The Efficacy of Botulinum Toxin A in Post-Mastectomy Breast Reconstruction: A Pilot Study

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Abstract

Background: Botulinum toxin A has been successfully used in a variety of areas to temporarily obliterate muscle mobility for either functional or aesthetic gain. Tissue expander–based breast reconstruction has been plagued with pain and discomfort.

Objective: The purpose of this pilot study was to evaluate the role of a neurotoxin (Botulinum toxin A) in expander-based breast reconstruction.

Methods: Thirty patients underwent mastectomies with immediate expander or acellular dermal matrix reconstruction. The neurotoxin group (n = 15) received 40 units of neurotoxin (Botulinum toxin A, Allergan, Inc, Irvine, CA) into each pectoralis major muscle through 4 serial injections and the placebo group (n = 15) received 4 serial injections of 0.9% NaCl. All patients were followed over 1 year, and patient demographics, VAS (visual analog score), laterality, office visits, amount of expansion and number of times to full expansion, and amount of narcotics required were recorded. Statistical significance was considered as p < .05.

Results: There were no significant differences between the two groups in terms of age, laterality, expander size, or complications (p = .46-66). There was a significant difference between the two groups in the VAS score, demonstrating decreased pain in the neurotoxin group (p < .05). In addition, there was a significant increase in the volume of expansion per visit in the neurotoxin group as compared to the placebo group (p < .05). There was no significant difference in narcotic use in the first 3 days after surgery; however, there was a significant decrease in use of narcotics from 7 to 45 days in the neurotoxin group (p < .05). There were no complications associated with the use of the neurotoxin.

Conclusions: The infiltration of the pectoralis major muscle with neurotoxin in immediate, expander-based reconstruction may be beneficial in reducing pain and expediting expansions.

Level of Evidence: 3

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Breast reconstruction with tissue expanders and implants offers patients satisfying aesthetic results with minimal donor site morbidity. Each year, the number of breast cancer survivors who choose post-mastectomy breast reconstruction keeps rising, and a majority choose expander or implant reconstruction. Post-mastectomy reconstruction with a tissue expander and implant involves a staged approach. The first stage...
consists of the placement of a tissue expander deep within the pectoralis major muscle. This may be done immediately following the mastectomy or as a delayed procedure. The purpose of the expander is to create a soft and precise pocket to contain the permanent implant. This is followed by a period of weekly tissue expansions that can last several months. In the second stage, the tissue expander is removed in a surgical procedure and replaced with a permanent breast implant. Despite the well-recognized advantages of this successful breast reconstruction technique, the subpectoral placement of a tissue expander is associated with significant pain and discomfort in the immediate postoperative period and during the phase of tissue expansion. A pectoralis major muscle spasm is a frequently reported problem during tissue expansion, and in certain instances has led to premature removal of expanders. Leggeby et al showed that women who underwent prosthetic breast reconstruction had higher pain scores and took more analgesics that those who did not choose post-mastectomy reconstruction. Therefore, numerous methods and technical variations have been attempted to decrease the pain associated with subpectoral placement of tissue expanders and implants, all with questionable success.

Botulinum toxin A is a neurotoxin approved for the treatment of several conditions, including wrinkles, strabismus, headaches, and cervical dystonia. In the past decade, the use of Botulinum toxin A for pain relief in a wide array of clinical conditions has been reported. Botulinum toxin A is a neurotoxin produced by Clostridium botulinum bacteria that modulates the release of neuropeptides, such as substance P and the calcitonin gene-related protein, and inhibits neurogenic inflammation, which likely underlies its independent antinociceptive effect. In particular, the sensory function of substance P is thought to be related to the transmission of pain information into the central nervous system. The analgesic action of Botulinum toxin A was initially thought to be related to its effects on muscular contraction, but has since been supplanted by in vitro studies of the inhibition of substance P by Botulinum toxin A in embryonic rat dorsal neurons. The presence of analgesic properties of Botulinum toxin A is increasingly supported by several clinical observations: pain relief with Botulinum toxin A injections has been reported for migraine headaches, chronic pelvic pain, chronic tennis elbow, and postoperative joint arthroplasty, among others. Furthermore, Botulinum toxin A has been used to treat various painful muscle spasms, such as paravertebral muscle spasm, fibromyalgia—myofascial pain, and temporomandibular joint pain. The profound number of biological and clinical applications of Botulinum toxin A is exhibited in the literature today.

