

A Study on the Usefulness of Bofu-tsusho-san in Treating Obesity-related Sleep Apnea Syndrome (SAS)

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Abstract

Obesity is an important complicating factor in Sleep Apnea Syndrome (SAS), and correction of obesity is a factor that must always be taken into account in the treatment of SAS. In this study, Bofu-tsusho-san – a Kampo preparation indicated for the treatment of obesity – was administered to obese SAS patients for a duration of eight weeks, and its usefulness was tested. To all patients, Continuous Positive Airway Pressure (CPAP) therapy, the standard treatment for SAS was provided. For this reason, the Apnea Hypopnea Index (AHI) was kept to a mild level or below, and changes were not observed in the approximate administration of Bofu-tsusho-san. Significant changes in Body Mass Index (BMI), neck girth and abdominal girth, were not observed, either. However, ESS scores were observed decreasing over time, with a significant difference after eight weeks of administration. Furthermore, in terms of subjective symptoms, constipation improved significantly after eight weeks of administration, and it was observed that appetite scores also decreased. Based on these findings, it appears that Bofu-tsusho-san, through combined use with CPAP therapy, is useful in limiting progression of obesity - a complicating factor in SAS - and improving SAS's subjective symptoms.

1. Introduction

Sleep Apnea Syndrome (SAS) is diagnosed when the Apnea Hypopnea Index (AHI) - the number of times apnea + hypopnea occur during one hour of sleep - is five or higher and is accompanied by symptoms related to sleep-disordered breathing, such as daytime drowsiness and fatigue, or when, regardless of presence or absence of symptoms, the AHI is 15 or higher. Its symptoms include daytime drowsiness, lowered ability to perform a task and depression; the biggest problem, however, is that it can induce potentially lethal complications, such as glucose intolerance, ischemic heart disease and cerebrovascular disease [1].

Generally, Obstructive Sleep Apnea Syndrome (OSAS), where the upper respiratory tract is obstructed, constitutes most cases of SAS (over 95%); in Japan, about 70% of OSAS patients are reported to have a Body Mass Index (BMI) of 25 or higher. Being linked to the build-up of fat in the upper respiratory tract's

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soft tissue, to macroglossia and to the assumption of a supine position during sleep [2], obesity has been identified as one of OSAS's background factors, and its correction is thought to contribute significantly to the treatment of SAS.

The authors are actively adopting Kampo treatments, and, in some cases, make use of Bofu-tsusho-san, which is an extract product of ten kinds of crude drugs (Table 1). It is a Kampo preparation prescribed for the "organ toxicity body type", and reported to be effective against obesity.

The present study investigated the usefulness of Bofu-tsusho-san in obese SAS patients.

Table 1 Bofu-tsusho-san's components

JP Japanese Angelica Root: 1.2 g	JP Ephedra Herb: 1.2 g	JP Platycodon Root: 2.0 g
JP Peony Root: 1.2	JP Rhubarb: 1.5 g	JP Forsythia Fruit: 1.2 g
JP Cnidium Rhizome: 1.2 g	JP Atractylodes Rhizome: 2.0 g	JP Scutellaria Root: 2.0 g
JP Gardenia Fruit: 1.2 g	JP Mentha Herb: 1.2 g	JP Licorice Root: 2.0 g
JP Ginger Root: 0.4 g	JP Gypsum: 2.0 g	JP Schizonepeta Spike: 1.2 g
JP Saposhnikovia Root: 1.2 g	Sodium Sulfate: 0.75 g	Talc: 3.0 g

Bofu-tsusho-san (KB-62) is an extract product of the above described crude drugs.

JP: Japanese Pharmacopoeia

2. Subjects and Methods

Forty-one patients who visited Keiyu Ginza Clinic from January to March 2012, and who were diagnosed with SAS and whose BMI was 25 or higher were enrolled as subjects for this study.

Target patients were administered 7.5 g/day of Kracie Bofu-tsusho-san-ryo Extract Fine Granules (KB-62) divided into two doses, and endpoints were assessed every four weeks of administration. Any particular restrictions were not set on the combined use of other drugs during the assessment period. Continuous Positive Airway Pressure (CPAP) therapy was also provided to all patients.

