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PRS GLOBAL OPEN

ORIGINAL ARTICLE

Breast

Botulinum Toxin A in Tissue Expander Breast Reconstruction: A Double-blinded Randomized Controlled Trial

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Background: Subpectoral tissue expander breast reconstruction is often associated with muscle spasms, pain, and discomfort during tissue expansion. In this study, we hypothesized that an intraoperative injection of botulinum toxin A (BTX-A) in the pectoralis major muscle reduces the pain associated with tissue expansion and improves women's physical well-being.

Methods: Between May 2012 and May 2017, women undergoing immediate subpectoral tissue expander breast reconstruction were randomized to administer 100 units of BTX-A or a placebo injection. A numeric pain intensity scale and the physical well-being scale of the BREAST-Q: Reconstruction Module were used to test our hypothesis. Data on postoperative oral narcotic consumption were not collected.

Results: Of the 131 women included in the analysis, 48% were randomized to placebo and 52% to BTX-A. The preoperative median pain intensity score was 0 [interquartile range (IQR), 0–1], and the median preoperative BREAST-Q score was 91 (IQR, 81–100). The median slopes for the change in pain intensity scores from baseline throughout tissue expansion for those randomized to placebo and BTX-A were −0.01 (IQR, −0.02 to 0.00) and −0.01 (IQR, −0.02 to 0.00), respectively ($P = 0.55$). The median slopes for the change in BREAST-Q scores from baseline throughout tissue expansion for those randomized to placebo and BTX-A were 0.04 (IQR, −0.17 to 0.14) and 0.02 (IQR, −0.06 to 0.13), respectively ($P = 0.89$).

Conclusion: In this study, we found that an intraoperative intramuscular injection of 100 units of BTX-A in the pectoralis major muscle did not reduce postoperative pain and patient-reported physical well-being when compared with placebo.
(Plast Reconstr Surg Glob Open 2020;8:e3030; doi: 10.1097/GOX.0000000000003030; Published online 18 August 2020.)

INTRODUCTION

In the United States, the number of breast cancer survivors who choose postmastectomy breast reconstruction keeps rising each year. Among women who elect to pursue breast reconstruction, approximately 80% will choose prosthetic breast reconstruction.[1] Traditionally, implant breast reconstruction (IBR) was performed using the total submuscular technique beneath the pectoralis major and serratus anterior muscles. With advances in surgical techniques and technology, acellular dermal matrix (ADM) has emerged as a tool to limit the extent of submuscular dissection while reinforcing the lower pole of the reconstructed breast in partial subpectoral surgical techniques. More recently, the widespread use of ADM has led plastic surgeons to adopt prepectoral IBR, where complete ADM coverage of the prosthetic device is performed. When total submuscular and partial subpectoral IBR is selected as a reconstructive technique, a tissue expander (TE) is frequently used during the first stage to allow for gradual muscle expansion. Over the years, several studies have shown that with these surgical methods, the subsequent period of tissue expansion can be associated with muscle spasms, prolonged postoperative pain, pectoralis major

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Received for publication December 26, 2019; accepted June 11, 2020.

The contents are solely the responsibility of the authors.

ClinicalTrials.gov Identifier: NCT01591746.

DOI: 10.1097/GOX.0000000000003030

Disclosure: *Dr. Lemaine is a Consultant for Allergan. All the other authors have no financial interest to declare. This work was supported by Investigator Initiated Research Grant, Allergan.*

animation deformity, and lateral displacement of the breast mound,[2–7] leading to their decreased use in favor of the prepectoral approach. Despite this, subpectoral IBR is still performed, especially when mastectomy skin flap perfusion and cost of ADM are a concern.

In the past decades, publications on the use of botulinum toxin A (BTX-A) for pain relief in a wide array of clinical conditions have increased tremendously. Although the potential for a therapeutic use of BTX-A as an analgesic agent is well established in various clinical problems,[8–13] there is paucity of high-level evidence assessing the effects of BTX-A in relieving pain associated with subpectoral TE breast reconstruction. We present the results of a double-blinded randomized controlled trial of women undergoing unilateral and bilateral mastectomies with immediate subpectoral TE placement to establish the efficacy of BTX-A on alleviating pain and improving physical well-being during the postoperative period. We hypothesized that an intraoperative injection of BTX-A in the pectoralis major muscle reduces pain associated with tissue expansion and improves women's physical well-being.