The antinociceptive action of Botulinum toxin A in breast cancer survivors who elect to pursue breast reconstruction with tissue expanders and implants is not known. The use of Botulinum toxin A in the pectoralis major muscle has not been studied extensively. Layeeque et al reported muscular infiltration of Botulinum toxin by direct visualization for mastectomy and tissue expander placement significantly reduced postoperative pain and discomfort without complications; interestingly, the neurotoxin group in this study used significantly less narcotic medication within 24 hours of administration. Figus et al reported the effects of Botulinum toxin A injections on muscle spasms in women undergoing breast reconstruction with latissimus dorsi flaps and subpectoral implants. Others have also objectively demonstrated some pain relief with use of botulinum toxin into the pectoralis major muscle. All of these studies have used a dose range of 75-100 units per pectoralis major or latissimus dorsi muscle group. The goal of this study was to establish the efficacy and safety of a lower dose of Botulinum toxin A in alleviating pain and expediting office-visit expansions. The investigators aimed to examine the effects of Botulinum toxin A in patients undergoing immediate breast reconstruction with expanders/implant breast reconstruction.

**METHODS**

Using a prospective study design, from January to December 2008, 30 enrolled eligible women were randomized into one of two different treatment groups: (1) a group receiving Botulinum toxin A (2 cc of 20 units/mL); and (2) a group receiving a placebo (2 cc of 0.9% NaCl). The study was approved by the Southwest Medical Center’s Institutional Review Board. All patients were referred to a plastic surgery clinic for potential implant-based immediate breast reconstruction following mastectomy. The data safety manager maintained the computer-generated randomization list using Microsoft Excel (Redmond, WA). The investigators provided a detailed explanation of “off-label” use of Botulinum toxin A injection (not approved by the US Food and Drug Administration for breast reconstruction), known potential adverse effects, as well as the potential risks of Botulinum toxin A injection into a muscle surrounding a prosthetic. All subjects gave written informed consent for receiving either a single injection of 40 units (20 units/mL) of neurotoxin (OnabotulinumtoxinA; BOTOX, Allergan, Inc, Irvine CA) or a placebo (0.9% NaCl), during surgery in the pectoralis major muscle. Forty units was arbitrarily chosen, as only one vial of Botulinum toxin A was purchased by the hospital per case, divided amongst each pectoralis muscle in a bilateral reconstruction, with targeted placement of neurotoxin in the tail. Inclusion and exclusion criteria are listed in Table 1. All patients underwent mastectomies with immediate reconstruction with release of pectoralis major origin and reinforcement of the caudal edge of pectoralis major with acellular dermal matrix (AlloDerm, Acelity, San Antonio, TX) to the inframammary fold. No serratus flaps were
utilized in either group. Device-based reconstruction for the first stage included expanders (133MV, Allegan Inc, Irvine, CA). Botulinum toxin A was ordered from the hospital pharmacy and was kept at 4°C. Once the dissection was completed, the 100 unit vial was constituted with 5 cc of 0.9% NaCl and 2 cc was transferred to a 3 cc syringe. A 25-gauge needle was used for injection and 0.25-0.5 cc increments were injected. Botulinum toxin A was injected after the release of the pectoralis major muscle and pocket dissection to ensure accurate placement of the neurotoxin. An accurate intra-muscular needle placement was confirmed in each case before injection (Figure 1). The 25-gauge needle was bent to 90 degrees to ease retrograde injection directly into the thin pectoralis major muscles.

All subjects were followed for 12 months. Two trained individuals were responsible for fills and data collection.

Fills per visit were determined by patient pain upon injection of saline and the feeling of uncomfortable chest tightness or pressure. Patients were asked to return to the clinic every 1-3 months for a clinical follow-up.

