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EFFECT OF BOSWELLIN® SUPER ON KNEE PAIN IN JAPANESE ADULTS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Objectives: *Boswellia serrata* extract is a traditional remedy for joint health with an anti-inflammatory effect. The present trial investigated the effect of Boswellin® Super (BS), a standardized extract from the gum resin of B. serrata containing Boswellic acids, on reducing knee pain. ***Methods:*** This study was a randomized, double-blind, placebo-controlled trial. Patients reported with knee pain were assigned to receive either BS or placebo as one capsule daily for 8 weeks. The primary outcome measures, Visual Analog Scale (VAS), the Japanese Knee Osteoarthritis Measure (JKOM) and the Western Ontario & Mc Master Universities Osteoarthritis Index (WOMAC) were used to evaluate knee pain. In addition, serum hyaluronic acid and high sensitivity C-reactive protein were measured as secondary outcome measures. ***Results:*** Compared with baseline, the BS group patients showed significant improvements in the VAS, JKOM, and WOMAC scores after 8 weeks of intervention. Serum hyaluronic acid levels were lower in the BS group than those in the placebo group after 8 weeks of intervention. This may play a vital role in alleviating pain in rheumatoid arthritis. ***Conclusion:*** The results of this trial suggest that BS inhibits the secretion of hyaluronic acid into the blood. In addition, intervention with BS resulted in improvements in the VAS, JKOM and WOMAC scores. Therefore, BS could find potential use to relieve knee pain patients and manage related inflammatory conditions.

KEYWORDS: *Boswellia serrata*, boswellic acids, knee pain, JKOM, WOMAC, hyaluronic acid.

INTRODUCTION

In recent years, the population of aging and elderly in Japan has seen a steady increase. Among them, several suffer from knee pain, lumbar pain, and shoulder pain.[1] The effective relief of knee pain may help and improve the quality of life of elderly people because it enables increased physical activity. In this trial, we investigated the extract of *Boswellia serrata* as a treatment to relieve knee pain.

Boswellia serrata is a tall tree of the family Burseraceae, native to India and parts of Pakistan. Extracts of *Boswellia serrata* are widely used in Ayurveda medicine, a traditional system of medicine practiced mainly in India. Boswellin® Super is a standardized extract from the gum resin of *B serrata* enriched to contain boswellic acids namely β-Boswellic Acid, Acetyl-β-Boswellic Acid, 11-keto- β -Boswellic Acid and Acetyl-11-keto- β -Boswellic Acid. *Boswellia serrata* is reported for several applications such as to slow the rate of breathing which leads to relaxation, maintaining healthy skin and pain relief. Knee pain in elderly people is most commonly caused by inflammation. Increased levels of arachidonic metabolism products are found in the synovial fluid of people suffering from chronic rheumatoid arthritis or osteoarthritis.[2, 3] Arachidonic acid bound with phospholipids in the cell membrane is isolated by phospholipase A2.[4] Thereafter, leukotrienes are produced, which are in turn metabolized by 5-lipoxygenase via the lipoxygenase pathway. Leukotrienes increase leukocyte migration and vascular permeability and play an important role in inflammation.[5, 6] Boswellic acids, which are the identified bioactives in *B serrata* extract, are found to inhibit the production of leukotrienes by selectively deactivating 5-lipoxygenase.[7, 8, 9, 10] Therefore, boswellic acids may be useful to reduce inflammation and prevent the damage to the connective tissue caused by inflammatory arthritis. Previous studies have reported that boswellic acids decrease the levels of glutamic

pyruvic transaminase, glycohydrolase and β-glucuronidase, all of which are increased in arthritis.[11, 12]

