of

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symptoms and it has not been evaluated objectively based on clinical parameters.

In 1988, brain natriuretic peptide (BNP) was isolated in pig brain,[7] and it was subsequently detected in the myocardium of pigs and humans.[8] BNP is a peptide hormone composed of 32 amino acids. BNP is involved in vasodilatation and sodium diuresis, and it can improve heart failure.[9] Thus, the plasma concentration of BNP is an indicator of the degree of heart failure[10] or of cardiac function.[11]

Consequently, we investigated the effect of Moku-boi-to in patients with heart failure based on the improvement of symptoms and on various clinical parameters, including the plasma concentration of BNP.

Patients and Methods

We studied 12 patients (68.1 ± 12.5 years of age, 5 men, 7 women) with abnormal plasma concentration of BNP (164.1 ± 75.1pg/ml) and moderate chronic heart failure; that is New York Heart Association (NYHA) class 2 to 3 (2.4 ± 0.5). All patients had been clinically stable without important changes in background treatment with digitalis, diuretics or vasodilators for at least 30 days. The etiology of cardiac dysfunction was old myocardial infarction in three patients, hypertension in five, sick sinus syndrome in one, dilated cardiomyopathy in one and valvular heart disease in two patients.

Patients were administered a granulated Moku-boi-to extract (TJ-36) (Tsumura Co., Ltd., Tokyo, Japan). Before and after oral administration of TJ-36 (7.5g/day) for more than 12 weeks, we investigated heart failure symptoms, NYHA class, systolic blood pressure, diastolic blood pressure and pulse frequency. We determined the plasma concentration of BNP, cardiothoracic ratio (CTR) on chest X-ray films, ejection fraction (EF) by echo cardiography and other clinical parameters. The plasma concentration of BNP was measured by a specific radio-immunoassay for human BNP using a commercially available kit (ShionoRIA BNP, Shionogi Co., Ltd., Osaka, Japan). The plasma concentration of BNP was measured under 20pg/ml in normal subjects.

Table I. Evaluation of treatment with TJ-36 for patients with heart failure

a) Improvement of symptoms: remarkably improved, improved, slightly improved, no change, worsening of symptoms, not evaluated
b) Adverse effects of TJ-36: yes and no
c) Clinical usefulness of TJ-36: remarkably useful, useful, slightly useful, no difference, not useful, not evaluated

We classified the therapeutic effects of TJ-36 into six grades based on the improvement of heart failure symptoms (Table I). "Remarkably improved" or "Improved" indicated remarkable improvement or improvement of heart failure symptoms associated with NYHA class improvement. "Slightly improved " or "No change " indicated slight improvement or no improvement without NYHA class improvement. "Worsening" indicated worsening of heart failure symptoms regardless of NYHA class. "Not evaluated " indicated that the effects of TJ-36 were not evaluated. In addition, we assessed the usefulness of TJ-36 for heart failure based on both its adverse effects and therapeutic effects.

Differences of the mean were tested using Wilcoxon's test. Statistical analysis was performed using StatView 4.5 (Abacus Concepts, Berkeley, CA).

Results

In this study we observed cardiac arrhythmia in 2 patients. One of the patients with valvular heart disease took TJ-36 for 4 days and had ventricular tachycardia (VT). The other patient with old myocardial infarction took TJ-36 for 36 days and had frequent premature ventricular contractions accompanied by palpitation. Before completion of treatment, we had to withdraw TJ-36 in these 2 patients and then they recovered. These two patients (16.7%) were considered to have developed an adverse reaction to TJ-36 and to present worsening of symptoms. In the other 10 patients (83.3%), no adverse effects of TJ-36 were noted during treatment.

Three patients (25.0%) and 5 patients (41.7%) showed remarkable improvement or improvement of heart failure symptoms together with NYHA class improvement (Fig. 1). One patient (8.3%) showed slight improvement. In addition to the 2 patients with arrhythmia, one patient (8.3%) showed worsening of symptoms as well as of NYHA class, and an increased plasma concentration of BNP after treatment with TJ-36 for 12 weeks.

