A Nutraceutical Combination of Bromelain and Boswellia Serrata Casperome® in Siben®: Effects on the Postoperative Course of Inguinal Hernioplasty with Mesh at One Year Follow up. A Randomized Multicentric Study

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AIM: We investigated the potential benefits of administering a nutraceutical combination of Bromelain (200 mg) and Boswellia serrata Casperome® (200 mg) on post-operative outcomes of hernioplasty with mesh.

METHODS: One hundred eighty patients (27 females, 153 males) were enrolled to undergo open tension-free hernioplasty with the use of Progrip®. Patients were randomized to receive either one tablet of Siben® (study group) or placebo (control group) on an empty stomach, every twelve hours for eleven postoperative days. All patients filled out a medical questionnaire focused on postoperative pain, based on the Visual Analogue Scale (VAS) scale and the Short Form-36 (SF-36) questionnaire, at time T0 (day of surgery) and T28 (28th day after surgery).

RESULTS: One-year results showed a significant improvement in the primary postoperative outcome in the study group. Perception of pain was significantly reduced in the Siben® group compared with controls, both on the seventh ($p < 0.05$) and the twenty-first ($p < 0.05$) postoperative day. Patients included in the Siben® group also resumed daily activities and returned to work earlier than the controls. Moreover, results of the SF-36 indicated better Quality of Life (QoL) scores in the study group compared to the placebo group.

CONCLUSIONS: Our analysis effectively demonstrates that the use of Siben® in open inguinal hernia mesh repair may improve short- and long-term surgical outcomes, contributing to a better QoL.

Keywords: inguinal hernioplasty; Bromelain; Boswellia serrata

Introduction

The current standard of postoperative therapy following the routinely performed inguinal hernioplasty procedure includes the administration of anti-inflammatory agents to control postoperative pain and discomfort. However, patients with renal and gastric comorbidities cannot receive a standard continuative therapy based on anti-inflammatory agents for several days after surgery, until their complete recovery to normal daily activities.

It is critically important to limit edema of tissues related to the mesh implant, which represents the main problem for patients after prosthetic wall restoration surgeries. Currently, there is an increased interest in nutraceutical compounds that may be substituted for anti-inflammatory agents commonly prescribed after abdominal hernia restoration.

Due to the results reported in urology and rheumatology, as well as those reported after incisional hernia restoration, nutraceuticals are of considerable interest as a way to control edema and discomfort after prosthetic hernia restoration.

The use of nutraceutical agents has been proposed as a method to control the inflammatory cascade activation after

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abdominal wall surgery, but the evidence for this is limited, and to the best of our knowledge, there are no randomized studies with an adequate sample size, and with qualitative data from questionnaires, comparing the effect of standard anti-inflammatory drugs to nutraceuticals on postoperative inflammation in hernia surgery [1].

We investigated the use of an original nutraceutical combination of Bromelain (200 mg) and Boswellia serrata Casperome® (200 mg) contained in Siben® (Italian Register of Health Ministry Supplements product code: 52829; Agaton Srl, via Pianodardine 23-83100, Avellino, Italy), as a potential alternative to the routine administration of anti-inflammatory drugs for ameliorating pain, the postoperative seroma formation, and the discomfort perceived by patients operated for inguinal hernias.

Materials and Methods

This prospective, randomized multicentric study is an analysis of registered groin hernia repair conducted in four different Surgical Departments (Hospital "San Giovanni Bosco" of Naples, University Hospital Tor Vergata of Rome, Hospital "Villa Betania" of Naples, and Hospital "Villa dei Fiori" of Acerra), gathering data from January 2016 to December 2019.

During the study period, one hundred eighty patients (27 females and 153 males respectively) were enrolled. In keeping with CONSORT 2010 guidelines, patients consenting to treatment protocol were randomized through random electronic sequence and sealed letters, and divided into two groups, the "treated" group (90 patients) and the "control" group (90 patients).