In another study, people with inflammatory arthritis showed an increased activity of hyaluronidase, a glycohydrolase that degrades hyaluronic acid, in both serum and synovial fluid.[13] Hyaluronic acid in synovial fluid protects the joint cartilage.[14] Therefore, inhibiting the degradation of hyaluronic acid in the knee joint may protect the cartilage and slow the progression of arthritis, with associated pain relief. The effect of *B. serrata* has been investigated in a number of clinical trials. Treatment with B serrata extract capsules improved knee pain in 42 patients with osteoarthritis in a randomized, double-blind, placebo-controlled crossover trial.[15] However, in another randomized, double-blind, placebo-controlled trial of patients with rheumatoid arthritis, there was no significant difference between treatment with a standardized B serrata extract and placebo.[16] Therefore, the effect of B serrata on joint pain has not been scientifically established and further studies are warranted. The present trial investigated the use of Boswellin® Super (BS) to relieve knee pain. The effect of BS on knee joint pain in otherwise healthy Japanese men and women with subjective symptoms of knee joint pain was examined.

METHODS

Trial design: This study was a randomized, double-blind, placebo-controlled trial with two groups: an intervention (BS) group and a placebo group. The ratio of assignment was 1:1. Subjects were included in the study if indicated "Yes" to all of the inclusion criteria and "No" to any of the exclusion criteria. Inclusion criteria: This trial recruited Japanese adults with knee pain. The participants were recruited by advertisements from all over Japan but most of them were from the Osaka area. Subjects aged in their 60s were preferentially recruited, followed by subjects in their 50s, 40s, 30s, and then 20s, until the required number of cases was achieved. No protocol amendments or changes to trial outcomes were made after the trial commenced. Exclusion criteria: The exclusion criteria were as follows: medical history of malignant tumor, heart failure, or myocardial infarction; current treatment for a trial fibrillation, cardiac arrhythmia, hepatic disorder, renal disorder, cerebrovascular disorder, rheumatism, diabetes mellitus, dyslipidemia, hypertension, or other chronic disease; current use of any medication, herbal medicines, or dietary supplements; allergy to medicines or foods related to the test compound; pregnancy, lactation, or planned pregnancy during the trial period; enrollment in any other clinical trial within the last 3 months prior to enrollment in the present study; or judged not suitable to participate in this trial by a physician.

Ethical considerations: The clinical investigation was conducted in accordance with the Declaration of Helsinki. The trial was approved by the ethics committee of Seishin-kai Medical Association Inc. Takara Medical Clinic (Shinagawa-ku, Tokyo) vide approval number (1406-1406-SJ01-01) prior to start of the study. The study was initiated at Takara Medical Clinic on June 17 2014. After approval, the trial has been registered with UMIN-CTR (UMIN000014324), Japanese clinical trial registry.

Sample size & study procedures: Total forty eight (48) subjects were equally distributed between two groups (BS and Placebo). Being a pilot exploratory study, no formal sample size calculations were done. The study was a double-blind trial. The subjects, the principal investigators, and the analysts were all blinded to trial information. The staff of ORTHOMEDICO Inc. (Bunkyo- ku, Tokyo) provided computer-generated random numbers using the Statlight#11Ver.2.10 software (Yukms Co., Ltd., Kawasaki-shi, Kanagawa). The allocation number was decided based on age with VAS in JKOM as a lay out adjustment factor, and four randomizations were assigned with one given to each study participant following a completely randomized design (24 subjects per group). This trial compared the BS group with the placebo group to determine the efficacy of BS. The details of this clinical trial were explained to all subjects, and they provided written informed consent. Subjects were recruited from June 20 to August 04, 2014. Subjects visited the Takara Medical Clinic three times (week 0, week 4, and week 8) between July 7 and October 31, 2014. The list of ingredients of the test compound and placebo used in this trial is depicted in table 1. Both BS and the placebo were administered in capsule form of same size and weight. The subjects were instructed to take one capsule of BS or placebo with water. The intervention was conducted from July 21 to October 31, 2014.