METHODS

Study Population

Following investigational new drug application to the Food and Drug Administration and Institutional Review Board approval, eligible subjects were recruited prospectively between May 2012 and May 2017. Women who are at least 18 years old were recruited if undergoing unilateral or bilateral mastectomies with immediate partial subpectoral TE placement with or without ADM. Ineligibility criteria included the following: (1) inability to read or speak English; (2) latissimus dorsi flap with TE; (3) diagnosis of chronic pain, upper limb spasticity, cervical dystonia, axillary hyperhidrosis, strabismus, or blepharospasm; (4) hypersensitivity to any botulinum toxin preparation or to any components in the formulation; (5) infection at the proposed injection site; (6) preexisting neuromuscular disorders; (7) aminoglycosides intake at the time of surgery; (8) pregnancy or lactation; (9) breast implants preoperatively; and (10) subjects with reported use of botulinum toxin within 4 months before the planned surgical date. A data safety monitoring board reviewed the progress and the adverse events.

Randomization

Consenting subjects were randomized to administer either a single dose of 100 units of BTX-A per operated side or a placebo. Treatment blinding, randomization, and study drug preparation were carried out in the hospital's research pharmacy. The treating surgeon and the study participants were blinded to the group allocation.

Surgical Technique

After completion of the mastectomy, a retropectoral pocket was created that extended from the lateral sternal border medially to the anterior axillary line laterally. The subpectoral dissection was completed in a cephalad direction. Following pocket irrigation with antibiotic solution selected according to a surgeon's preference, the study drug was injected into the pectoralis major muscle (as described in the following section). The TE was then inserted into this newly created partial retropectoral pocket. The decision to use ADM or not was left to the operating surgeon and preoperatively discussed with the study subject (Table 1). When used, an appropriate-sized sheet of human ADM was used to bridge the gap between the lower edge of the pectoralis major muscle and the inframammary fold.

Study Drug and Intraoperative Injection Protocol

BTX-A (onabotulinumtoxinA; BOTOX, Allergan, Inc., Irvine, Calif.) was supplied in single-use vials of 100 units and reconstituted in the research pharmacy with non-preserved 0.9% sodium chloride injection USP to a total volume of 5 mL. The placebo was 5 mL of 0.9% sodium chloride. The surgical team received 1 vial of study drug for each operated breast. Intraoperatively, the content of each vial was injected retrogradely into the pectoralis major muscle with a 22-gauge spinal needle into 5 equidistant points in the inferior third of the pectoralis major muscle.

Follow-up Visits and Study Procedures

The 2 outcome measures selected to test our hypothesis, a numeric pain intensity scale and the physical well-being scale of the BREAST-Q: Reconstruction Module,[14] were administered to the study participants at the preoperative appointment, the first postoperative visit, and at each expansion visit or subsequent plastic surgery appointment until the end of the study (last plastic surgery appointment before removal of the TE).

Endpoints and Statistical Power

The primary endpoint was to determine the efficacy of a single intraoperative BTX-A injection in the pectoralis major muscle on pain and physical well-being in women undergoing tissue expansions following immediate subpectoral TE breast reconstruction. Safety endpoints included the incidence of side effects attributable to BTX-A.

The only available preliminary data were obtained from a retrospective study by Layeeque et al.[15] In this study, pain was scored using a visual analog scale ranging from 0 to 10. The authors reported a mean ± SD pain score during the initial tissue expansion of 1.95 ± 1.88 for the BTX-A group compared with 5.61 ± 2.77 for the placebo group. For our trial, the planned sample size was 128 patients to provide 80% power to detect a 25% decrease in mean pain scores from 4.0 to 3.0, assuming an SD of 2.0 (2-sample t test, $\alpha = 0.05$).

Statistical Analysis

A modified intent-to-treat analysis was used in this study. All patients who completed the study were included in the analysis, as were 3 patients who did not complete the study. Continuous features were summarized with means and SDs if approximately normally distributed and

