PLASTIC RECONSTRUCTIVE & REGENERATIVE SURGERY

2023;2:49-54
DOI: 10.57604/PRRS-227

RESEARCH

THE TREATMENT OF CAPSULAR CONTRACTURE AFTER BREAST SURGERY WITH IMPLANTS USING CAPSULASE®

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Summary

Objective. The management of the capsular contracture after breast surgery with implants is challenging for the plastic surgeon. For years leukotriene antagonists have been used off-label, but they are not without adverse effects. Since boswellic acids inhibit the synthesis of leukotrienes, the purpose of this study was to evaluate their efficacy in treating the capsular contracture.

Methods. Twenty-eight patients who showed a capsular contracture higher than Baker I from March 2020 to June 2022 were included in the study. After informed consent was obtained, they were offered the treatment with Capsulase®. The patients were assessed clinically at 1, 2, 3 and 6 months and the response was defined as complete, partial or nil. At the same time, they were also asked to answer a questionnaire and the outcomes were rated on a four-point Likert scale.

Results. Forty-two breasts presented capsular contracture. Two patients (four breasts) left the study because of mild adverse effects (stomachache). A positive response (complete or partial) was obtained in 71% of treated breasts ($p < 0.05$). None of the patients worsened. The improvement was maintained until the 6th month in 77.7% of the cases who responded positively. Subjectively, the consistency improved by 50% and the pain by 91.1% at 6 months.

Conclusions. Our preliminary study shows that Capsulase® improves capsular contracture. Mild capsular contracture appeared to better improve rather than more severe ones. Capsulase® is well tolerated with minimal side effects.

Key words: breast reconstruction, boswellic acid, breast implantation*/adverse effects, breast implants*/adverse effects, contracture*/prevention & control, contracture*/drug therapy, implant capsular contracture/prevention & control, leukotriene antagonists/therapeutic use, mammaplasty, humans

Received: March 26, 2023
Accepted: April 27, 2023

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How to cite this article: D'Andrea F, Errico C, D'Andrea L, et al. The treatment of capsular contracture after breast surgery with implants using Capsulase®. PRRS 2023;2:49-54. https://doi.org/10.57604/PRRS-227

INTRODUCTION

Breast surgery with implants represents the most widely practiced

procedure in reconstructive and aesthetic surgery. Despite many improvements, capsular contracture continues to be the most common complication after protheses implantation and the main reason of unsatisfaction for both the patient and the plastic surgeon [1].

Usually, a fibrous capsule forms around the silicone implant as it is a physiological chronic inflammatory response to a foreign body. In 0.5 to 30% the capsule undergoes progressive thickening and shrinkage and produces symptoms such as tenderness or pain [2,3].

Capsular contracture is usually classified according to the Baker scale, which considers the appearance, texture, and tenderness of the breast. Severity of the contracture ranges from Baker grade I, when the breast looks natural, up to Baker grade IV when the breast is hard, painful, and deformed [4]. Nevertheless, past studies have shown that the Baker score is highly subjective regarding the individual examiner [5].

The treatment of the capsular contracture may be surgical (i.e., capsulectomy or capsulotomy and implant exchange) or pharmacologic, through the inhibition of the inflammatory process [6].

Many studies demonstrated the effect that anti-leukotriene drugs have on reversing the symptomatology of the capsular contracture [1,7]. But, to date there is no consensus on their off-label use because of their adverse effects, such as liver dysfunction, acute renal failure, nephrotic syndrome, systemic eosinophilia, Churg-Strauss syndrome, hematologic abnormalities, arthralgia, and myalgia [3,8].

In nature, there are several substances which have been extensively studied for their anti-inflammatory properties. In particular, boswellic acids inhibit the synthesis of leukotrienes via inhibition of 5-lipoxygenase [9].

Considering the therapeutic potential as well as non-toxic nature, we evaluated the efficacy and safety of using Capsulase® (boswellia serrata phospholipid INDENA®, palmitoylethanolamide (PEA), quercetin phytosome INDENA®, bromelain 2500 GDU/g, and vitamin E acetate, by Biosphaera Pharma srl) for treating established capsular contracture after breast surgery with implants.