Assessed items were patient background (age, gender), BMI, neck girth, abdominal girth, AHI, Epworth Sleepiness Scale (ESS) (Table 2) and subjective symptoms, and were assessed every four weeks of administration. Subjective symptoms - constipation, shoulder stiffness, hot flashes, appetite - were evaluated on a four-level scale (0: no symptoms, 1: mild, 2: moderate, 3: severe).

Statistical processing was conducted with paired t-tests or Wilcoxon signed-rank tests. Stat-View for Windows ver.4.54 (Japanese version, by HULINKS, Tokyo) was used for statistical examination, setting the statistically significant difference at $p < 0.05$.

This study was conducted on patients who visited Keiyu Ginza Clinic. After giving sufficient explanation to the patients and obtaining their consent, CPAP therapy and Bofu-tsusho-san were given, as those therapies are also covered by health insurance.

3. Results

3.1 Patient background

Patient background was shown in Table 3. Thirty-four patients were male and seven patients were female, aged from 19 to 67. CPAP therapy was provided to all patients. Before using CPAP, AHI was 20 or higher in all patients, but the use of CPAP kept it down to less than 15.

3.2 BMI, abdominal girth, neck girth

BMI at baseline, after four weeks and after eight weeks, was 31.63 ± 4.54 , 31.69 ± 4.37 , and 31.31 ± 4.03 ,

Table 2 Epworth Sleepiness Scale (ESS)

Situation	0	1	2	3
1. When sitting down to read	0	1	2	3
2. When watching television	0	1	2	3
3. When sitting down in a crowded place (for example, at conferences, theaters, etc.)	0	1	2	3
4. When sitting in a car driven by someone else non-stop for one hour or longer	0	1	2	3
5. When laying down to rest in the afternoon	0	1	2	3
6. When sitting down and talking to someone	0	1	2	3
7. When sitting quietly after lunch (without drinking alcohol)	0	1	2	3
8. When stopping for several minutes while driving because of congested traffic or traffic lights	0	1	2	3

0 : I rarely feel sleepy

1 : I sometimes feel sleepy

2 : I often feel sleepy

3 : I always feel sleepy

A subjective evaluation method for drowsiness; one of the methods for evaluating excessive daytime drowsiness.

Table 3 Patient background

Gender	Male: 34 patients Female: 7 patients
Age	19-67 years old (average: 47.1±8.9 years old)
BMI	
From 25 to less than 30	16 patients
From 30 to less than 35	15 patients
35 or higher	10 patients
AHI (before using CPAP) (n=41)	
From 20 to less than 30	4 patients
From 30 to less than 40	2 patients
40 or higher	35 patients
AHI (while on CPAP) (n=34)	
Less than 5	22 patients
From 5 to less than 15	12 patients
15 or higher	0 patient

BMI : Body Mass Index

AHI : Apnea Hypopnea Index

normal: AHI<5, mild: 5≤AHI<15, moderate: 15≤AHI<30, severe: 30≤AHI^[2]

CPAP : Continuous Positive Airway Pressure

respectively; neck girth was 41.32 ± 3.96 , 41.16 ± 3.86 , and 40.91 ± 3.94 , respectively; abdominal girth was 101.89 ± 9.41 , 101.56 ± 9.61 and 101.95 ± 10.17 , respectively, with no significant difference observed before and after administration.

3.3 ESS

The ESS score at eight weeks of administration was significantly ($p<0.05$) lower than at baseline, with the score at baseline, after four weeks and after eight weeks of 6.24 ± 4.09 , 5.61 ± 3.98 , and 4.24 ± 3.33 , respectively (Fig. 1).

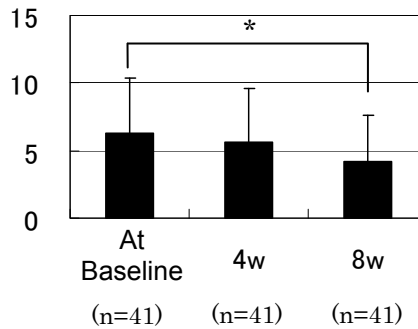


Fig. 1 Changes in Epworth Sleepiness Scale (ESS)

Values show changes in ESS scores at baseline, after four weeks and after eight weeks of Bofutsusho-san administration. Data are shown as the mean \pm S.D.