Inclusion criteria were as follows: patients with inguinal hernia (direct, indirect, and inguinoscrotal), age of majority, surgically treated with the open flat *Trabucco* modified technique using the *Progrip*® mesh, body mass index (BMI) ranging from 20–35. Exclusion criteria were: patients affected by crural hernia, patients submitted to anticoagulant therapy with high risk of bleeding, BMI above 35, and hernioplasties performed in an emergency setting since the postoperative stay could have been in intensive care.

The study group was treated with one tablet of *Siben*® twice daily, every twelve hours, for 11 days on an empty stomach, whereas the control group was treated with no supplement tablet (placebo) at the same time. Every patient enrolled in the study was guaranteed, only on demand, the administration of a maximum of 2 g of paracetamol per day to control moderate to severe perceived postoperative pain or discomfort.

Data collected were: days of hospitalization; postoperative pain with the use of Visual Analogue Scale (VAS) scale at 1, 7, and 21 days after surgery; home convalescence and recovery to daily and work activities.

This postoperative treatment started on the first postoperative day. All patients filled out a medical questionnaire regarding pain, based on the Visual Analog Scale (VAS scale, ranging from zero to ten).

In addition, all patients completed the Short Form-36 (SF-36) questionnaire at T0 (day of surgery) and T28 (28th day after surgery). This consists of a 36-item questionnaire that evaluates Quality of Life (QoL) across eight domains, which are both physically and emotionally based, as follows: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue; emotional well-being, social functioning, pain, general health. Higher scores on the SF-36 indicate better QoL.

Statistical Analysis

Statistical analysis for nonparametric variables was conducted using the Mann-Whitney U test to compare the differences between groups. The chi-square test was assessed for evaluating group differences in qualitative variables. p values less than 0.05 were considered statistically significant. All statistical analyses were conducted using the statistical platform R vers. 4.0.1 (R Core Team (2020). R: A language and environment for statistical computing. version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

Results

Features of groups are reported in Table 1. The groups were balanced with respect to age, gender, BMI, medical comorbidities, and type of groin hernia (direct, indirect and inguinoscrotal).

Table 1. Demographic characteristics of the patients at baseline.

	Siben group	Control group	p value
Patients	90	90	
Gender	75 M; 15 F	78 M; 12 F	0.531
Age (mean)	57.04 (±12.07)	57.01(±11.06)	0.986
BMI	27.03 (±2.5)	27.3 (±2.6)	0.479
Type of groin hernia			0.714
Direct hernia	55	59	
Indirect hernia	18	18	
Inguinoscrotal hernia	17	13	
Comorbidities	16	15	0.844

180 patients were divided into two homogenous groups for age, body mass index (BMI), comorbidities, and type of groin hernia.

Comparison on the first postoperative day revealed a significant ($p < 0.001$) difference between the two groups (Fig. 1, Table 2); the control group displayed lower Visual Analogue Scale (VAS values) (median: 3; Interquartile Range (IQR): 2–4; range: 2–4) compared to the experimental group (median: 5; Interquartile Range IQR: 4–6; range: 3–7).

