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A randomized trial of Boswellia in association with betaine and myo-inositol in the management of breast fibroadenomas

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Abstract. – OBJECTIVE: Breast fibroadenoma is a common finding in young women and actually accounts for the majority of benign breast lumps. Fibroadenoma does not require any treatment unless clinical symptoms (mostly mastalgia) or histological markers of cancer risk (atypia) impose specific medical or surgical intervention. In symptomatic fibroadenoma, anti-estrogenic treatments provided evidence of success. Yet, these therapies are often associated with relevant side effects that lead to drug treatment discontinuation. Additionally, in such cases, relapse is a frequent issue. Therefore, an optimal strategy is still warranted. Boswellia, betaine and myo-inositol have already been proved to modulate different pathways – inflammatory, metabolic, oxidative and endocrine processes – in a wide array of human tissues. Based on that background, we hypothesized that these substances can effectively synergize in inducing the regression of fibroadenoma.

PATIENTS AND METHODS: We included 64 patients ≤ 30 years of age with fibroadenoma. The patients were randomized into two groups. The experimental group was treated with an association of Boswellia, betaine, myo-inositol, B-group vitamins and N-acetylcysteine for 6 months; otherwise, the placebo group was treated only with B-group vitamins and N-acetylcysteine. Patients were monitored at the enrollment and the end of the study for evaluating the clinical response.

RESULTS: A significant clinical improvement was observed in the experimental arm. Fibroadenoma median volume reduction averaged 17.86% in the experimental group and 5.96% in the placebo group. Moreover, 14 out of 36 (38.88%) patients showed a reduction of fibroadenoma volume compared to 5/28 (17.85%) observed in the placebo group (p = 0.005).

CONCLUSIONS: A supplementation with Boswellia, betaine and myo-inositol reduces fibroadenoma dimension in young women. No relevant side effects have been recorded.

Key Words:
Fibroadenoma, Benign breast disease, Boswellia, Betaine, Myo-inositol.

Introduction

Benign breast lumps are mostly constituted by fibroadenoma, particularly in young women between 15 and 25 years of age[1]. Fibroadenoma is usually considered as an aberration in the development of ducto-lobular structure with further associated involution. Fibroadenoma begins as a hyperplasia of the lobules, with a progressive increase in size from 1 to 3 cm. Most breast lumps remain unchanged, but some increase in size up to 5 cm or more. Multiple fibroadenomas may occur on the same breast or bilaterally. Moreover, almost 10-15% of lesions regress spontaneously over a period that can range from 6 to 60 months[1-3].

Simple fibroadenoma, without atypia and asymptomatic, is usually not treated but kept under observation, though the risk of cancer transformation is deemed to be very low[3]. Complex

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fibroadenoma is instead associated to a moderate risk of develop breast cancer, and if associated to atypia or arising in women with a family history of breast cancer, is surgically removed[4-7]. Furthermore, in a significant proportion of cases, some patients prefer to remove the lumps because of pain, discomfort, for psychological reasons, including the fear of tumor risk[8,9].

Current treatments are usually based on the hormonal drug with anti-estrogen activity, such as tamoxifen[10] or ormeloxifene[11]. The rationale of such approach is mainly based on the growth-inhibitory effect of anti-estrogens, since it has been hypothesized that fibroadenomas arise in response to prolonged exposure to deregulated estrogen metabolism. Moreover, high levels of estrogen receptors have been evidenced in fibroadenoma tissues[12]. However, endocrine treatment is often associated with a relevant number of side effects, leading to therapy discontinuation in a higher percentage of patients.

Previous studies[13,14] on Boswellia and betaine have highlighted the protective and therapeutic effects of these natural compounds on breast physiology. Moreover, different studies[15-18] on myo-inositol showed that this six-fold alcohol of cyclohexane is able to modulate different pathways and endocrine processes in a wide array of human diseases, including cancer. In a preliminary study, on the synergic use of Boswellia, betaine and myo-inositol, we showed the effectiveness of such a medical device in improving both clinical symptoms and radiological signs of benign breast disease, namely by significantly reducing mammographic breast density in women with extremely dense breasts[19].

Based on these previous results, a double-blind, randomized, placebo-controlled, parallel group design was conducted to evaluate the effectiveness of a combination of Boswellia, betaine and myo-inositol, on the proliferation and regression of fibroadenomas. The primary outcome of the study was, therefore, to investigate the efficacy of these substances on fibroadenomas by assessing measurements of the volume with ultrasound examinations up to 6 months.

