A Double-Blind Randomized Placebo Controlled Parallel Group Study Demonstrates Analgesic Effects of Sheanut Oil Extract [BSP-201] in Exercise Induced Muscle Tenderness

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A Double-Blind Randomized Placebo Controlled Parallel Group Study Demonstrates Analgesic Effects of Sheanut Oil Extract [BSP-201] in Exercise Induced Muscle Tenderness

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ABSTRACT. Objectives: Oral sheanut oil extract [BSP-201] is an active bio-complex obtained from a fraction of sheanut oil with approximately 50 to 70 percent unsaponifiables that reduced dose-dependently interleukin-6 production from the rat pristine-induced peritonitis exudates cells. The primary objective of this placebo-controlled study was to investigate the effects of BSP-201 on development of post-exercise muscle tenderness.

Methods: Three grams of BSP-201 or placebo was given orally daily in 4 × 750 mg soft gel capsules for 22 days to 20 healthy men aged, 26 ± 0.61 years [mean ± standard deviation] in a double-blind, randomized control study. Subjects carried out an intensive eccentric exercise of the first dorsal interosseous muscle of the left hand on a standardized hand exerciser on the day 14. Muscle tenderness was tested on days 0, 14 [before exercise], 14 [immediately after exercise], 15 [one day after exercise], 16 [two days after exercise with maximal tenderness], and 22 [eight days after exercise] by pressure algometry.

Results: Muscle tenderness on days 0 and 14 [before exercise] was not different in the two groups. Muscle tenderness was significantly reduced [24.3 ± 4.8 mm] in the group that consumed BSP-201 as compared to the placebo group [47.4 ± 6.5 mm] at day 14 [immediately after, P < 0.01] and at day 16 [P < 0.04] after the exercise. None of the participants reported any adverse effects.
**Conclusion**: Oral administration of BSP-201 reduces muscle tenderness after eccentric exercise presumably by inhibiting the muscle inflammatory processes via a reduction of pro-inflammatory cytokine interleukin-6.

**KEYWORDS.** Sheanut oil, eccentric exercise, muscle tenderness, experimental muscle pain, triterpenes

**INTRODUCTION**

The history of the West African Mangifolia shea tree Butyrospermum parkii is well known and documented in the Western world since the days of Mungo Park, the British explorer who first described the tree from his journeys in West Africa in the 18th century. In the semi-arid sub-Saharan region the shea tree is a valuable asset, yielding edible oil for domestic use and products for cosmetic and pharmaceutical uses. The oil can be used for frying oil and after hardening, in margarine and toffee fat.

Refined sheanut oil [shea olein], obtained from the kernels of shea trees was introduced to the western diet more than 50 years ago and the oil sterols are assumed to be responsible for the lowering effect on cholesterol levels (1).

Sheanut oil contains approximately eight percent unsaponifiable material, which is a mixture of fatty acid and cinnamic acid esters of such triterpene alcohols as α-amyrine, butyrospermol, lupeol, β-amyrine and to a minor extent, sterols, aliphatic alcohols, and karitene (2–5).

The triglyceride composition of BSP-201 is made up of approximately 44 percent monosaturated [oleic acid], 47 percent saturated fatty acids [stearic and palmitic acids], and five percent of polysaturated fatty acids (6).

Triterpene alcohols such as lupeol and α/β-amyrine have been shown to possess anti-inflammatory effects, especially in their esterified forms (7–10). In the study by Alander and Andersson (11), normal human epidermis keratinocytes in a growth medium were exposed to a nonsensitizing irritant [croton oil] in the presence of different concentrations of shea oil. An increased intracellular synthesis and release of proinflammatory cytokines, measured by intracellular interleukin-1α [IL-1α] and extracellular IL-8, were taken as signs of an increased irritant stress induced by the croton oil. A consistent reduction of the levels of IL-1α and IL-8 were observed in the presence of hydrocortisone 21-hemisuccinate which was used as a positive control. The results showed that the production of IL-1α was reduced by approximately 25 percent at concentrations between 0.5 and 2.5 mg/ml while the production of IL-8 was unaffected. It was concluded that the fractionated shea butter gave a significant reduction of the inflammatory response of human keratinocytes to croton oil.