Table 1. Patient and Clinical Characteristics

Patient-specific Factors	Placebo (n = 63)	BTX-A (n = 68)	*P*
Age, y, mean (SD)	48.4 (11.5)	49.9 (11.1)	0.44
BMI, kg/m^2, mean (SD)	26.6 (8.1)	27.6 (5.9)	0.40
Operative time, h, mean (SD)	5.0 (1.7)	5.1 (1.4)	0.86
Smoking within 4wk preoperative, n (%)	5 (8)	4 (6)	0.74
Hypertension, n (%)	14 (22)	10 (15)	0.27
Diabetes, n (%)	3 (5)	5 (7)	0.72
Neoadjuvant chemotherapy, n (%)	14 (22)	22 (32)	0.19
Breast cancer diagnosis	52 (83)	57 (84)	0.84
Breast cancer laterality in n = 109, n (%)			0.73
Left	22 (42)	25 (44)	
Right	25 (48)	29 (51)	
Bilateral	5 (10)	3 (3)	
Preoperative pain intensity score, median (IQR)	0 (0–0)	0 (0–1)	0.19
Preoperative BREAST-Q score, median (IQR)	85 (77–100)	91 (81–100)	0.64
Paravertebral block, n (%)	29 (46)	40 (59)	0.14
Liposomal bupivacaine, n (%)	20 (32)	15 (22)	0.21
Surgery laterality, n (%)			0.35
Right	3 (5)	8 (12)	
Left	8 (13)	8 (12)	
Bilateral	52 (83)	52 (76)	
Type of right mastectomy in n = 115, n (%)			0.033
Skin-sparing	33 (60)	47 (78)	
Nipple-sparing	22 (40)	13 (22)	
Areola-sparing	0	0	
Type of left mastectomy in n = 120, n (%)			0.03
Skin-sparing	35 (58)	46 (77)	
Nipple-sparing	25 (42)	13 (22)	
Areola-sparing	0	1 (2)	
Sentinel lymph node biopsy, n (%)	45 (71)	46 (68)	0.64
Axillary dissection, n (%)	7 (11)	17 (25)	0.04
Type of breast reconstruction, n (%)			0.58
Complete muscle coverage	1 (2)	2 (3)	
Acellular dermal matrix	60 (95)	61 (90)	
Other	2 (3)	5 (7)	
Right initial percent volume expansion, mL, n = 115, mean (SD)	60.4 (20.0)	63.5 (23.0)	0.45
Left initial percent volume expansion, mL, n = 120, mean (SD)	60.0 (21.1)	60.1 (23.1)	0.98
No. expansion visits, n = 128, median (IQR)	3 (2–4)	3 (2–4)	0.43
Rate of tissue expansion, mL, n = 120, median (IQR)	75 (56–100)	80 (63–104)	0.37
Postmastectomy radiation, n (%)	5 (8)	1 (1)	0.10

BMI, body mass index.

medians and interquartile ranges (IQRs) otherwise; categorical features were summarized with frequency counts and percentages. Preoperative and postoperative features, pain intensity, and BREAST-Q scores at the first postoperative visit were compared between patients randomized to placebo and BTX-A using 2-sample *t*, Wilcoxon rank sum, χ^2, and Fisher exact tests. The slopes of the changes in pain intensity and BREAST-Q scores from baseline to the first postoperative visit and from baseline throughout tissue expansion were calculated using linear regression models. Specifically, a slope was calculated for each patient using the days from baseline as the predictor and the pain intensity or BREAST-Q score as the outcome. These slopes were compared between patients randomized to placebo and BTX-A using Wilcoxon rank sum tests. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, N.C.) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

A total of 141 patients were enrolled and randomized. Ten patients withdrew or were considered screen failures before intervention. Three of the remaining 131 patients did not complete the study but were included in the analysis in a modified intent-to-treat approach. Of the 131 patients included in the analysis, 63 (48%) were randomized to placebo and 68 (52%) were randomized to BTX-A. A comparison of patient and clinical characteristics between the 2 groups is shown in Table 1.

Among all the patients, the preoperative median pain intensity score was 0 (IQR, 0–1) and the median preoperative BREAST-Q score was 91 (IQR, 81–100). The median pain intensity score at the first postoperative visit was 3 (IQR, 2–4), and the median BREAST-Q score at this visit was 63 (IQR, 57–68). For patients randomized to placebo and BTX-A, the median pain intensity scores were 3 (IQR, 2–4) and 2 (IQR, 1.5–4), respectively ($P = 0.43$), and the median BREAST-Q scores were 60 (IQR, 57–68) and 63 (IQR, 57–68), respectively ($P = 0.56$).