Visual Analog Scale (VAS), Japanese Knee Osteoarthritis Measure (JKOM)[17] and subjective symptoms of knee pain were considered as primary outcome measures. Subjects filled in their degree of knee pain on a visual analogue scale (VAS) and measured the distance from the left edge of the scale. The JKOM score was calculated based on the answers to 25 questions about "knee pain and stiffness," "state of the daily life," "regular activity," and "condition of health," which were rated from 0 (mildest) to 4 (seriously worst).

The secondary outcome measure was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[18], subjective symptoms of knee pain were also assessed using WOMAC. The WOMAC score was calculated based on the answers to 24 questions about "pain," "stiffness," and "difficulty of the daily activity," which were rated from 0 (mildest) to 4 (seriously worst). In addition to these evaluations, blood samples (15mL of venous blood) were collected from all subjects for serum hyaluronic acid and high sensitivity C-reactive protein (hs-CRP) measurements. The samples were collected at

the Takara Medical Clinic and analyzed by LSI Medience Corporation (Chiyoda-ku, Tokyo). Patients also responded to the questionnaire using a Likert scale ("1: does not fit me at all," "2: hardly fits me," "3: really does not fit me," "4: slightly fits me," "5: somewhat fits me," or "6: almost completely fits me").

Safety evaluation was done through physical examination. Urine analysis, peripheral blood test and medical interview was done to evaluate the safety of the test compound and the health status of subjects at week 0 and week 8. Body measurement, physical examination, urine analysis, blood draws and medical analysis were performed at the Takara Medical Clinic. Analysis of peripheral blood tests was performed by LSI Medience Corporation.

Medical interview

Subjects were interviewed about the quality of sleep, frequency of bowel movements, consistency and shape of stools, sense of defecation, headache, dizziness, stomach ache, anorexia, nausea, menstrual cycle (only women), and presence of any other subjective symptoms. No interim analysis was done during the course of the study.

Statistical methods

Statistical analysis was done on the data generated towards end of the trial. With comparisons between measured values at weeks 4 and 8 and those at week 0 were n-group performed using Dunnett's test. Between-group comparisons among the measured values at each time point (weeks 0, 4, or 8) were performed using analysis of variance (ANOVA). Effect size (d) was calculated from the difference of average values and standard deviations. All statistical analyses were performed using PASW Statistics 18 (IBM Japan, Ltd., Tokyo). All tests were two-sided and the level of significance was set at 5%.

RESULTS

1 Participant flow

Figure 1 shows the flowchart for this trial. In total, 54 subjects agreed to participate in the trial but two were considered unsuitable by the investigator. In addition, four subjects were excluded based on the interview by the coordinating investigator and/or exclusion criteria. Therefore, forty eight subjects (24 in each group) participated in the trial. One subject in the BS group was lost to follow-up. Finally, data for 47 subjects was analyzed to compare BS and placebo in this trial. The mean ages in the BS and placebo groups were 48.2 ±10.9 years and 49.0 ±9.8 years, respectively (Table 2).There were no statistically significant differences between the BS and placebo groups at week 0.

2 JKOM, WOMAC, blood test

Table 3 shows measured values at each analysis point, and effect size (d) in this trial. In the BS group, there were significant differences compared with week 0 and week 8 in the VAS score, JKOM total score, and WOMAC total score. Between-group comparison showed a lower hs-CRP and hyaluronic acid levels at week 8 in the BS group than that in the placebo group.

3 Questionnaires (Likert scale)

Table 4 shows the questionnaire results at each analysis point in this trial. In the BS group, compared with week 0, there was a decrease in the Likert scale score for the following : "My feet feel cold" (week 4); "My body feels cold" (week 4); "I have pain in my stomach" (week 4 and week 8); "My range of activities is smaller" (week 4); "I feel troubled about life" (week 4 and week 8); and "I have fits of coughing"(week 4). In the placebo group, compared with week 0, there was a decrease in the Likert score for the following: "My range of activities is smaller" (week 8) and "I feel troubled about life" (week 4 and week 8). Between-group comparison at week 0 showed a significantly higher Likert scale score in the BS group than that in the placebo group for "My hands feel cold" and "I have constipation". At week 8, between-group comparisons showed a significantly higher Likert scale score for the BS group than that in the placebo group for "I feel physical fatigue", "My skin condition is bad", and "I have a stuffy nose".