The clinical usefulness of TJ-36 based on both its adverse effects and therapeutic effects was as follows: in

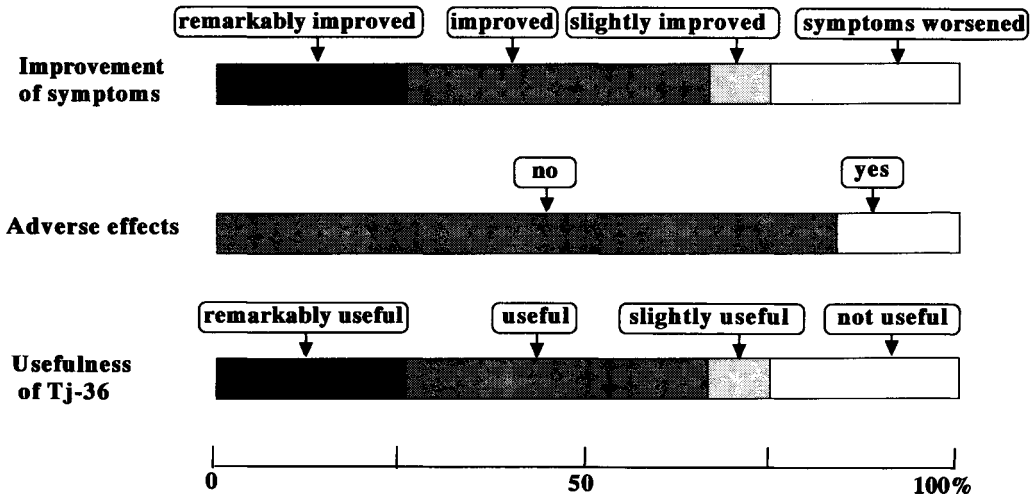

Fig. 1 Evaluation of treatment with TJ-36 for patients with heart failure.

Table II. Effect of treatment with TJ-36 in patients with heart failure

	Before TJ-36	After TJ-36	
NYHA classification	2.3±0.5	1.6±0.7	P<0.01
Plasma BNP concentrations (pg/ml)	168.7±75.1	92.0±61.2	P<0.01
CTR (%)	54.1±2.6	53.5±2.7	n.s.
Ejection fraction (%)	51.3±6.5	53.2±4.2	n.s.
Systolic blood pressure (mmHg)	143±17	141±21	n.s.
Diastolic blood pressure (mmHg)	78±19	81±13	n.s.
Pulse frequency (bpm)	82±21	79±18	n.s.

CTR: carddiothoracic ratio (n=10)

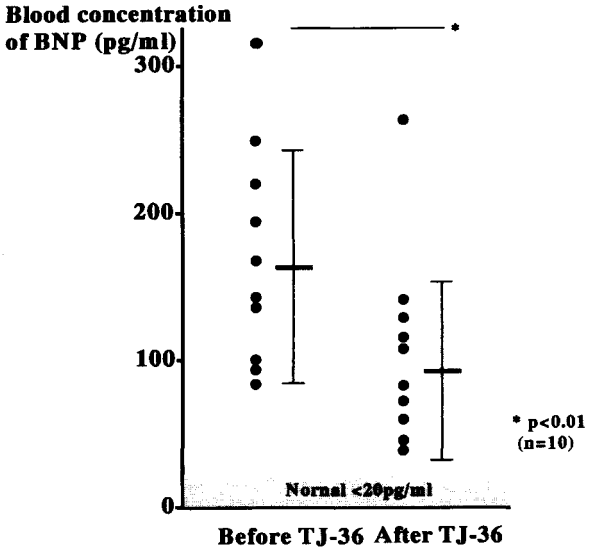

Fig. 2 The effect of TJ-36 for blood concentration of BNP in heart failure patients.

25.0% of the patients, TJ-36 was estimated as remarkably useful; in 41.7% as useful; in 8.3% as slightly useful; and, in 25.0% as not useful. Therefore, in 8 of the patients (66.7%), TJ-36 was evaluated as useful or remarkably useful.