The median slope for the change in pain intensity scores from baseline to the first postoperative visit among all patients was 0.25 (IQR, 0.10–0.43), indicating an increase in pain from baseline to the first postoperative visit. The median slopes for the change in pain intensity scores from baseline to the first postoperative visit for those randomized to placebo and BTX-A were 0.29 (IQR, 0.14–0.46) and 0.22 (IQR, 0.08–0.43), respectively ($P = 0.18$). The median slope for the change in BREAST-Q scores from baseline to the first postoperative visit among all patients was −2.6 (IQR, −4.6 to −1.4), indicating a decrease in physical well-being from baseline to the first

postoperative visit. The median slopes for the change in BREAST-Q scores from baseline to the first postoperative visit for those randomized to placebo and BTX-A were −2.6 (IQR, −4.9 to −1.5) and −2.7 (IQR, −4.5 to −1.3), respectively ($P = 0.90$).

The median slope for the change in pain intensity scores from baseline throughout tissue expansion among all patients was −0.01 (IQR, −0.02 to 0.00). The median slopes for the change in pain intensity scores from baseline throughout tissue expansion for those randomized to both placebo and BTX-A were −0.01 (IQR, −0.02 to 0.00; $P = 0.55$). The median slope for the change in BREAST-Q scores from baseline throughout tissue expansion among all patients was 0.02 (IQR, −0.12 to 0.14). The median slopes for the change in BREAST-Q scores from baseline throughout tissue expansion for those randomized to placebo and BTX-A were 0.04 (IQR, −0.17 to 0.14) and 0.02 (IQR, −0.06 to 0.13), respectively ($P = 0.89$). Results for the pain intensity score and BREAST-Q scores preoperatively, at the first postoperative visit and during the expansion period are summarized with boxplots in Figures 1 and 2, respectively.

Postoperative complications within 30 days of surgery are shown in Table 2. During the course of the study, no adverse events were attributable to the injection of the study drug. Postoperative reconstruction failure at any time during the study period did not differ between subjects randomized to placebo and BTX-A (2% versus 1%, respectively; $P = 1.0$).

DISCUSSION

Designed to detect a 25% decrease in mean pain scores, this study found that an intraoperative intramuscular injection of 100 units of BTX-A in the pectoralis major muscle did not reduce postoperative pain and patient-reported physical well-being when compared with placebo in women undergoing subpectoral TE breast reconstruction with ADM. In the current context of widespread opioid crisis, the use of intraoperative agents to control postoperative pain and minimize narcotic consumption has gained national attention. BTX-A is one of the neurotoxins produced by the Gram-positive, anaerobic *Clostridium botulinum* bacteria, causing botulism. It blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BTX-A produces a partial chemical denervation of the muscle, resulting in a localized reduction in muscle activity. By reversibly inhibiting neurotransmitter release, BTX-A has both analgesic[16] and paralytic properties. The presence of analgesic properties of BTX-A is increasingly supported by several clinical observations: pain relief with BTX-A injections has been reported for migraine headaches,[17] chronic pelvic pain,[11,18–20] chronic tennis elbow,[12] and postoperative pain control for lower limb lengthening correction,[21,22] among others.

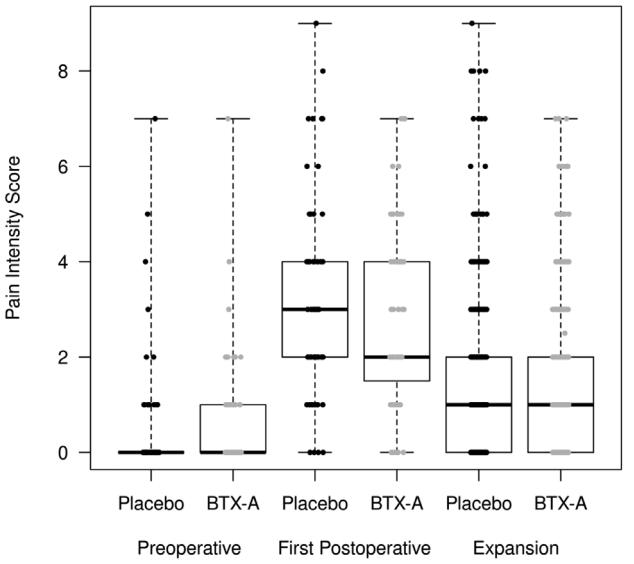

Fig. 1. Comparison of median pain intensity scores between the placebo group and the Botox group (BTX-A) preoperatively, at the first postoperative visit, and during the expansion period.