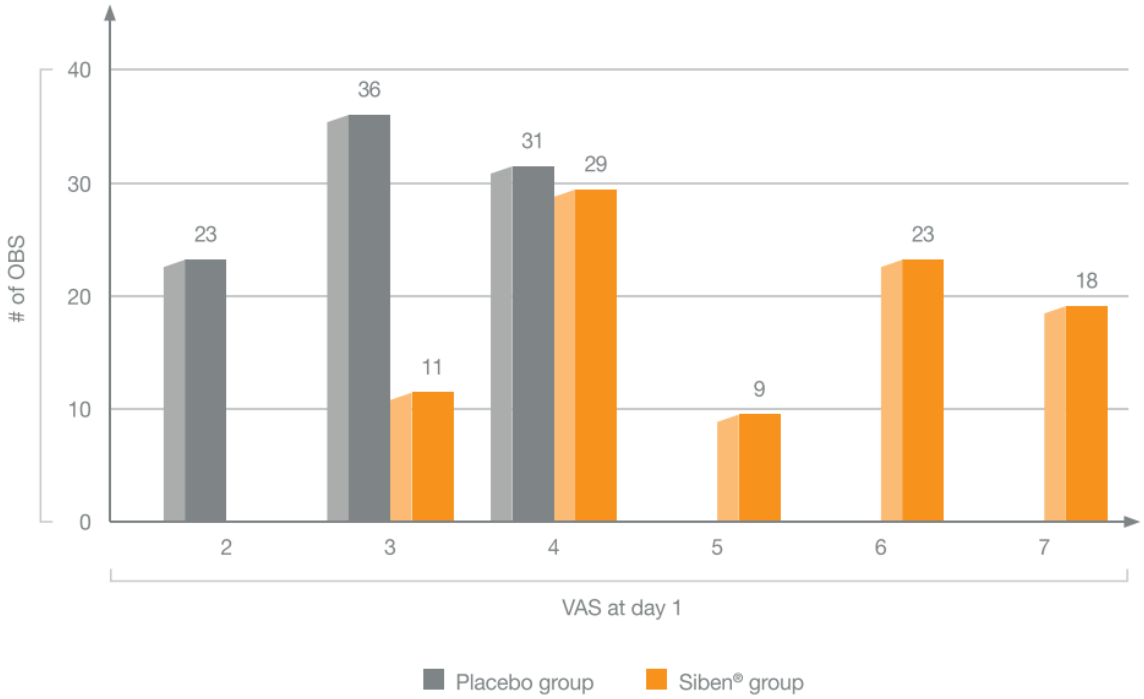

Fig. 1. Comparison between the study group and the control group, after 1 day of follow-up. VAS, Visual Analogue Scale. # correspond to number of observations

On the seventh postoperative day (Fig. 2, Table 2), Visual Analogue Scale VAS values were significantly ($p < 0.001$) lower in the Siben group (median: 2; Interquartile Range IQR: 2–3; range: 2–7) than in the control group (median: 3; Interquartile Range IQR: 3–4; range: 1–5).

On the twenty-first postoperative day, all VAS values ranged from 1 to 2 for both groups (Fig. 3, Table 2). The group difference in these postoperative values was statistically significant ($p = 0.010$).

Visual Analogue Range VAS score median values were observed at 1, 7, and 21 postoperative days and, as reported in Table 2, demonstrated decreased pain in patients of the study group, compared to the controls.

Table 2. Groups VAS median values at 1, 7, and 21 postoperative days.

Group	VAS median at postoperative day		
	1	7	21
Siben	5 [4; 6] (3 to 7)	2 [2; 3] (2 to 7)	1 [1; 1] (1 to 2)
Placebo	3 [2; 4] (2 to 4)	3 [3; 4] (1 to 5)	1 [1; 1] (1 to 2)
p value	<0.001	<0.001	0.010

Furthermore, the treated group reported a shorter recovery period before restarting daily and work activities compared to the control group, as shown by the boxplot depicted in Fig. 4. Figs. 1,2,3,4 were created with the software R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria)

Discussion

Inguinal hernia repair is one of the most common general surgical procedures performed worldwide, with about 20 million patients operated on annually. Postoperative pain is the most common complication of this kind of procedure; there is an estimated 8–10% incidence of mesh-related complications, and mesh removal is required in up to 6% of cases [2]. Pain can have multifactorial pathogenesis, and systemic pharmacological analgesics are routinely used in the postoperative period in order to ameliorate symptoms. Several treatments have been described in the literature, as described by *The HerniaSurge Group* using a conventional NSAID or a selective COX-2 inhibitor plus paracetamol [3, 4, 5].

Several factors have been analyzed as potential correlates of postoperative groin pain: type of mesh, patient's comorbidity, the expertise of the surgeons, relapses, surgical technique, and surgical (open-flat, laparoscopy and robotic) approach.

Landry *et al.*'s [6] observational study showed how a preoperative multimodal treatment for chronic groin pain, after groin hernia repair, can improve clinical quality, as demonstrated in 27 patients who underwent cognitive behavioral therapy. Furthermore, groin hernia repair by using the laparoscopic transabdominal preperitoneal (TAPP) repair approach presents lower post-operative pain with a quicker return to normal patient activity compared to the open technique.

