

One single drug combination of bromelain and *Boswellia serrata casperome*[®]: Effects on postoperative edema in open incisional abdominal hernia repair. Prospective randomized clinical trial

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Abstract

Introduction: Aim of this study is to investigate the significant postoperative benefits on patients about edema of tissues after incisional hernia repair with synthetic mesh using a combination of *Bromelain* (200 mg) and *Boswellia Serrata Casperome*[®] (200 mg), evaluated by ultrasound (US), and compared to control patients group (not treated with drugs).

Material and method: From May 2018 to May 2019, fifty adult patients submitted to onlay incisional hernia repair using synthetic mesh with component separation of the abdominal wall and were divided into two homogenous groups (27 females, 23 males, mean age 61 years, mean BMI 32). Only the treated group took one tablet of drug for 30 days on an empty stomach, starting from the first post-surgery day. Checks were made on all patients from the first post-surgery day and going on 15th, 30th and 60th post-surgery days by US linear probe measuring edema, defining its thickness and average diameter.

Results: The two groups were homogeneous compared to the initial diameter of the abdominal wall defect ($p=0.877$). Therefore, the edema thickness was independent of the size of the starting defect in the two groups examined. The edema was already reduced in the treated group compared to the control group at 15 post-surgery days; therefore this reduction became statistically significant starting from US result at 30 post-surgery days of drug treatment ($p=0.043$) and was even greater in the US result after 60 post-surgery days ($p=0.001$).

Conclusion: Results obtained in this preliminary study showed a rapid and significant improvement in postoperative edema outcome of incisional hernia repair in patients treated with drug. Benefits of treatment are also found in patients even after one month of drug suspension.

Introduction

Incisional hernia is a significant problem occurring after laparotomy, reporting recurrences rate of 10-20% of laparotomy cases.

General consensus in literature is represented by tension-free hernia repair with use of mesh, observing a significantly reduction of recurrence rates. Currently, the question of which surgical technique is better, between laparoscopic approach (intraperitoneal onlay mesh=IPOM) versus open (sublay), is still debated [1].

It is certain that, even today, perfect mesh for incisional hernia repair doesn't exist like as doesn't exist a standardization technique for repairing this kind of wall post-operative defect.

Incisional hernia repair with mesh reduces recurrence rates but doesn't exist a technique standardization.

One of major complicate of this kind of repair is seroma formation or tissues' edema near the mesh. For this reason, it is also important to reduce edema and inflammation incidence [2].

Use of Bromelain in combination with other drugs has been widely adopted in several fields, such as urology and rheumatology. Therefore,

we investigated if a novel dietary supplement based on a combination of Bromelain (200 mg) and *Boswellia Serrata Casperome*[®] (200 mg), can demonstrate a suitable reduction of postoperative inflammation and seroma formation in patients subjected to abdominal incisional hernia repair, in order to avoid synthesis of pro-inflammatory agents, such as leukotriene-4, 5-lipoxygenase, 5-hydroperoxydeicetraenoic acid, prostaglandins and kinins.

Materials and methods

This randomised prospective longitudinal cohort double center no profit study was performed at “D. Camberlingo” Francavilla Fontana hospital, Italy, department of general surgery and “San Pio” Castellaneta Hospital, Italy, department of general surgery, from May 2018 to May 2019. Criteria of admitted patients were: Age>18;

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incisional hernia from previous laparoscopic or open operation; informed consent to clinical study; BMI not more than 40; incisional hernia diameter from 2 to 10 cm.

All patients were submitted to open incisional abdominal hernia repair, using a composite double layer partially absorbable mesh. Study group was treated with a daily tablet of drug on an empty stomach starting by the first post-surgery day and going on for the next 30 days after operation.

Main purpose of the present study was to observe seroma reduction in patients treated with Bromelain (200 mg) and Boswellia Serrata Casperome® (200 mg).

Like biometric measurements, all patients were submitted to ultrasound to evidence areas of the abdominal wall affected by seroma formation. For each identified area were executed 6 thickness measurements and was calculated the mean diameter of these areas after incisional hernia repair. All patients were submitted to ultrasound post-operative controls at first, 15th, 30th and 60th post-surgery days. The ultrasound equipment was composed by a linear 7.5-15 MHz probe.

Statistical analysis

Several numerical variables have been described using the mean ± standard deviation [min; max] in the case of variables with symmetric distribution, or the median with the range [min; max] in the case of variables with an asymmetric distribution. The categorical variables were synthesized using absolute frequencies and percentages. Coherent with the nature of the variables, the comparison between two groups was made using the Student's T-Test, the Mann-Whitney Test or the Chi-Square Test.