Patients and Methods

Patients' Selection

The study was carried out between February 2014 and November 2015. The study design was based on the enrolment of 64 women, aged between 15-30 years (mean age 22.5 ± 7.5), with a diagnosis of fibroadenoma made on a triple assessment (clinical examination, ultrasound, and a core needle biopsy (CNB). Patients with the following characteristics were excluded from the study: patients above 30 years of age; patients with fibroadenoma equal to or greater than 5 cm (giant fibroadenoma); past history of breast cancer or a family history of breast cancer; pregnancy; women with underlying pre-neoplastic diseases such as atypical lobular hyperplasia or sclerosing adenosis; patients under endocrine treatment or hormonal contraceptives. Baseline patients' characteristics are reported in Table I.

Patients were provided with an information sheet explaining the nature of fibroadenoma and the possible benefit derived from the product. They were recruited for the study after signing the informed consent form.

To ascertain the clinical benefit provided by the experimental treatment we used a randomized, placebo-controlled, parallel group. Patients were randomized to treatment using a minimization procedure[20].

Patients in the placebo group were treated with a preparation of B-group vitamins and N-acetylcysteine (NAC) with a dosage of two capsules two times a day (Table II). Women in the experimental group were treated with a formula comprising Boswellia, betaine, myo-inositol, in association to NAC and the vitamins administered to the control group. Placebo as well as the experimental treatment (Eumast□s®), were kindly provided by the Lo.Li. Pharma Srl, Rome, Italy. The capsules were manufactured for both groups to have the exact same appearance.

Quantitative Assessment of Fibroadenoma

A breast ultrasound was made using a linear probe of 7.5 MHz on ultrasound. Fibroadenoma

Table I. Baseline characteristics of randomized patients who concluded the study.

Clinical data	Placebo group	Experimental group
No. of patients	28	36
Age (mean, years)	22.57±7.53	22.43 ± 7.57
Mean n. Nodules*/patient	2.8 ± 1.5	2.2 ± 1.2

Table II. Drug formula.

Component (mg)	Placebo group	Experimental group
Myo-Inositol	–	200
Boswellia	–	50
Betaine	–	175
Vitamin B6	2.1	2.1
Folic acid	0.3	0.3
Vitamin B2	2.1	2.1
Vitamin B12	0.003	0.003
N-acetyl-Cysteine	100	100
Posology	2 capsule twice a day	2 capsule twice a day

morphology was evaluated and dimensions were recorded. Patients were evaluated prior and after 6 months of treatment to assess the clinical response. Ultrasound examination of the breast was used as an objective measurement of baseline volume and at the end of the study in both groups.

The volume of fibroadenoma in cm^3 was calculated using the following simplified formula[11]: volume of fibroadenoma = a x b x c x 12:52 where a is the largest dimension, b is the dimension measured at right angle to a, and c = average of a and $b = (a + b)/2$.

Statistical Analysis

We adopt Fisher exact test for assessing statistical significance instead of chi-square (cells with < 5 units) due to a limited number of patients within the two groups. In addition to Fisher exact test significance, a confidence interval (CI) at 95% of the odds ratio is reported. The CI was estimated by means of Wald approximation. Changes in fibroadenoma volume over time were analyzed and p-value less than 0.05 was considered significant.

Results

From February 2014 to November 2015, 64 patients with breast fibroadenoma were studied. Some patients had more than a fibroadenoma. Of the 64 patients, 36 cases were randomized to the experimental group and 28 cases in the placebo group. 36 women in the experimental group had 72 fibroadenomas and 28 cases in the experimental group had 78 fibroadenomas. Table III describes basic features and average volume of fibroadenomas in the two groups. At the baseline, no significant differences in fibroadenoma volume were recorded between the two groups.

Ultrasound Volume

At the end of the study, a statistically significant reduction in the median volume of fibroadenomas was found in the experimental treated group when compared to placebo-treated patients. Indeed, the median volume in the experimental group decreases from 2.24 to 1.84 cm^3 after 6 months, whereas no differences were found in the control group (Table III).

The reduction in fibroadenoma median volume was 17.86% in the experimental group and only 5.96% in the placebo group. Additionally, a significant higher proportion of patients experienced a relevant reduction in fibroadenoma volume among the experimental group (15 out of 36, 38.8%) when compared the number of responsive patients within the control group (5 out of 28, averaging 17.8%). Patients of both groups in no case showed signs of worsening (i.e., increase in dimension).

Table III. Size of fibroadenomas at baseline and after treatment.