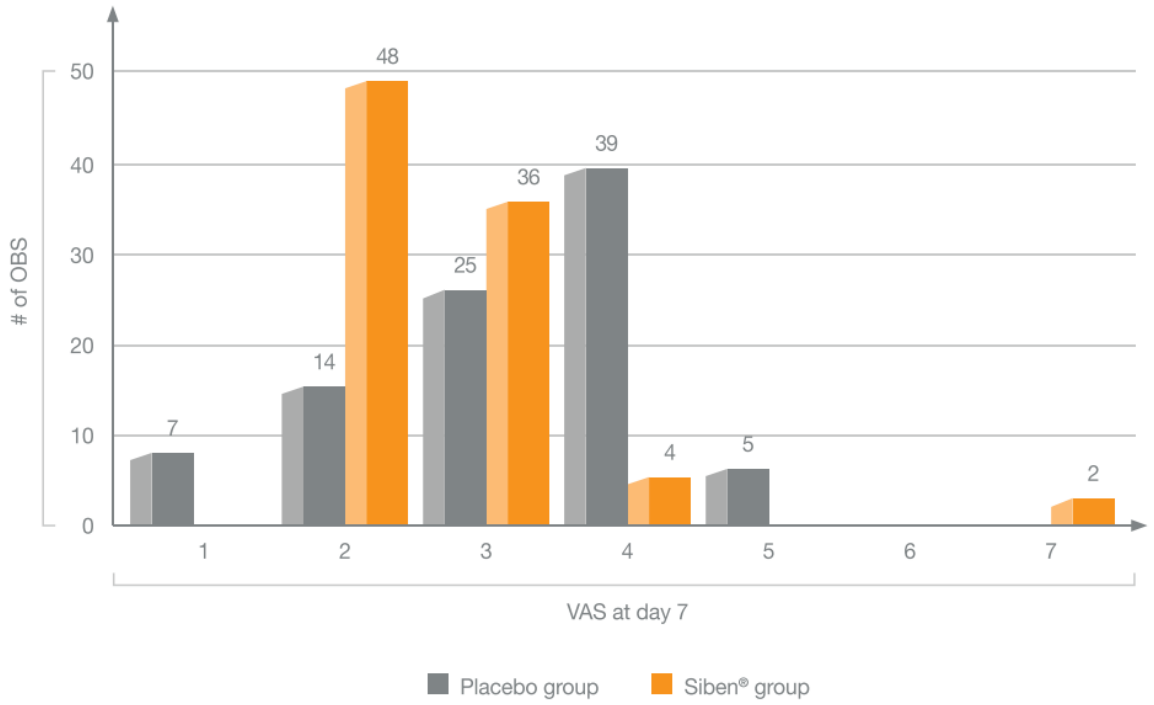

Fig. 2. Comparison between the study group and the control group, after 7 days of follow-up. # correspond to number of observations.

