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## Treatment of Post-Breast Surgery Pain Syndrome with Botulinum Toxin: Analysis of The Response to the Addition of Levobupivacaine and to the Type of Surgery

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### ABSTRACT

**Background:** The spasm and/or contracture of the pectoralis major contribute to the post-breast surgery pain. The purpose of our study was to evaluate changes in the post-breast surgical pain syndrome after the infiltration of botulinum-toxin type-A (BTX-A), according to the type of surgery and the reconstitution of the botulinum-toxin.

**Methods:** This retrospective study was conducted at the Rehabilitation Department with two cohorts: BTX-A reconstituted with saline solution (SS group) or with levobupivacaine (LV group). Data about pectoralis major contracture and pain (global, at night, at rest and during activity) before the infiltration and six weeks after that were collected from the medical records and compared between SS and LV groups, and between conservative breast surgery and mastectomy cases.

**Results:** in the study, 48 women aged 53.3 ( $\pm 11.10$ ) years were included, with 26 (54.2%) in SS group and 22 (45.8%) in LV group. There were no differences between both groups except transitory paresis (3.8% vs 22.7%;  $P=0.022$ ). In all patients, baseline circumstances vs after 6 weeks were compared, and we found significant differences in contracture (1.77 ( $\pm 0.57$ ) vs 0.97 ( $\pm 0.79$ )), VAS global (5.45 ( $\pm 1.92$ ) vs 3.46 ( $\pm 2.48$ )), VAS night (3.17 ( $\pm 3.13$ ) vs 1.61 ( $\pm 2.29$ )), VAS rest (2.14 ( $\pm 2.56$ ) vs 1.21 ( $\pm 1.98$ )) and VAS activity (4.31 ( $\pm 2.55$ ) vs 2.78 ( $\pm 2.58$ )). We found higher improvements in the breast conservative surgery.

**Conclusion:** A significant lower pain and contracture after BTX-A injection in the pectoralis major was observed, but its reconstitution in levobupivacaine may not be an effective method to increase the analgesic effect. There were higher improvements in the breast conservative surgery than in the mastectomy.

### Introduction

The post-mastectomy pain syndrome or post-breast surgery pain (PBSPS) is defined as a chronic pain with neuropathic qualities, located in ipsilateral

breast/chest wall, axilla and/or medial arm which lasts at least 6 months following any breast surgery.<sup>1-4</sup> This is an underdiagnosed entity which impacts on the patients' quality of life.<sup>1-4</sup>

Considering that the spasm and/or contracture of the pectoralis major contribute to the PBSPS, there are some pre-operative analgesic therapies (nerve blocks, infiltration of botulinum toxin type A –BTX-A, etc.) which act on this muscle.<sup>1-4</sup>

The purposes of this study were: (i) to quantify changes in the pain intensity and in the severity of the

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pectoralis contracture in the PBSPS six weeks after the intramuscular infiltration of the BTX-A; (ii) to assess if there were differences in the response according to the type of surgery; and (iii) to verify if the reconstitution of the BTX-A with levobupivacaine increased the analgesic and relaxing effect versus the reconstitution with saline solution.

## Methods

Infiltration of BTX-A in the pectoralis major, due to a painful contracture of this muscle after breast cancer treatment is an usual clinical practice in Rehabilitation. All patients were duly informed and signed the consent before the infiltration. BTX-A is often infiltrated intramuscularly with 100 units (U) of onabotulinumtoxin-A or 250 U of abobotulinum-A in just one point. Some physicians reconstitute the BTX-A with 1.1 ml of saline solution and others with 1.1 ml of levobupivacaine. In order to study which is the best cohort (saline solution or levobupivacaine), a retrospective cohort study was conducted. Data of all women treated from January 2018 to January 2020, with infiltration of BTX-A in the pectoralis major reconstituted with saline solution or with levobupivacaine were obtained from the Physical Medicine and Rehabilitation Department database.

Demographic data and information on risk factors related to the development of chronic pain were collected on type of breast surgery, mastectomy versus conservative surgery (excision of the tumor and/or adjacent tissues), number of axillary lymph nodes removed, adjuvant therapy and number of months from breast surgery until infiltration. Before the BTX-A infiltration and six weeks later, the

severity of the pectoralis contracture was evaluated from 0 (none) to 3 (severe) and the pain (global during the entire day, at night, at rest and during activity) with the visual analog scale (VAS) from 0 to 10, the satisfaction of patients from 0 (none) to 10 (maximum) and the adverse effects were assessed.