MATERIALS AND METHODS

From March 2020 to June 2022, we considered the patients who came to our attention suffering from capsular contracture grade II to IV according to Baker scale in at least one breast after reconstructive or aesthetic breast surgery with implants.

Exclusion criteria were hypersensitivity to one of the substances or excipients, previous treatment for capsular contracture, pregnancy, and breastfeeding. Inclusion and exclusion criteria are shown in Table I.

Informed consent was obtained from all the patients included in the study.

They were taken 2 tablets of Capsulase® per day for one month and 1 tablet per day for the next two months.

The patients were evaluated clinically, according to the Baker grading system, by three senior plastic surgeons at baseline (T0), after 1 month (T1), 2 months (T2), 3 months (T3), and 6 months (T4). Responses were scored as either complete (return to Baker grade I), partial (reduction in capsular contracture index by 1), or nil (Baker grade the same despite therapy). Improvement was analysed with the Wilcoxon signed rank test.

The patients were also asked to answer a questionnaire which subjectively evaluated the consistency, shape and position of the breast and the presence of pain at baseline and until the sixth month (T0 to T4). Each outcome was rated on a four-point Likert scale (Tab. II).

RESULTS

We enrolled 28 female patients who satisfied our inclusion criteria. Their age ranged between 29 and 68 with an average of 48.6. Among them, 10 underwent primary reconstructive breast surgery, 8 had implant replacement for previous capsule contracture or prosthesis rupture, while 10 had augmentation mammoplasty for aesthetic purposes. The mammary reconstruction was monolateral in 8 cases and bilateral in 2 cases. A total of 48 prostheses had been implanted. The surgical approach was inferior hemi-periareolar in 14 patients, Wise Pattern in 2 patients, through the inframammary

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Capsular contracture II-IV Baker following:	Hypersensitivity
Primary breast reconstruction with implants	Previous treatment for capsular contracture
Primary aesthetic breast augmentation	Pregnancy
Tuberous breast correction with implants	Breastfeeding
Breast implant exchange	
Symmetrization of the contralateral breast with implants	

Table II. Self-assessment questionnaire.

Consistency
Soft
Mildly increased
Moderately increased
Extremely increased
Shape
Natural
Mildly distorted
Moderately distorted
Extremely distorted
Position
Normal
Mildly dislocated
Moderately dislocated
Extremely dislocated
Pain
No pain
Mild
Moderate
Extreme

fold in 4 patients and through the mastectomy incision in 8 cases. They were used microtextured round prostheses filled with cohesive silicone gel in 14 patients and microtextured anatomic prostheses filled with cohesive silicone gel in 14 patients. The size of the implants ranged from 275 cc to 400 cc. In aesthetic breast augmentation patients, a retromammary pocket was used in 14 of them, while a dual plane pocket was used in 2 cases. A retromuscular pocket location was used in all the cases of breast reconstruction.

We found 42 breasts suffering from capsular contracture. Stratification of the patients revealed the following: 12 breasts were graded IV (28.6%), 16 breasts graded III (38.1%), 14 breasts graded II (33.3%). Since two patients who had bilateral capsular contracture (grade III and grade IV respectively) interrupted the treatment because of mild occurring adverse effects (stomachache), we considered a total of 38 breasts with capsule contracture. All the patients who continued the study were followed up for 6 months. Examination of contracted breasts after 3 months of therapy (T3) revealed a statistically significant reduction in contracture grades (Tab. III). Specifically, 14 out of 38 breasts (36.8%) showed a complete response, while 13 of 38 (34.2%) had a partial response. The remaining 11 of 38 (29%) demonstrated no response. None of the patients worsened. Thus, a positive response (complete or partial) was obtained in 71% of treated breasts ($p < 0.05$). When we examined the longevity of the response, we found that 21 up to the 27 breasts which had a positive result (77.7%) maintained the improvement until the 6th month (Fig. 1). We noticed the ones which improved the most were the breasts with a lower grade of capsular contracture (100% of Baker II, 71.4% of Baker III, and 20% of Baker IV).

The results above are summarized in Table III.

We also demonstrated an overall improvement of patients' subjective perception, especially regarding breast consistency (50%) and pain (91.1%), apart from the Baker grade (Tab. IV).