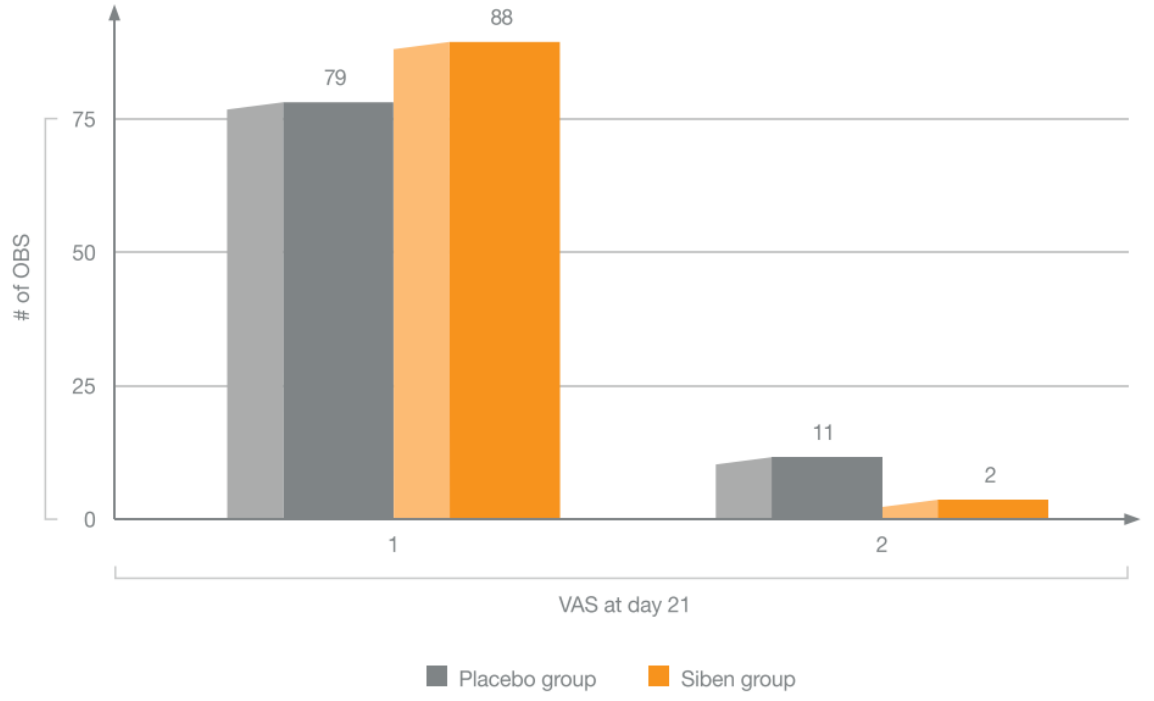

Fig. 3. Comparison between the study group and the control group, after 21 days of follow-up. # correspond to number of observations.

No previous studies have evaluated the efficacy of specific anti-inflammatory drugs in post-operative groin hernia repair with an adequately large cohort of patients.

Cai *et al.*'s [7] expertise-based randomized study described the relationship between chronic pain after groin hernia repair in 412 patients, and the kind of technical operation, independently of the type of mesh used. No differences in