*Statistically significant compared with the score at baseline ($p<0.05$, paired t-test).

3.4 AHI

There were no significant changes in AHI scores before and after administration, with scores at baseline, after four weeks and after eight weeks of 4.26 ± 2.68 , 4.07 ± 2.61 , and 4.25 ± 2.88 , respectively (Fig. 2).

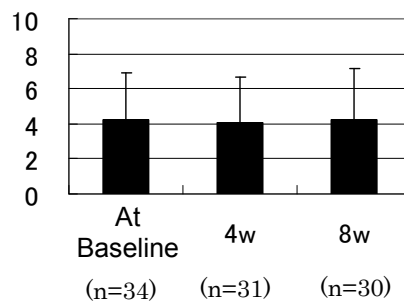


Fig. 2 Changes in Apnea Hypopnea Index (AHI)

Values show changes in AHI scores at baseline, after four weeks and after eight weeks of Bofutsusho-san administration. Data are shown as the mean \pm S.D.

Not Significant at $p<0.05$ (paired t-test).

3.5 Subjective symptoms

The overall subjective symptom score after eight weeks of administration was significantly ($p<0.05$) lower than at baseline, with the score at baseline, after four weeks and after eight weeks of 2.90 ± 1.87 , 2.83 ± 2.11 , and 2.44 ± 2.06 , respectively (Fig. 3).

Changes in the scores by symptom before administration, after four weeks and after eight weeks are shown in the figure (Fig. 4). The score for constipation at eight weeks of administration was significantly ($p<0.05$) lower than at baseline. While there was no significant difference with regard to appetite, the score did decline over time.

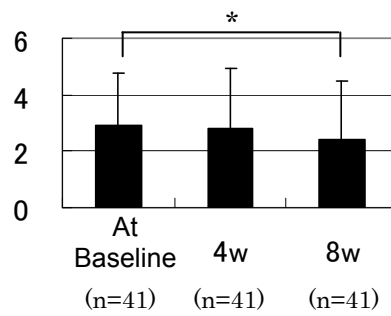


Fig. 3 Overall subjective symptom score

Values show changes in the sum of scores by subjective symptom (constipation, shoulder stiffness, hot flashes, appetite) at baseline, after four weeks and after eight weeks of Bofu-tsusho-san administration. Data are shown as the mean \pm S.D.

*Statistically significant compared with the score at baseline ($p < 0.05$, Wilcoxon signed-ranks test).