4 Safety evaluations

The results of body measurement, physical examination, urine analysis, peripheral blood test, and medical interview revealed no new health problems during the trial period. No subjects showed medically significant changes related to the test compounds (data not shown), and no adverse events were reported.

Table 1: Nutritional Information of test compounds.

Ingredients	Unit	Boswellin® Super	Placebo
Boswellin® Super – *Boswellia serrata* extract	mg	100.02	-
Starch syrup of reduced malt sugar	mg	60.00	127.50
Crystalline cellulose	mg	129.48	165.00
Calcium stearate	mg	9.00	6.00
Micro silicon dioxide	mg	1.50	1.50
Total	mg	300.00	300.00

Table 2: Demographic Characteristics of trial subjects.

Item n (male/female)	Unit people	BS 23(5/18)	Placebo 24 (8/16)
Age	years	48.2 (10.9)	49.0 (9.8)
Height	cm	159.8(8.2)	162.1 (9.3)
Weight	kg	55.7 (8.7)	60.9 (10.1)
Body mass index	kg/m2	21.7 (2.2)	23.4 (3.3)
Body fat rate	%	25.9 (5.0)	26.3 (7.2)

Mean (standard deviation)

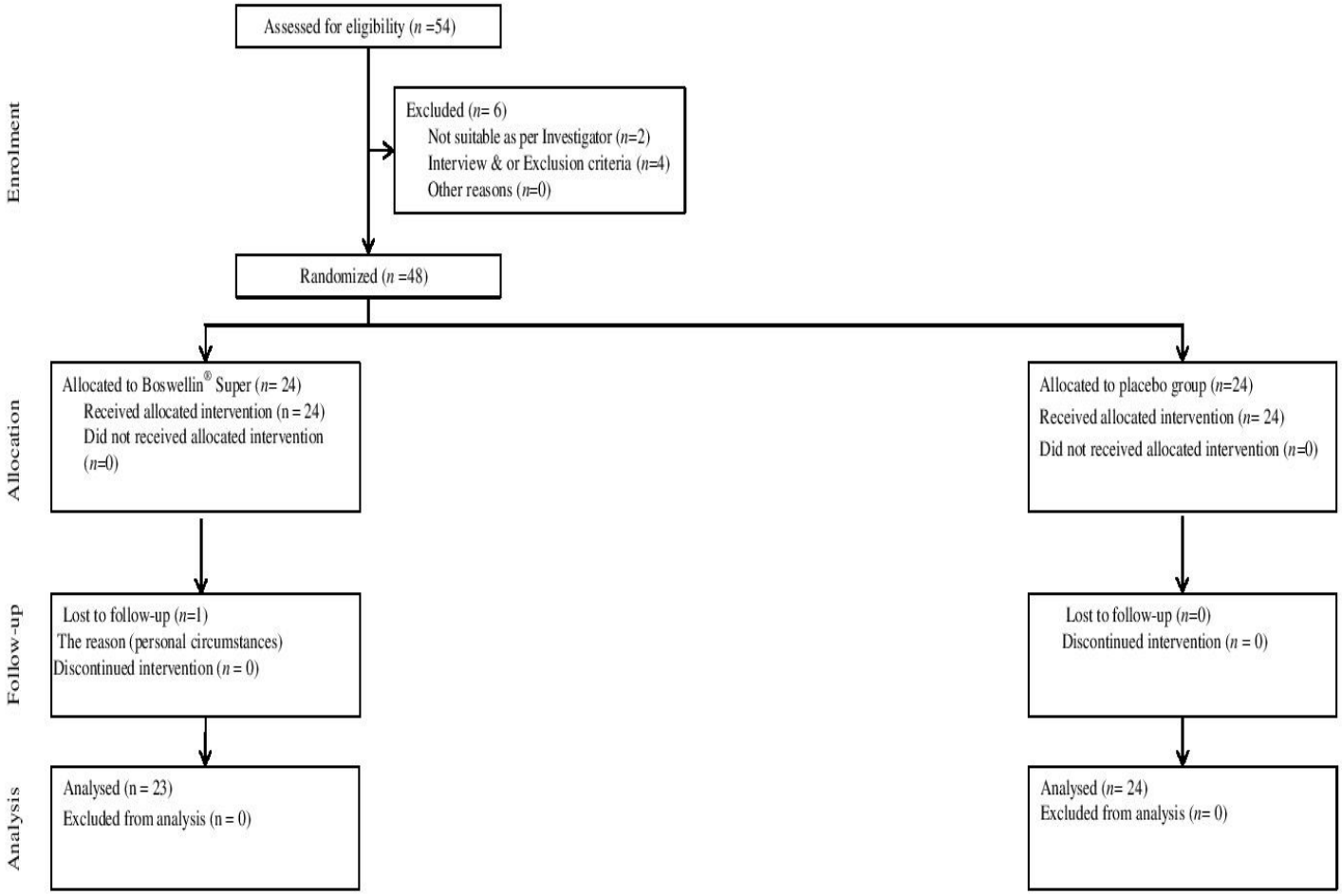

Figure 1: Flow chart of subjects

Table 3: Measured values of JKOM total score, WOMAC total score and blood tests.

Item	Unit	Group	Week 0	Week 4	Week 8
VAS	mm	Boswellin® Super Placebo	68.8 (12.1) 71.8 (10.3)	34.4 (23.8) 41.8 (24.2)	35.6 (22.3) 39.6 (27.3)
JKOM total score	Point	Boswellin® Super Placebo	48.3 (13.0) 48.5 (11.8)	39.4 (11.0) 39.5 (8.2)	38.8 (12.1) 36.4 (6.9)
WOMAC total score	Point	Boswellin® Super Placebo	23.7 (16.7) 24.0 (15.9)	14.3 (13.3) 14.6 (11.4)	12.7 (14.2) 9.8 (8.8)
Hyaluronic acid	ng/mL	Boswellin® Super Placebo	18.8 (14.3) 24.8 (24.8)	15.9 (6.4) 50.3 (101.4)	18.4 (8.9) 42.9 (66.8)
High sensitivity CRP	mg/dL	Boswellin® Super Placebo	0.03 (0.03) 0.09 (0.14)	0.05 (0.10) 0.04 (0.05)	0.04 (0.05) 0.05 (0.07)

Data expressed as Mean (SD)

Table 4: Measured values for the questionnaire.