DISCUSSION

Capsular contracture represents the most common and yet unpredictable complication after breast prostheses implantation [1]. The development of a capsule around a foreign body is considered a para-physiological process [2]. Nevertheless, an exaggerated inflammatory or local immune response may occur: the levels of cytokines and growth factors, such as IL-1, IL-6, TNF-α, and TGF-β, increase and some histological alterations of the fibrous tissue that surrounds the implant happen [2,10]. Despite the numerous theories, the etiology of the capsular contracture is still unknown [2].

Numerous measures have been used to correct or prevent this process [2]. Capsulectomy and capsulotomy are not free from potential complications and have a 21 and 54% recurrence rates respectively [2,11].

In recent years, several studies investigated the role of pharmacologic regulation of inflammation, specifically concentrating on the main pathway, the arachidonic acid cascade, to prevent and improve established capsular contractures [12]. Leukotrienes have been reported to play a critical role in the periprosthetic fibrotic response [13]. In

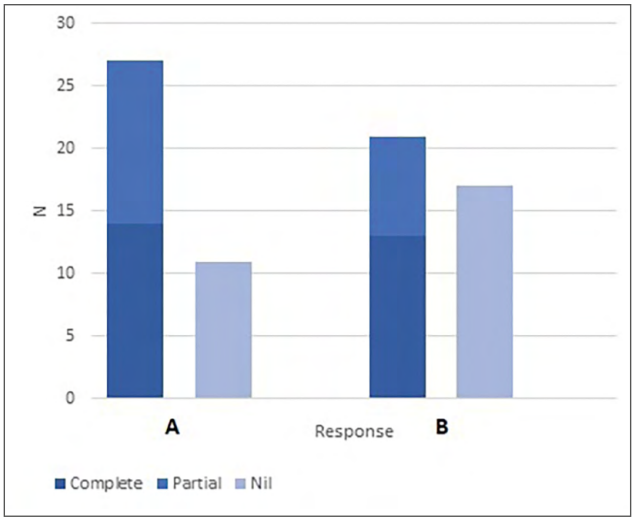

Figure 1. A graph that shows the response to Capsulase® in contracted breasts after (A) 3 months, and (B) 6 months. Complete: conversion to Baker grade I; nil: no improvement or worsening grade; N: number of breasts.

Table III. Patient demographics and results.

Patient	Age	Previous surgery	Incision	Position	Side and Baker Grade	Result (T3)
1	51	Implant exchange	Hemi-batwing	Subpec	R II, L II	Complete response (R, L)
2	68	Primary reconstruction	Batwing	Subpec	R IV	No response
3	48	Primary reconstruction	Periareolar	Subpec	L III	Partial response
4	48	Primary reconstruction	Batwing	Subpec	R III	Partial response
5	51	Primary reconstruction	LD flap	LD	L III	Partial response
6	48	Primary reconstruction	Batwing	Subpec	R IV, L II	Partial response (R) Complete response (L)
7	29	Primary augmentation	Periareolar	Submam	R III, L II	No response (R) Complete response (L)
8	50	Primary augmentation	Periareolar	Submam	R IV, L III	Partial response (R, L)
9	45	Implant exchange	Periareolar	Submam	R II, L II	Complete response (R, L)
10	33	Primary augmentation	Inframammary	Dual Plane	L II	Complete response
11	49	Implant exchange	Periareolar	Submam	L III	Partial response
12	57	Primary augmentation	Periareolar	Submam	R IV, L II	No response (R) Complete response (L)
13	54	Implant exchange	Wise Pattern	Submam	R III, L III	/
14	50	Primary augmentation	Inframammary	Submam	R IV, L IV	No response (R) No response (L)
15	51	Primary reconstruction	Periareolar	Subpec	R IV, L IV	/
16	48	Primary augmentation	Periareolar	Submam	L III	Partial response
17	51	Primary reconstruction	Batwing	Subpec	R IV	No response
18	29	Primary augmentation	Inframammary	Dual Plane	R III, L III	Partial response (R, L)
19	45	Primary augmentation	Inframammary	Submam	R II, L II	Complete response (R, L)
20	49	Primary reconstruction	Hemi-batwing	Subpec	R III	No response
21	54	Implant exchange	Periareolar	Submam	L II	Complete response
22	68	Implant exchange	Wise Pattern	Submam	R II, L III	Complete response (R) Partial response (L)
23	48	Primary augmentation	Periareolar	Submam	R II, L III	Complete response (R) No response (L)
24	48	Implant exchange	Periareolar	Submam	R IV	No response
25	50	Primary reconstruction	Periareolar	Subpec	R IV	No response
26	33	Primary augmentation	Periareolar	Submam	R II, L III	Complete response (R) Partial response (L)
27	57	Implant exchange	Periareolar	Subpec	L III	Partial response
28	50	Primary reconstruction	LD flap	LD	L IV	No response