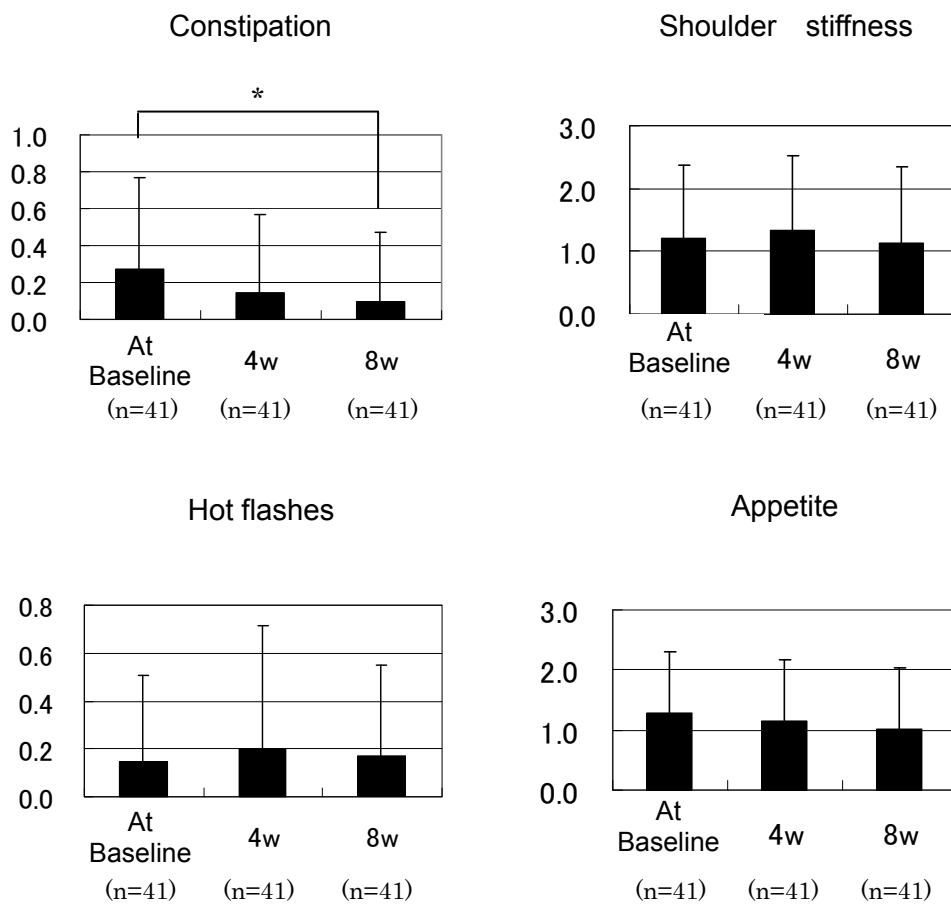


Fig. 4 Subjective symptom scores, by symptom

Values show changes in the scores of each subjective symptom (constipation, shoulder stiffness, hot flashes, appetite) at baseline, after four weeks and after eight weeks of Bofu-tsusho-san administration. Data are shown as the mean \pm S.D.

*Statistically significant compared with the score at baseline ($p < 0.05$, Wilcoxon signed-ranks test).

3.6 Changes in patients with improved ESS

Table 4 shows the results of stratified analysis performed in the patients with improved scores of ESS of more than 1 over the eight-week period from the baseline.

Although BMI and abdominal girth did not change in patients who had improvement in ESS with Bofu-tsusho-san at the eight-week mark, neck girth showed a tendency toward improvement. In addition, overall scores for subjective symptoms and constipation scores were significantly improved, and appetite scores also showed an improvement tendency.

Table 4 Changes in symptoms in patients with improved Epworth Sleepiness Scale (ESS)

	At baseline	8w	p value		At baseline	8w	p value		At baseline	8w	p value
BMI	31.2±4.0	31.2±3.7	0.59	Neck girth	41.7±3.8	41.2±3.6	0.06	Abdominal girth	101.1±7.8	100.9±8.0	0.69
ESS	7.9±3.6	3.8±2.7	<0.00	AHI	4.15±2.6	3.99±2.3	0.22				
Subjective symptoms	3.1±1.7	2.4±1.9	0.03	Constipation	0.3±0.4	0.1±0.3	0.03	Shoulder stiffness	1.3±1.1	1.2±1.1	0.41
Hot flash	0.1±0.4	0.1±0.4	>0.999	Appetite	1.4±1.0	0.9±1.0	0.06				

Values indicate changes in symptoms in patients with improved ESS more than 1 after the use of Bofu-tsusho-san (n=27).

4. Discussion

As shown by the results of a survey that found about two million OSAS patients suffering from symptoms such as daytime hypersomnia, OSAS is an extremely common illness in Japan [2]. However, as this syndrome shows few distinctive symptoms, the vast majority of patients are still untreated, and it is necessary to further raise awareness. The factors causing apnea can roughly be divided into functional abnormalities and morphological abnormalities, with the most important factor among morphological abnormalities being fat deposits in the upper respiratory tract's soft tissue. As can also be surmised from reports linking the AHI to increases in body weight due to obesity [3], obesity is a factor that must always be considered in the treatment of OSAS.