In other studies plant sterol-sterolin mixtures have shown to reduce carrageenan induced inflammation in animals (12) and reduce in vitro inflammatory cytokines IL-6 and TNF-α (13). In marathon runners, plant sterol-sterolin mixture is able to abrogate the immunesuppression related to endurance event and improve the cell-mediated response (14).

The BSP-201 is a product with an active biocomplex obtained from sheanut oil, contains approximately 50 to 70 percent unsaponifiables, and is found to be safe for human use (15). A hydrolyzed version of BSP-201 containing approximately 0.5 percent unsaponifiables reduced dose-dependently IL-6 and TNF-α production from the rats pristine-induced peritonitis exudates cells (16). Furthermore, BSP-201 reduced carrageenan-induced inflammation in animals to a degree comparable with ibuprofen (16).

Post-exercise induced muscle tenderness [PEMS] is described as a dull, aching pain combined with tenderness and stiffness (17), usually following unaccustomed eccentric exercise (18–21). Significant relationship of the severity of PEMS one day after eccentric exercise and IL-6 has been shown in humans (22). Extensive eccentric exercise stimulates endothelial cells during an acute inflammatory response to release IL-6 (22) and other inflammatory cytokines and later on as a delayed response macrophages and fibroblasts produce IL-6 (23).

The aim of this double-blind randomized prospective parallel group study was to investigate if BSP-201 reduces muscle tenderness after eccentric exercise.
MATERIAL AND METHODS

Experimental Protocol

Approval for this study was granted by the Independent Ethics Committee [project number KF 02-092/02]. Furthermore, an application to the Data Protection Agency has been submitted and approved [journal number 2003-41-2665]. The study was designed as a randomized, prospective, double blind, placebo controlled, parallel group investigation. The randomization number was entered on the case report form by the investigator and neither the subject nor the assessor had access to the randomization code. The demographic characteristics of the recruited participants were not statistically different and there were no dropouts. Subjects who were not engaged in jogging, running, or weight training and were not involved in competitive sport participated in the study. Individuals without any neuromuscular or medical disease, history of any allergy, those taking nonsteroidal anti-inflammatory medication, or those involved in recreational exercise for more than six hours a week were recruited through advertisement in local newspapers. It has been shown that in the trained individuals, eccentric exercise is not associated with any increase in inflammatory cells in the muscles (24) and is not associated with adequate muscle soreness. Therefore, only untrained individuals were included in the present study.

On day 14, PEMS was developed in the left first dorsal interosseous [FDI] muscle by means of an exercise program carried out on an established PEMS pain model (18, 25, 26).

Muscle Exercise and Assessment of Tenderness

The subjects’ hands were positioned on the PEMS hand apparatus as described previously (18, 25–27). On the first visit, the hand was positioned on the exerciser by fully pronating the forearm while the elbow was flexed and shoulder abducted to the right angles, then the pressure-pain threshold over the first dorsal interosseous muscle was estimated using an electronic algometer (18). Muscle tenderness defined by a visual analog scale [VAS] score on a 0–100 mm scale after a pressure equal to baseline pressure-pain threshold was applied over the FDI muscle. Tenderness VAS was measured on days 0, 14 [before exercise], 14 [immediately after exercise], 15 [one day after exercise], 16 [two days after exercise], and 22 [eight days after exercise]. Compliance to the treatment was monitored on days 14 and 22 by counting unconsumed capsules in the patient’s container at the corresponding visits. The number of days on trial was recorded. The number of remaining capsules and the total consumption was computed. The trial followed the guidelines and standard operating procedures based on the recommendation of the International Conference of Harmonization and Good Clinical Practice.