In 2 patients with ventricular arrhythmias, we were not able to estimate clinical parameters before and after oral administration of TJ-36 over 12 weeks. In the remaining 10 patients in whom we could measure clinical parameters before and after oral administration of TJ-36 over 12 weeks, we also estimated the effects of TJ-36 based on the changes of those parameters (Table II). NYHA class improved significantly ($p<0.01$) accompanied by a significant decrease of the plasma concentration of BNP from 168.7±75.1 pg/ml to 92.0±61.2 pg/ml ($p<0.01$) (Fig. 2). But no patients had the plasma concentration of BNP within normal range. There were no significant changes in CTR, EF, systolic blood pressure, diastolic blood pressure or pulse frequency.

Discussion

Since treatment of heart failure patients with Moku-boi-to was accompanied with a decrease of plasma BNP in this study and an improvement of symptoms, we considered Moku-boi-to was effective in patients with cardiac dysfunction.

Concerning the effect of Moku-boi-to, this medicine has been reported to make cardiac contraction stronger, slower heart rate and lower blood pressure.[12] These effects were suppressed by β-blockers; thus they were thought to be mediated by β receptors.[13] Moku-boi-to is made from *Gypsum fibrosum* (石膏), *Sinomeni caulis rhizoma* (防已), *Cinnamomi cortex* (桂皮) and *Ginseng radix* (人参).[6] It was reported that *Gypsum fibrosum, Sinomeni caulis rhizoma* and *Ginseng extract* made cardiac contraction stronger, and that *Sinomeni caulis rhizoma* extract made norepinephrine action stronger.[14] Moreover, *Sinomeni caulis rhizoma, Cinnamomi cortex* and *Ginseng radix* were described to dilate peripheral vessels and lower blood pressure.[15-17] From these data we thought that Moku-boi-to improved cardiac dysfunction through those mechanisms.

Moku-boi-to has been expected to have an anti arrhythmic effect because Moku-boi-to has an effect which elongates the plateau portion in the 2nd phase of monophasic action potential on atrium.[12] However, it was reported that in the case of Ouabain-induced VT, Moku-boi-to made blood pressure higher and VT even more rapid, and then the arrhythmia worsened. So Moku-boi-to was thought to worsen arrhythmias.[16] Because of those effects, we suspected that the 2 cases of cardiac arrhythmias in this study were due to Moku-boi-to. We should be aware of the possibility of cardiac arrhythmias when using Moku-boi-to in a clinical setting.

Study limitations

There are numerous limitations to this study. The 12 weeks duration and sample size of this study do not permit a true assessment of the effects of Moku-boi-to from the view point of its long-term efficacy and complications. Trials using an appropriate sample size and longer treatment and follow-up periods are necessary for an accurate assessment of the impact of Moku-boi-to on mortality. This study included only ambulatory patients who remained symptomatic despite treatment with digitalis, diuretics and vasodilators. Thus, additional studies are needed to assess the effects of Moku-boi-to in patients with milder or more severe heart failure.

Conclusion

This is the first time the efficacy of Moku-boi-to in patients with cardiac dysfunction has been confirmed both on the basis of the improvement of symptoms and the decrease of the plasma concentration of BNP. We think that Moku-boi-to is useful for the treatment of cardiac dysfunction.

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和文抄録

脳性ナトリウム利尿ペプチド（BNP）の血中濃度の測定によって，心機能の程度や心不全の重症度の評価が可能である。我々は心不全症例に対して木防已湯を投与し，臨床症状の評価と血中BNPの測定を行い，木防已湯の心不全に対する効果を検討した。NYHA 分類 2～3 度の心不全 12 例を対象とした。木防已湯エキス顆粒（ツムラ）7.5g/day の投与前，投与後について心不全症状や，血中 BNP 濃度の他に胸部X-Pの心胸郭比，心エコーによる心駆出率，収縮期血圧，拡張期血圧，脈拍について検討した。不整脈の出現が2例にみられ投与を中止した。残りの 10 例については，心胸郭比，心駆出率，収縮期血圧，拡張期血圧，脈拍には変化はみられなかったが，NYHA 分類の改善と血中 BNP 濃度の低下がみられた。自覚症状の改善は 9 例（75.0%）が得られた。木防已湯の投与により自覚症状の改善が得られるとともに，血中BNPの有意な改善もあり，心不全に対する木防已湯の投与は有用と考えられた。

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