LD: Latissimus Dorsi flap; R: Right; L: Left; Complete response: return to Baker grade I; Partial response: reduction in capsular contracture index by 1; No response: same Baker grade than before therapy.

Table IV. Summation of the scores each patient gave to consistency, shape, position and pain at T0, T1, T2, T3 and T4.

	T0	T1	T2	T3	T4	Improvement (%)
Consistency	108	95	86	74	73	50%
Shape	72	69	69	67	67	14.7%
Position	62	64	62	61	60	8.3%
Pain	72	56	45	43	41	91.1%

2002, a leukotriene antagonist (zafirlukast) was administered to women with contracted breasts, which resulted in a reduction of fibrosis [7]. Subsequently, these observations were corroborated by additional evidence [14,15]. The main limitation on the use of antileukotrienes drugs for capsular contracture is the weak safety profile which makes the risk-to-benefit ratio unfavorable [3,8].

Various natural substances were extensively studied for their anti-inflammatory properties. In particular, boswellic acids seem to have an anti-leukotrienes action [9].

Omega-3 fatty acids, which are found in oily fish and food supplements, play a role in the arachidonic acid cascade and seem to have a positive impact in diminishing the thickness of the capsule which forms around silicone gel implants in mice [16]. Menkü Özdemir et al. showed how cromolyn sodium, a mast cell membrane stabilizer, could reduce acute inflammation giving a lower foreign body reaction, mast cell count, and capsular thickness than the control, montelukast and zafirlukast groups in a rat model [17].

Some studies associate severe capsular contracture to the Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) and strongly recommend performing a CT/PET in those patients who present type IV capsular contracture and seroma or locoregional lymphadenopathy [18]. The establishment of breast implant registries would represent the most effective tool for monitoring short and long-term complications and improving patients' safety [19].

Our preliminary results point to a favorable response to the treatment of capsular contracture with Capsulase® for at least 3 months. Overall, 71% of breasts receiving treatment had a complete or partial response at 3 months. This response was maintained for 6 months (77.7%).

Although these results support the use of boswellic acids in this setting, there are limitations to this study. First, the lack of a placebo-control arm makes any conclusion preliminary. Furthermore, the patients were not randomized, making this study susceptible to bias.

As leukotriene blockade would be effective in an early phase of the contracture process, when inflammatory factors are still highly active, we assume that our treatment would work better on mildly contracted breasts. For more severe forms of contracture, surgery may still be the gold standard.

CONCLUSIONS

The treatment of capsular contracture with Capsulase® is supported by the results of our study. Although an objective improvement occurs especially in mild capsular contractures, the patients refer a lower breast consistency and pain relief. More prospective, randomized, double-blinded studies are warranted.

Conflict of interest statement

The authors have not signed any agreement with the sponsor that would bias the results of the research in any way. The sponsor was not involved in any phase of the study.

Funding

All the tablets of Capsulase® the authors prescribed to perform the study had been provided by Biosphaera Pharma srl and they had been given to the patients for free. The sponsor had no role in the study design, nor in the acquisition analysis and interpretation of data, nor in drafting the manuscript.

Author contributions

FD'A: A, O (revision of the paper).
LD'A: D, S.
CE: D, DT, S.
AZ: A, D, S, W.

Abbreviations

A: conceived and designed the analysis
D: collected the data
DT: contributed data or analysis tool
S: performed the analysis
W: wrote the paper
O: other contribution (specify contribution in more detail)

Ethical consideration

This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, and written informed consent for the use of clinical data were obtained from all patients.

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