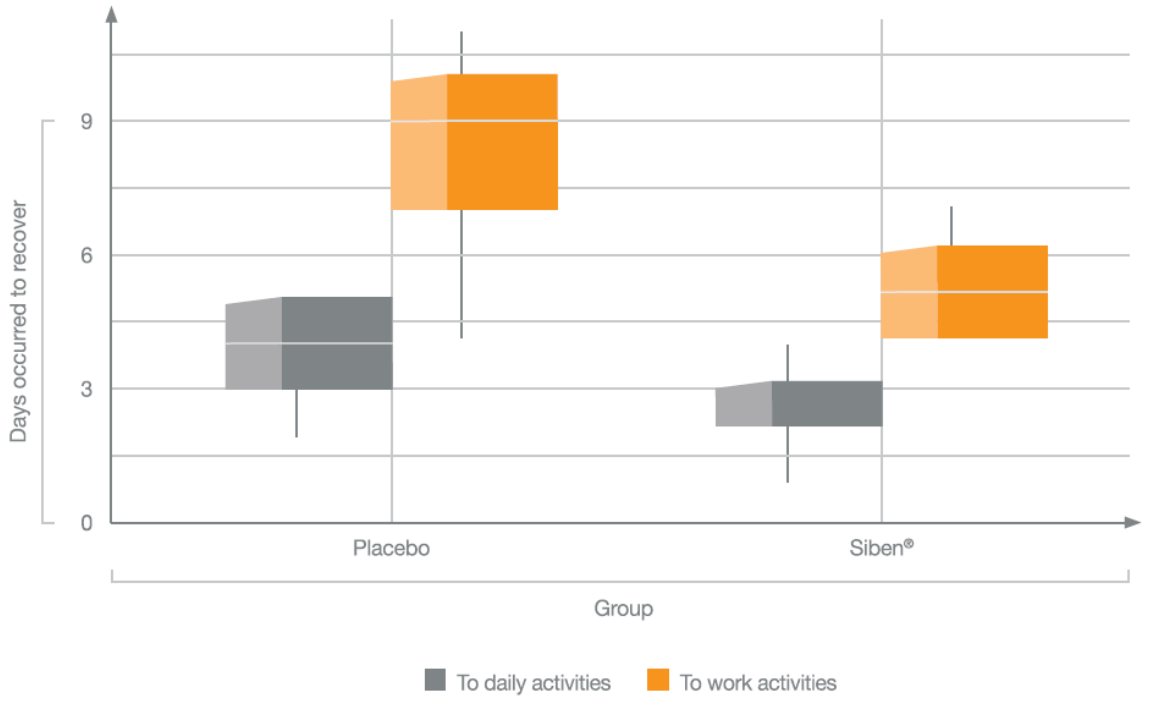

Fig. 4. Recovery to work and daily activities time for both groups.

QoL between groups could be detected, but both groups had a substantially better postoperative QoL as compared to pre-operative. In the analysis of the impact on sex life, no differences between mesh groups were found.

Bischoff *et al.*'s [8] systematic review suggests an association between surgical expertise and chronic postoperative inguinal pain after inguinal hernia repair in a total of 3086 patients undergoing the same procedure; the analysis showed an incidence of chronic inguinal pain between two study groups (expert vs non-expert), equal to 11.7% vs 39.4%, respectively.

The use of Bromelain in combination with other drugs has been widely adopted in several fields, such as urology [7] and rheumatology. Its anti-inflammatory characteristics are rather well known, as demonstrated by De Luca *et al.* [1] in his prospective randomized clinical trial with use of a combination of *Bromelain* (200 mg) and *Boswellia Serrata Casperome*® (200 mg) in *Siben*® for reduction of seroma formation in patients undergoing incisional hernia repair. This kind of nutraceutical supplement acts specifically on tissue edema, which is critical since in most cases postoperative pain is related to the seroma caused by surgery and the inflammatory reaction that subsequently occurs at the mesh placement. This treatment may ameliorate both conditions and help to promote the correct incorporation of the prosthesis.

Other trials in the literature, as described by Bischoff *et al.* [8] in their randomized double-blind placebo-controlled study, analyzed the effects of ultrasound-guided ilioinguinal/iliohypogastric nerve blocks after groin hernia repair, and concluded that this technique is ineffective for postoperative pain control. This point reinforces the need for medical treatment to reduce postoperative groin pain. Results of the present study, taking into account the SF-36 results at T0 compared to T28, suggest that the QoL of the *Siben*® group is better than that of the placebo group. This outcome measure can be considered a useful indicator of postoperative recovery for this kind of surgery.

Conclusions

This multicentric study, with an adequately large number of patients, demonstrated that supplementation with *Bromelain* (200 mg) and *Boswellia Serrata Casperome*® (200 mg) as contained in *Siben*®, from the seventh postoperative day on, helps reduce groin pain and discomfort, as well as edema formation, in patients undergoing prosthetic hernioplasty. Furthermore, our analysis demonstrates that the use of *Siben*® in open inguinal hernia repair improves short- and long-term surgical outcomes and helps to provide a better QoL. We attribute these effects to a substantial reduction of tissue inflammation around the mesh.

Availability of Data and Materials

The data used to support the findings of the present study are available from the corresponding author upon request.

Author Contributions

GMDL, ADL, LF, AS designed the research study. FPP, DNI, FDG, MGM performed the research. VD, FLDL evaluated clinical cases. FV, MD reviewed bibliography, as-

sisted in analysing data. PM, GM evaluated randomization. GMDL wrote the original draft of this manuscript. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors contributed to the study, and read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate are not applicable: the 2015 ministerial guidelines, inspired by the indications of the E.F.S.A. (European Food Safety Authority), say that the ethics committee is required exclusively to studies concerning the efficacy and safety of specific components (foods) of the food supplement, therefore to attribute to these specific components well-determined health claims (indications), or aimed at deny and therefore avoid any warning relating to specific component codes. We wanted to investigate, in essence, how food supplement (and therefore a food advice given by the investigator) acted on the state of health of patients, and not on the activity of a specific component, and therefore on the lawfulness of attributing or minus a health claim the Italian's regulatory regolatory affairs do not provide for an ethical committee.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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