This work was approved ethically by the Research Committee.

## Statistical Methods

To determine the sample size, a pilot study was conducted. Previous data from ten patients were obtained where the VAS average was 5.45 +/- 1.5, and with a confidence level of 95%, 80% statistical power and an effect size of 1 in the VA between groups, a sample size of 48 patients was decided. The descriptive analysis was carried out using an arithmetic mean (standard deviation) for quantitative variables and the counting (percentage) for qualitative variables. To compare differences between infiltration with saline and levobupivacaine, we used the Mann-Whitney U-Test for the quantitative variables and Chi-Square test for the categorical variables, with the Fisher's approximation if the application conditions were not met. To compare the values before and 6 weeks after the infiltration, we used the Wilcoxon Signed-Rank Test. A test was considered statistically significant when the corresponding p value was less than 0.05.

## Results

In the study, 48 patients aged 53.3 (11.10) years were included. In 21 (44.7%) of them a mastectomy was performed, and 6.13 (4.5) axillary lymph nodes

**Table 1.** Comparison of the different studied variables according to the administration of BTX-A reconstituted in levobupivacaine or in saline groups in all the patients.

	Levobupivacaine (N=22) (45.8%)	Saline (N=26) (54.2%)	P
Age (years)	54 (10.91)	52.76 (11.45)	0.706
Body Mass Index	27.5 (4.97)	25.8 (4.23)	0.467
Breast-surgery			
conservative	12 (54.5%)	15 (57.7%)	
mastectomy	10 (45.5%)	11 (42.3%)	0.827
Expander	2 (9.5%)	4 (15.4%)	0.678
Number of lymph node removed	5.80 (4.58)	6.13 (4.70)	0.862
Radiotherapy	19 (86.4%)	21 (80.8%)	0.710
Months from breast surgery until infiltration	54.05 (36.96)	50.26 (52.42)	0.321
Number of infiltrations	1.45 (1.14)	1.6 (1.00)	0.508
Contracture	1.81 (0.64)	1.70 (0.50)	0.484
VAS global basal	5.81 (1.93)	5.29 (2.03)	0.375
VAS night basal	2.83 (3.20)	3.76 (2.84)	0.305
VAS rest basal	2.29 (2.51)	2.11 (2.58)	0.826
VAS basal activity	4.47 (2.72)	4.06 (2.41)	0.594
Contracture 6 weeks	0.82 (0.89)	1.11 (0.68)	0.245
VAS global 6 weeks	3.47 (2.45)	3.28 (2.56)	0.808
VAS night 6 weeks	1.33 (2.16)	1.70 (2.37)	0.612
VAS rest 6 weeks	1.33 (2.19)	1.33 (2.24)	1.000
VAS activity 6 weeks	3.04 (2.64)	2.45 (2.52)	0.476
Patient's satisfaction	7.70 (1.79)	7.11 (2.69)	0.440
Secondary effects: excessive transitory paresis	5 (22.7%)	1 (3.8%)	0.022

The categorical data are expressed as counting (percentage) and the quantitative ones as average (standard deviation). VAS: visual analog scale



**Table 2.** Comparison between the baseline circumstances and after 6 weeks with the contracture and the pain (VAS) at different time points, analyzed (i) in all the patients, (ii) in patients with conservative surgery and (iii) in patients with mastectomy.

Variables	All patients		Conservative Breast Surgery		Mastectomy	
	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks
Contracture	1.77 (0.57)	0.97 (0.79)*	1.65 (0.48)	0.78 (0.67)*	1.92 (0.65)	1.21 (0.88)*
VAS global	5.45 (1.92)	3.46 (2.48)*	5.38 (2.17)	3.25 (2.48)*	5.52 (1.62)	3.72 (2.53)†
VAS night	3.17 (3.13)	1.61 (2.29)*	3.54 (3.07)	1.47 (2.21)*	2.65 (3.25)	1.81 (2.45)
VAS rest	2.14 (2.56)	1.21 (1.98)‡	2.47 (2.69)	1.24 (2.13)‡	1.64 (2.37)	1.18 (1.83)
VAS activity	4.31 (2.55)	2.78 (2.58)*	4.27 (2.46)	2.24 (2.40)*	4.37 (2.75)	3.53 (2.71)

The quantitative variables are expressed as an average (standard deviation). Statistical significance comparing every basal variable with its value after 6 weeks: \*p<0,001, † p<0,01, ‡ p<0,05.

were removed on average and 40 patients (83.3%) received radiotherapy. Out of 48 patients, 26 (54.2%) patients received BTX-A injections reconstituted in saline solution and 22 (45.8%) reconstituted in levobupivacaine. Also, 19 patients (34.1%) needed further injections when the effects of BTX-A decreased.