Eccentric exercise was carried out by lifting the weights attached to the finger splint as described in previous studies (18, 25–27). Briefly, subjects were provided with a foot pedal to lift the weights attached to the finger splint, so that the finger could be fully abducted without having to lift any weight. This apparatus was so designed that an eccentric exercise could be carried out on the FDI muscle to induce significant muscle tenderness. Encouragement from the examiner and visual feedback from the angular displacement of the index finger served as the motivation for the subjects to apply maximum resistance to the sliding weights. The exercise was repeated continuously for two minutes and was followed by a rest of approximately two minutes between the subsequent two-minute bout. Six such sets were carried out by each participant.

Trial Medication and Blinding

Each BSP-201 capsule contained 750 mg BSP-201 [50 percent unsaponifiables], whereas the placebo capsule contained rapeseed oil. The BSP-201 group received $2 \times 2$ capsules of BSP-201 per day [morning and evening] and the placebo group received the placebo capsules. Only the patient randomization number printed on the label of the trial medication compared with the randomization list revealed which product the subject received. The randomization number was entered on the case report form by the investigator and neither the subject nor the assessor had access to the randomization code. Emergency code envelopes were produced in which the product allocation.
for each randomization number was given. The emergency code envelope was only to be opened if, in an emergency situation, the allocation of the subject was important for the medical management of the person.

Statistics

The data were expressed as means ± standard error of the mean [SEM]. For the normally distributed data, the parameters were evaluated with a one-way repeated measures analysis of variance [ANOVA, for individual groups when time is a factor] and two-way repeated measures analysis of variance [ANOVA, for group comparisons treatment and time are factors, Sigma Stat 3.0; Statistical Package for the Social Sciences Inc., Chicago, Ill., USA]. If significant, a post hoc Tukey test for multiple comparisons was used. The factors in the ANOVA were treatment [BSP-201 or placebo] and time (six levels: days 0, 14 [before exercise], 14 [immediately after exercise], 15, 16, and 22).

Spearman’s rank order correlation was applied to measure the strength of correlation between muscle tenderness VAS and time duration in two groups. Significance was accepted at $P = 0.05$. Unpaired $t$ test was used for comparing demographic data.

RESULTS

None of the participants reported any adverse effects. Drug accountability showed that all the subjects complied with the medication intake, and none of the capsules were left unconsumed. No emergency situation occurred in the trial.

Volunteers

Twenty healthy right-handed Caucasian male subjects [26 ± 0.6 years old] participated in the study. The placebo group included 10 males, aged 25.8 ± 0.9 years, weighing 77.5 ± 3.9 kg, and height of 182.7 ± 2.5 cm. The BSP-201 group included 10 males, aged 26.3 ± 1.9 years, weighing 76 ± 3.6 kg, and height of 182.7 ± 1.7 cm. No difference [t test] in age, weight, or height was found between the two groups.

Muscle Tenderness

Muscle Tenderness in the Placebo Versus BSP-201 Groups

For both the placebo and BSP-201 groups, the muscle tenderness VAS on day 0 and day 14 [before exercise] were similar [Figure 1]. The two-way ANOVA demonstrated differences between the groups and the Tukey’s post hoc test indicated that the muscle tenderness immediately after the eccentric exercise was lower in the BSP-201 group [24.3 ± 4.8 mm] as compared to placebo [47.4 ± 6.5 mm, $P < 0.01$]. Also two days after the exercise, the muscle tenderness in the BSP-201 group was significantly reduced [40.8 ± 4.3 mm] as compared to the placebo group [54.8 ± 4.8 mm, $P < 0.04$]. On day 22 [eight days after the exercise] muscle tenderness in the BSP-201 group [29.3 ± 5 mm] was not significantly different from the placebo group [43 ± 5.7 mm].