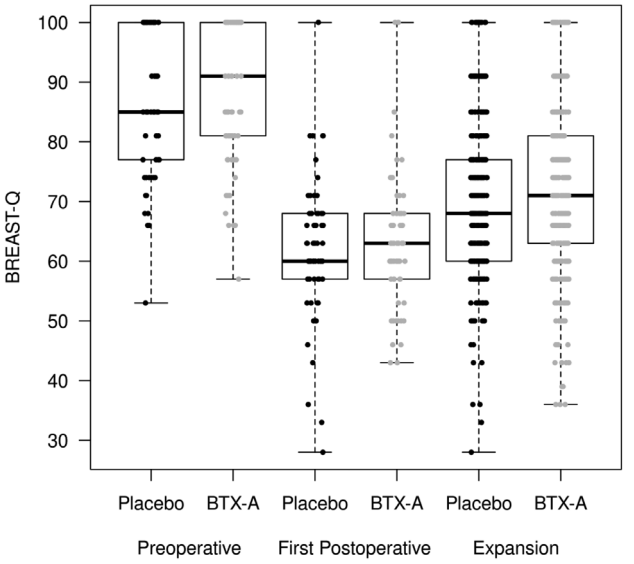

Fig. 2. Comparison of median BREAST-Q scores between the placebo group and the Botox group (BTX-A) preoperatively, at the first postoperative visit, and during the expansion period.

In a systematic review of the use of BTX-A with subpectoral breast implants, Winocour et al[23] assessed 7 studies enrolling a combined total of 427 women. All the included studies demonstrated improvements in postoperative pain with intraoperative intramuscular BTX-A injection, suggesting a possible benefit for patients. Of note, in these studies, either ADM was not used or its use was not specified by the authors. This systematic review also highlighted a lack of high-quality published data assessing the efficacy and safety of BTX-A in relieving postoperative pain associated with

Table 2. Postoperative Complications within 30 Days

Complication	Placebo (n = 63)	BTX-A (n = 68)	*P*
Surgical site infection, n (%)	2 (3)	1 (1)	0.61
Hematoma requiring reoperation, n (%)	2 (3)	1 (1)	0.61
Seroma, n (%)	4 (6)	0	0.051
Mastectomy skin flap necrosis, n (%)	0	1 (1)	1.0
Delayed wound healing, n (%)	2 (3)	5 (7)	0.44
Reconstruction failure, n (%)	0	1 (1)	1.0
Unplanned reoperation, n (%)	4 (6)	7 (10)	0.42

subpectoral prosthetic device placement. In a retrospective study, Layeeque et al[15] reported that intraoperative injection of 100 units of BTX-A significantly reduced postoperative pain in submuscular TE placement. ADM was not used in this study. Gabriel et al[24] published a pilot study on 30 women that supported the findings reported by Layeeque et al[15] with lower injection doses of 40 units of BTX-A in each pectoralis major muscle in women undergoing subpectoral TE breast reconstruction with ADM. The small sample size is an important limitation of this study.

Our study has several limitations. First, the study was designed to detect a 25% decrease in mean pain scores. It is possible that a decrease smaller than 25% may still be clinically meaningful to patients undergoing subpectoral TE placement. Second, there was some heterogeneity in perioperative care, with patients enrolled earlier in the study all receiving paravertebral blocks preoperatively. Due to a practice change over the course of the study period, paravertebral blocks were no longer performed later in the study and instead were replaced with intraoperative field blocks with liposomal bupivacaine. However, the anesthetic agents used in both of these techniques are no longer providing an analgesic effect when the antinociceptive and paralytic actions of BTX-A take effect and when the first postoperative pain assessment was made in this study. In addition, our study results may have been different had total submuscular approaches been used more frequently in our patient population. Our enrollment period spans over 5 years, and breast reconstruction approaches changed tremendously with the increased use of ADM. This was another practice change that could not be controlled, given that the best interest of patients had to be taken into account. Finally, another limitation of this study is that data on postoperative oral narcotic consumption were not collected. The decision to not obtain this information was carefully weighed at the time of study design and thoroughly vetted with experts in pain investigational study design at our study's inception. The decision was made based on the fact that the randomization process would generate balanced and comparable groups when it comes to postoperative and postdischarge narcotic consumption, which are both known confounding variables. Due to inherent challenges in accurate narcotic consumption data collection, which relies solely on patient report, we elected to focus exclusively on pain scores and patient-reported physical well-being.

CONCLUSIONS

To our knowledge, this is the first double-blinded randomized controlled trial of the use of BTX-A in women undergoing subpectoral TE breast reconstruction with ADM. We found that the intraoperative injection of 100 units of BTX-A in each pectoralis major muscle in this patient population is safe but did not influence postoperative mean pain scores and patient-reported physical well-being when compared with placebo.

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