	N. patients	Mean n. nodules*/patient	Median volume (cm^3) at baseline	Median volume (cm^3) at 6 months	p-value[a]
Experimental arm	36	2.2 ± 1.2	2.24 ± 0.8	1.84 ± 1.1	0.005
Placebo	28	2.8 ± 1.5	2.18 ± 0.7	2.05 ± 0.6	ns

[a]p-values were estimated by Fisher Exact test comparing volume before and after treatment in experimental and placebo groups.

Side Effects

No side effects were recorded among patients participating in both groups of treatment.

Discussion

Fibroadenoma is the most common benign breast condition in young women and accounts for up to 50% of all breast biopsies being performed. Despite it is a widely recognized benign condition, some young women prefer to remove fibroadenoma for the fear of breast cancer[21]. However, surgical treatment surgery should be limited because of possible complications, especially if benign lumps are near to the nipple areola complex[2]. Studies by Khanna et al[12] and Viviani et al[10] have described the use of hormonal treatments in the management of fibroadenoma. Tamoxifen, an anti-estrogenic drug, may induce a mass reduction of about 20%[10]. Furthermore, significant benefits have been achieved by using Danazol in estrogen-positive patients[11,12]. However, relevant side effects are associated to endocrine treatment, leading to therapy discontinuation in a high proportion of patients. Therefore, it is preferable in clinical practice to keep women under observation. Fibroadenomas are typically composed of stromal and epithelial cells. The growth of normal breast epithelial cells is controlled by the ovarian steroid hormones estrogen and progesterone, as well as by cytokines and associated transcription factors, suggesting that multiple receptor signaling pathways could be involved in its growth and differentiation[22-24]. Modulation of these pathways may be related to downstream modifications in tissue architecture that, in turn, lead to changes in the control of cell proliferation, adhesion and migration[22,25].

It generally assumed that complex mechanisms between inflammatory processes and metabolic factors might efficiently interact with endocrine deregulation, and thus participate in fibroadenoma pathogenesis. In previous studies Boswellia, betaine and myo-inositol have been proven to display significant anti-inflammatory and endocrine-modulating activity, for this reason, we hypothesized a synergy of action in improving fibroadenoma clinical features when they are administered together.

Results herein show that a supplementation with betaine, myo-inositol and Boswellia, significantly reduces fibroadenoma mass in a significant percentage of patients. Benefits were comparable to those achieved by conventional hormonal manipulation, without any significant side effects. After 6 months of treatment, fibroadenoma volume measured by ultrasound technique decreases significantly in the experimental group, whereas no differences had been found in the placebo group. This effect may probably be ascribed to the pleiotropic mechanism of action of myo-inositol on different metabolic, inflammatory and endocrine pathways. Myo-inositol has been shown to prevent other inflammatory-based diseases such as pulmonary fibrosis[26] and chronic inflammation of the colon[27]. Moreover, myo-inositol can contrast inflammation-induced fibrosis interfering with TGF-β activity[28]. TGF-β is a potent pro-fibrogenic agent that induces the synthesis of collagen and regulates the balance between metalloproteinases and their inhibitors. Accordingly, it may be deemed a prominent factor in the cross-talk between epithelial cells and microenvironment[29]. Indeed, myo-inositol significantly modulates the expression of genes that encode TGF-βs and their receptors, and in this way, it exerts immune regulatory effects on colonic epithelium in inflammatory conditions[30-33]. Experimental evidence supports the involvement of both TGF-β deregulation and inflammatory pathways in the pathogenesis of fibroadenoma. Therefore, myo-inositol could exert beneficial effects by modulating these pathways[34]. Boswellia also has been recognized to exert many anti-inflammatory actions[35-40]. Additionally, investigations carried out in vitro have demonstrated the apoptotic, antiproliferative activities of Boswellia on different (MDA-MB-231 and MCF7) breast cancer cells[40]. Moreover, the betaine, substance involved in homocysteine metabolism, has been demonstrated to be involved also in collagen biosynthesis and in modulating cell-microenvironment cross talk, thus modulating genomic pattern expression within breast tissue[41,42].

Conclusions

The synergy of action displayed by Boswellia, betaine and myo-inositol, promotes fibroadenoma mass reduction in a significant percentage of young women. It is worth noting that this treatment is safe and well tolerated. This study suffers from some limitations. Furthermore, data presented herein are only up to 6 months, and a follow-up study needs to be carried out in order

to evaluate the relapse rate. Yet, a large survey is currently ongoing in order to provide a better statistical basis. Besides being preliminary, this pilot study could represent a new and safe treatment for fibroadenoma management.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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