P-values less than 0.05 were considered statistically significant.

Randomization criteria

All patients were randomized, according to CONSORT 2010, in parallel two groups with randomization 1:1 [3] and divided as study group, called "treated" because was administered *Bromelain* (200 mg) and *Boswellia Serrata Casperome®* (200 mg) therapy for 30 days after operation and control group, called "not treated" in which patients were not treated with any drugs.

Results

Fifty Caucasian patients (27 females, 23 males, mean age 61 years old, mean BMI 32) were enrolled from May 2018 to May 2019.

Patients were considered homogeneous for sex, age, incisional hernia diameter and chronic illness (Table 1).

All patients were submitted to 60 days follow-up. Mean age of all patients was 61 years old, 54% female and 46% male gender, in which was performed an open technique repair of abdominal incisional hernia using a composite double layer partially absorbable mesh in all patients. 39 patients were affected by chronic systemic illnesses (78%): 12 cases of diabetes (24%), 5 in the treated group and 7 in control group; 19 cases of hypertension (38%), 11 in the treated group and 8 in the control group; 8 patients were affected by heart diseases (16%), 5 in the treated group and 3 in the control group. In 42 patients was performed a modified surgical only technique, adding to the standard procedure, a plication of the residual lateral fascia on the close margin of the mesh to stimulate mesh ingrowth. In a single female study group patient was performed appendectomy and cholecystectomy. In 3 cases, 1 of treated group and 2 of control group, was also positioned post-operative VAC-therapy for maintaining clean the abdominal incision in obese increased risk patients (BMI>35). In 3 patients the wall defect was multilobular, but in most cases there was a homogeneity compared to the initial diameter of the abdominal wall defect (p=0.877). The overall complication rate was registered in 22% of patients, with 5 abdominal infections treated with antibiotic therapy, 5 localized hemorrhages and 1 bronchitis, in obese patient, treated with antibiotic therapy of cefazolin in combination with levofloxacin for 5 days. In 47 patients was administered a prophylaxis with LMWH 4000 UI per day for 10 post-surgery days. The mean BMI was 32, (range from 24 to 40). The mean pain scale according to VAS scale (Visual Analog Scale) was estimated at mean 4,4/10 point. Tissue edema was independent by the size of the defect in the two groups, and it was already reduced in the treated group compared vs control group after 15 post-operative days but without statistical significance, p=0,723 (Table 2). This data acquires statistical significance after 30 post-operative days in the treated group (p=0.043) and it becomes even more significant after 60 post-operative days (p=0.001), after 30 days suspension of drugs (Figure 1).

Discussion

In literature is still debated the way of reduction of post-operative seroma formation in patient submitted to incisional hernia repair. As suggest by Massey LH et al. there are no evidences about the reduction of seroma formation using differents surgical devices [4] and no evidence for use of post-operative drainages to prevent wound complications and seroma formation have been shown [5,6].

This study shows that a novel dietary supplement based on combination of Bromelain (200 mg) and Boswellia Serrata Casperome®

Table 1. Characteristics of two groups (treated vs control group)

	Patients (n=50)	Treated (n=29; 58.0%)	Not treated (n=21; 42.0%)	p value
Age; mean ± Standard deviation [min ; max]	61.2 ± 15 (31 to 90)	60.4 ± 15.3 (31 to 89)	62.2 ± 14.8 (36 to 90)	0,682
Female; n (%)	27 (54)	17 (58.6)	10 (47.6)	0,567
Diabetes; n (%)	12 (24)	5 (17.2)	7 (33.3)	0,314
Hypertension; n (%)	19 (38)	11 (37.9)	8 (38.1)	1,000
Cardiopathy; n (%)	8 (16)	5 (17.2)	3 (14.3)	1,000
Plication of the abdominal fascia; n (%)	42 (84)	24 (82.8)	18 (85.7)	1,000
Grid type:				1,000
Ultrapro mesh	3 (6.4)	2 (7.4)	1 (5)	
Ventralight	44 (93.6)	25 (92.6)	19 (95)	
Incisional hernia diameter;	5 ± 2.2 (2 to 10)	5 ± 2.3 (2 to 10)	5 ± 2.1 (2 to 10)	0,877
Complications; n (%)	11 (22)	8 (27.6)	3 (14.3)	0,319