In the present study, Bofu-tsusho-san was administered to obese SAS patients in combination with CPAP, and obtained significant improvements in ESS scores and constipation. Out of subjective symptoms, appetite scores also registered a decrease, albeit not significant. Bofu-tsusho-san is a Kampo preparation prescribed for the "organ toxicity body type", and has been used to treat diseases and conditions accompanied by obesity and high blood pressure due to excessive consumption of high-nutrition foods [4]; several studies are available on this preparation's effectiveness in treating obesity[5-8]. According to a report by Yoshida et al.[9], its mechanism is believed to entail fat burning in brown adipocytes and promotion of heat production. Also, Ito et al.[10] suggest that Bofu-tsusho-san may be effective in reducing body weight by suppressing appetite. In this study, any significant changes were not observed in BMI, neck girth and abdominal girth over the eight-week study period; however, significant improvements were observed in the overall score for subjective symptoms and the constipation score as well as a decreasing tendency in the appetite score. ESS showed an improvement over time, with a significant difference at the eight-week mark.

In addition, stratified analysis in the patients who had improved ESS after using Bofu-tsusho-san showed no changes in BMI and abdominal girth, but a decreasing tendency in neck girth was indicated. The overall score for subjective symptoms and the constipation score were improved significantly, with

a decreasing tendency in the appetite score. This suggests that Bofu-tsusho-san could improve ESS by alleviating obesity through reductions in constipation and appetite; favorable results could be expected through a longer term study in the future.

One possible reason for improvement in ESS in this study is that Bofu-tsusho-san limited obesity; in addition to this, however, it is undeniable that the sympathomimetic effect exerted by ephedrine – the Ephedra Herb's main component – may also have contributed. Also, SAS's aggravating factors include nasal obstruction[2], and ephedrine is effective in correcting nasal obstruction through its constrictive effect on nasal mucosal vessels and nasal mucosae. Furthermore, we believe that the heat clearing effect of Gypsum and Mentha Herb, etc. may also have contributed to the correction of nasal obstruction, and that correction of nasal obstruction by these crude drugs may have prevented snoring and apnea from worsening, facilitating more comfortable use of CPAP. Among medical extract products, other Kampo preparations indicated for obesity aside from Bofu-tsusho-san are Dai-saiko-to and Boi-ogi-to; neither of these, however, contains Ephedra Herb, Gypsum and Mentha Herb. Therefore, Bofu-tsusho-san's advantage lies in its multiple possible mechanisms in correcting SAS.

Note that, in this study, we did not have any control group which received CPAP therapy alone; in the study performed by Berbe et al.[11], patients with $AHI \geq 30$ and $ESS < 10$ were examined on nasal CPAP (NCPAP) in RCT, and Berbe concluded that no significant difference was observed in NCPAP titrated group and the control group (non-titrated group) in all of ESS, intellectual tasks and QOL in the six-week use. In our study, 36 patients out of 41 showed ESS 10 or less (average 6.24 ± 4.09); however, we observed improvements over time by combined use with Bofu-tsusho-san (Figure 1), with a significant difference over the eight-week period. We believe that combined use with Bofu-tsusho-san has contributed to this efficacy; in the future, however, it will be necessary to perform a comparative study having a control group to examine the influence of the concomitant use of CPAP and Bofu-tsusho-san on ESS.

All patients have already been pretreated by CPAP therapy. As shown in the patients' background, thanks to the use of CPAP, AHIs were kept at mild to normal levels compared to moderate/severe levels before use. For this reason, we observed no further improvement of AHI after administering Bofu-tsusho-san. At present, CPAP is considered unquestionably effective in treating OSAS, and is a treatment standard[2]; however, its effects only appear when the mask is being worn, making it necessary to continue treatment semi-permanently. For this reason, it is possible that combining CPAP therapy with oral administration of Bofu-tsusho-san, which can be expected to act against obesity, may become a radical treatment for SAS. In the future, in addition to Bofu-tsusho-san's effectiveness in aiding weight loss over the long term, we also intend to study the extent of lingual and parapharyngeal fat accumulation, which can directly cause SAS.

5. Conclusion

It appears that, in combination with CPAP therapy, administration of Bofu-tsusho-san, a Kampo preparation indicated for the treatment of obesity, is useful in limiting obesity - a complicating factor in SAS - and improving subjective symptoms in obese SAS patients.

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