Item	Group	Week 0	Week 4	Week 8
My hands feel cold	Boswellin® Super Placebo	2.2 (1.3) 2.1 (1.0)	2.3 (1.2) 1.9 (1.0)	2.5 (1.1) 2.3 (1.2)
My feet feel cold	Boswellin® Super Placebo	3.0 (1.4) 2.9 (1.5)	2.8 (1.3) 2.7 (1.3)	3.2 (1.4) 2.8 (1.4)
My body feels cold	Boswellin® Super Placebo	2.6 (1.1) 2.8 (1.3)	2.5 (1.2) 2.4 (1.1)	2.9 (1.1) 2.7 (1.1)
I have pain in my stomach	Boswellin® Super Placebo	3.7 (1.5) 3.4 (1.3)	3.2 (1.5) 3.5 (1.3)	3.2 (1.3) 3.4 (1.2)
I feel stressed	Boswellin® Super Placebo	3.1 (1.5) 3.1 (1.2)	3.0 (1.3) 3.3 (1.1)	3.1 (1.3) 3.1 (1.1)
My range of activities is smaller	Boswellin® Super Placebo	2.3 (1.1) 2.9 (1.1)	2.2 (1.0) 2.4 (1.1)	2.3 (1.1) 2.3 (1.0)
I feel physical fatigue	Boswellin® Super Placebo	3.0 (1.1) 3.3 (1.2)	2.8 (1.1) 3.3 (1.0)	3.1 (1.3) 3.1 (0.9)
I feel troubled about life	Boswellin® Super Placebo	2.9 (1.2) 2.8 (1.0)	2.3 (1.1) 2.3 (0.9)	2.4 (1.1) 2.4 (0.9)
I have constipation	Boswellin® Super Placebo	2.5 (1.3) 2.3 (1.2)	2.3 (1.3) 2.5 (1.1)	2.2 (1.3) 2.2 (1.2)
I have stiffness in my body	Boswellin® Super Placebo	3.9 (1.6) 4.2 (1.3)	3.8 (1.7) 4.3 (1.6)	3.8 (1.5) 4.0 (1.5)
My skin condition is bad	Boswellin® Super Placebo	3.0 (1.1) 3.1 (0.9)	2.8 (1.2) 2.8 (1.0)	2.9 (1.3) 2.8 (1.0)
My quality of sleep is bad	Boswellin® Super Placebo	3.0 (1.3) 3.2 (1.2)	2.9 (1.4) 3.2 (0.9)	3.0 (1.5) 3.0 (1.0)
I have stuffy nose	Boswellin® Super Placebo	2.1 (1.4) 2.0 (1.0)	1.9 (1.1) 2.1 (1.2)	2.0 (1.0) 1.9 (1.1)
I have fits of coughing	Boswellin® Super Placebo	1.7 (1.0) 2.0 (1.2)	1.9 (1.2) 1.8 (1.1)	1.9 (1.0) 1.8 (1.2)
I cannot concentrate on things	Boswellin® Super Placebo	1.9 (0.9) 2.6 (0.8)	2.2 (0.9) 2.5 (1.0)	2.2 (1.1) 2.3 (1.0)

Items were scored using a Likert scale of 1–5, with 1 indicating "strongly agree" and 5 indicating "Strongly disagree." (NS=Not Significant), Data expressed as Mean (SD)

DISCUSSION

This trial examined the effect of BS in otherwise healthy Japanese men and women with knee joint pain. Subjective symptoms of knee pain were assessed using the VAS, JKOM, and WOMAC scores. The objective measurements in the trial were analysed by serum hyaluronic acid and hs-CRP. In the between group comparison, BS group showed decrease in the VAS, JKOM, and WOMAC scores compared to baseline, suggesting that BS relieved knee pain in these subjects. This finding may be the result of the anti-inflammatory action of B. serrata extract.[7, 8, 9, 10] On further analysis, serum hyaluronic acid levels were significantly lower in the BS group than those in the placebo group after 8 weeks of intervention. Although the variation within each group was not significant, the mean serum hyaluronic acid level in the BS group decreased while that in the placebo group increased. Therefore, these results suggest that B. serrata extract may inhibit hyaluronidase activity[11], which in turn suppresses the outflow of hyaluronic acid to serum. Patients with chronic rheumatoid arthritis or juvenile rheumatoid arthritis who felt joint pain showed high levels of serum hyaluronic acid.[19] Higher amounts of hyaluronic acid in the serum were thought to reflect an outflow from cartilaginous tissue and were possibly associated with stiff joints in the morning.[20] Therefore, knee joint pain could be correlated with high serum hyaluronic acid levels. In the between groups comparison the BS group showed improved VAS, JKOM, WOMAC scores and subjective symptoms of knee pain. In addition, serum hyaluronic acid levels were also significantly reduced in the BS group compared with those in the placebo group, it is possible that improvements in subjective symptoms in the BS group were the result of the inhibition of hyaluronic acid secretion into the blood.

CONCLUSION

The findings of this trial indicate that BS inhibits the secretion of hyaluronic acid into the blood. Compared to the placebo group, the subjective symptoms of knee pain tended to improve. Therefore, BS may be useful to relieve knee pain in Japanese adults.

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