Table 2. US Biometric measurements results, comparison between two groups

	Patients (n=50)	Treated (n=29; 58.0%)	Not treated (n=21; 42.0%)	p value
Ultrasound 24h; median [min ; max]	7 [3.5 ; 10]	5 [2.5 ; 10]	10 [5.5 ; 12.4]	0,054
Ultrasound 15 days; median [min ; max]	13 [7.5 ; 20]	15 [6 ; 20.9]	11.6 [8.2 ; 18.5]	0,723
Ultrasound 30 days; median [min ; max]	13.8 [6.2 ; 23]	10 [5 ; 19.6]	18 [10.7 ; 25]	0,043
Ultrasound 60 days; median [min ; max]	10 [5 ; 15.2]	5 [3.5 ; 10.5]	18 [7.5 ; 22.5]	0,001

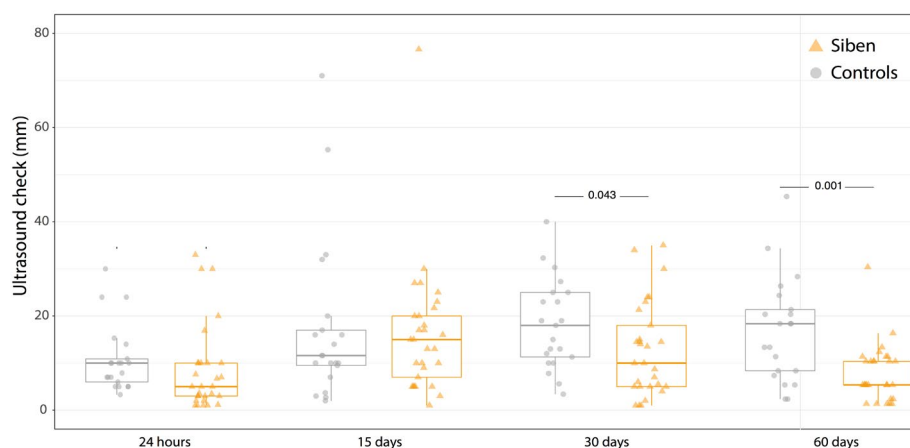


Figure 1. Comparison between two study groups, Treated group vs Control group, after 60 days follow-up. Siben: Bromelain + Boswellia Serrata Casperome

(200 mg) improves a rapid and significant post-operative tissues edema in patients submitted to incisional hernia repair with mesh.

Bromelain is a proteolytic enzyme able to degrade a protein called fibrin as suggest from Lotz-Winter [7] in fact the pro-inflammatory role of fibrin in tissues edema formation is known from 1986 [8]. Moreover, Bromelain is a drug without multiple adverse effects [9,10], such as hepatotoxicity or gastrointestinal hemorrhage, and that can be taken even by patients affected by chronic diseases (diabetes, hypertension, heart disease, obesity).

Boswellia Serrata has a singular anti-inflammatory property as suggest by Siddiqui [11]. Recently, the effect of Boswellia Serrata has been shown in animal model of Rheumatoid Arthritis as adjuvant to conventional therapy for contrasting the pro-inflammatory activity of Tumor Necrosis Factor- α [12].

US biometric measurements control of the patients has allowed to perform a statistical analysis that has shown reduction of edema that becomes significant after 30 post-operative days of drug treatment ($p=0.043$) and it's more significant after 60 post-operative days ($p=0.001$), underlining the benefits of this treatment also after one month of drug suspension.

Bromelain, under form of coated tablets, with its maximum proteolytic activity (2500 GDU/g), is efficacy and safety and their anti-inflammatory properties are improving in association with Boswellia Serrata Casperome® contained in it, giving a demonstrated therapeutic result. Therefore, administered in adequate doses, this association has an anti-inflammatory effect on tissues. This drug plays a role in reduction of postoperative inflammation and seroma formation thickness by blocking synthesis of inflammatory agents, such as leukotriene-4, 5-lipoxygenase, 5-hydroperoxydeicoteetraenoic acid, prostaglandins and kinins.

Conclusion

This study demonstrates as the use of Bromelain (200 mg) and Boswellia Serrata Casperome® (200 mg) improves a rapid and significant

post-operative tissues' edema in patients submitted to incisional hernia repair with mesh and demonstrates as the US post-operative wall control represents a valid technique to follow-up of patients.

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Authors' contribution

All authors have contributed to the design this study and have approved final version.

Authors disclosures

All authors have no conflicts of interest or financial ties to disclose

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