Muscle Tenderness in the Placebo Group

A one-way ANOVA for the tenderness VAS assessment in the placebo group indicated a main effect between different times [$P < 0.001$, Figure 1]. Muscle tenderness VAS was higher at one day after exercise [56.5 ± 6.5 mm] as compared to day 0 [39.8 ± 5.4 mm], day 14 before exercise [41.8 ± 5.1 mm], and day 22 [eight days after exercise] [43 ± 5.7 mm, $P < 0.03$]. Muscle tenderness VAS was higher two days after exercise [54.8 ± 4.8 mm] as compared to day 0 and day 14 before the exercise [$P < 0.04$]. Muscle tenderness immediately after the exercise [47.4 ± 6.5 mm] was no different than one day and two days after the exercise.

Muscle Tenderness in the BSP-201 Group

A one-way ANOVA for the muscle tenderness VAS assessment in the BSP-201 group indicated a main effect between different times [$P < 0.004$, Figure 1]. Muscle tenderness VAS was higher at one day [39.8 ± 5 mm] and two days [40.8 ± 4.3 mm] after exercise, as compared to immediately after the exercise [24.3 ± 4.8 mm, $P < 0.02$].
DISCUSSION

This randomized, prospective, double blind, placebo-controlled, parallel group study demonstrated that prophylactic supplementation of BSP-201 significantly relieves muscle tenderness associated with intensive eccentric exercise.

There is evidence from the literature that the unsaponifiable material in sheanutoil contains triterpene alcohols as α-amyrine, butyrospermmol, lupeol, and β-amyrine (2–5). Triterpene alcohols are known to possess anti-inflammatory effects (7–13) most likely by reducing inflammatory cytokines such as IL-6 and TNFα.

Post-Exercise Muscle Soreness

Muscle tenderness in the placebo group induced by an intensive exercise of FDI in the present study followed a typical time course pattern, i.e., muscle tenderness increased muscle immediately after, at one day after [day 15], and two days after [day 16] (25–27). In the sheanut oil extract group, this pattern was altered and there was significant reduction of muscle tenderness immediately after the exercise, one day after, and two days after the exercise as compared to the placebo group. Within the sheanut oil extract group, fairly low overall muscle tenderness was developed. The fact that the muscle tenderness was not different from the placebo group on day 0, before exercise, and on day 22 suggests that sheanut oil extract is most effective on the mechanisms specifically operating within these times, i.e., immediately after the exercise until two days after the exercise. Significant relationship of the severity of PEMS one day after eccentric exercise and IL-6 has recently been shown in humans (22).
It has previously been shown that the nonsteroidal anti-inflammatory drug aspirin relieved PEMS two days after the exercise in a considerably higher dose of 3,000 mg/day (28). Indirect support of inflammatory pathology in PEMS is indicated by the reduced PEMS and prostaglandins E₁ and F₂ following intake of ibuprofen (29). However, other studies employing ibuprofen (30) and flurbiprofen (31, 32) showed no relief of PEMS. This suggested that there is only minimal role of prostaglandins in the muscle tenderness associated with eccentric exercise.

Intense eccentric exercise results in high tension and mechanical damage in the muscles that is followed by increased amounts of IL-6 release, which corresponds to the time-course development of muscle soreness (22, 33–35). A recent in vitro study has shown that hydrolyzed BSP-201 significantly inhibited the production of IL-6 (16). From the comparison of time course inhibition of muscle tenderness between the placebo group and the BSP-201 group in the present study, it appears that sheanut oil extract effectively inhibits muscle tenderness from immediately after an intense eccentric exercise to 48 hours after, which may correspond to the pattern of release of IL-6 in eccentric exercise (35). The BSP-201 displayed inhibition in vitro of nuclear factor κB response element-lac Z plasmid in human jurkat cells (16). This pharmacodynamic property of BSP-201 is interesting because NF-κB activation is involved in the expression of IL-6 (36).

In conclusion this current study showed that sheanut oil extract reduces muscle tenderness most likely via reduction of pro-inflammatory cytokine IL-6.

REFERENCES


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