Table 1 shows the differences regarding the variables between the saline and levobupivacaine groups. Table 2 shows the differences in pain variables and the contracture before and 6 weeks after the infiltration, both in the mastectomy group and in the conservative surgery group, as well as the results in all patients.

In the analysis of the adverse effects, 6 (12.5%) presented a slight temporary paresis at the proximal upper limb. The average satisfaction 6 weeks after the post-infiltration of the whole sample was 7.37 (2.33).

## Discussion

Most of studies on the infiltration of the pectoralis major with BTX-A to treat PBSPS are optimistic due to its dual action, both relaxing and analgesic.<sup>2,3,5-7</sup> Some studies practice intra-operative BTX-A infiltration as a preventive treatment for post-surgery pain.<sup>6, 8</sup> The analgesic effect and obtaining a more natural breast appearance are two reasons for applying BTX-A in aesthetic surgeries of breast augmentation with implants.<sup>6,9,10</sup> The study of Lo et al. is one of the few studies that has not obtained any analgesic improvement infiltrating BTX-A as opposed to placebo after the breast reconstitution with expanders.<sup>8</sup>

The PBSPS is found most frequently after more invasive treatments such as mastectomy, axillary lymphadenectomy, reconstruction with expanders or after radiotherapy, but it can also be found also after any other surgical procedures involving breast parenchyma or underlying muscle.<sup>14,6</sup> The fact that we have observed a more complete analgesic response to the BTX-A in conservative surgery over the mastectomy leads us to consider the possibility of additional factors in the mastectomy related to a greater tissue lesion.

The technique performed in our study can be extrapolated to other studies. Most of them use onabotulinumtoxin A, with the most frequent dose of

100 U (75-140U), reconstituted with 1 to 5 ml of saline solution.<sup>2,3,5,6</sup> The analgesic effect begins 6-36 hours later, with a maximum peak after 7-14 days, being reversible after 3-6 months; thus, further injections may be required.<sup>2</sup> The VAS is the most common method for assessing pain, although in many cases it is just the patient's report.<sup>2,6,8</sup>

Local anesthetics infiltration before the BTX-A have been used to decrease the pain during the technique. This has led some researchers to reconstitute the BTX-A with an anesthetic to reinforce the analgesic effect of both drugs, both in the short and the long term.<sup>11,12</sup> On the other hand, the anesthetics have also a myotoxic effect with the possibility of obtaining a faster onset of paresis.<sup>12</sup> Although there are few and heterogeneous studies, many of them are clinical cases, it seems that reconstituting with anesthetics does not limit the efficacy of the BTX-A.<sup>11</sup> A clinical trial to treat the hyperhidrosis, which compared the BTX-A reconstituted in a local anesthetic or in a saline solution, has shown lower pain during the injections, and no difference regarding the sweat production.<sup>11</sup>

The excessive level of transitory paresis was one of the most frequent adverse effects of the BTX-A.<sup>2,6,7</sup> In our study, this effect was more frequent when reconstituting it with an anesthetic and it was reversible in all the cases.

Reconstitution with local anesthetic has been applied to treat other painful pathologies such as the complex regional pain syndrome.<sup>13,14</sup>

The main limitation in the study is that it was retrospective with short follow-up period. Further properly conducted trials providing high-level evidence assessing benefits and risks of reconstitution in local anesthetic and maximizing the effect and duration of the BTX-A are required, since our study does not show any advantage with regard to the saline solution.

In conclusion, a single intramuscular BTX-A injection significantly decreased pain intensity and pectoralis major contracture after six weeks; this improvement was complete in the conservative breast surgery and incomplete in the mastectomy. The BTX-A reconstitution in levobupivacaine was not clinically relevant whereas it produced a higher level of reversible paresis. These findings need to be



confirmed by prospective studies.

### Conflict of Interest

The authors declare no conflict of interest.

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