We reviewed prospectively-collected clinical pain and other data (patient demographics, VAS [visual analog score], laterality, office visits, amount of expansion, number of times to full expansion, and amount of narcotics) was recorded on a sample of the 30 eligible patients. A standardized chart abstraction form was used to extract prospectively-collected data and comparisons were made using the analyses of variance (ANOVA) for repeated measures. Statistical significance was considered as $p < .05$. Primary outcome measurements included the change from baseline in average pain scores using a visual pain score. The visual analog score was completed at various time frames, and has been used extensively to assess clinical pain. Other primary outcomes included the amount of narcotic usage in the immediate postoperative period (days 0-3) and thereafter (days 3-45). Other outcome measures included the incidence of side effects attributable to Botulinum toxin A, the rate of reconstruction failure (as defined as tissue expander removal), rate of tissue expansion (measurement of expansion volume at each tissue expansion and number of tissue expansions completed), demographic data, treatments, pain severity, amount of narcotic, and number of fills.

No funding was obtained for this study. The hospital included the vial of neurotoxin for the treatment group as part of the hospital expense.

RESULTS

Of the 30 patients enrolled in this study, 15 patients underwent Botulinum toxin A injections of 40 units into the pectoralis major muscle during tissue expander placement for immediate breast reconstruction. Mean age was 44.5 years (range, 27-64), tumor size varied between 0.3 mm and 2 cm, the expander size varied between 133 mv 250 cc and 133 mv 400 cc, and 100% were bilateral cases. Average fill at time of surgery was 112 cc and there were no significant differences between the Botulinum toxin A group and the placebo group in terms of initial fill and expander sizes. Follow-up ranged between 12-36 months with a mean follow-up of 23.4 months. There were no significant differences in complication rates in either group, including rates of seroma, infection, skin necrosis, expander loss, and hematoma. There was no significant difference in narcotic use (hydromorphone, oxycodone, valium, NSAIDS) in the first three days after surgery ($p = 0.59-0.79$). However, there was a significant decrease in the use of narcotics from 7 to 45 days in the Botulinum toxin A group for oxycodone ($p < .0001$) and valium ($p < .0001$; Figure 2), but not for oral NSAIDS ($p = .23$; Figure 3). In addition, there was a significant increase in the volume of expansion per visit in

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<td>Women at least 18 years of age, who underwent immediate unilateral or bilateral tissue expander breast reconstruction following therapeutic skin-sparing or nipple-sparing mastectomy.</td>
<td>Subjects who are unable to read or speak English.</td>
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<td>Women at least 18 years of age, who underwent immediate unilateral or bilateral tissue expander breast reconstruction following risk-reduction (prophylactic) skin-sparing or nipple-sparing mastectomy.</td>
<td>Breast reconstruction using the latissimus dorsi flap combined with a tissue expander.</td>
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<td>Hypersensitivity to any Botulinum toxin preparation or to any of the components in the formulation.</td>
<td>Documented diagnosis of chronic pain, upper limb spasticity, cervical dystonia, axial hyperhidrosis, strabismus, or blepharospasm.</td>
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<td>Cancer involvement at the proposed site of injection.</td>
<td>Pre-existing neuromuscular disorders (myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis).</td>
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<td>Aminoglycosides intake at the time of surgery (these antibiotics can potentiate the effect of Botulinum toxin A).</td>
<td>A documented diagnosis of chronic pain, upper limb spasticity, cervical dystonia, axial hyperhidrosis, strabismus, or blepharospasm.</td>
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<td>Women who are pregnant or breast-feeding.</td>
<td>History of prior radiation.</td>
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<td>Presence of submuscular implants from previous breast surgery.</td>
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<td>Reported use of Botox within 4 months prior to surgical date.</td>
<td>Requirement for postoperative radiation therapy.</td>
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<td>History of prior radiation.</td>
<td>Insulin- and noninsulin-dependent diabetes mellitus.</td>
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the Botulinum toxin A group as compared to the placebo group \((p < .05; \text{Figure 4})\). Patients underwent their second stage reconstruction in an average of 16.5 (Botulinum toxin A) versus 13.2 (placebo) weeks. The mean number of fills was 2.2 and the mean volume/fill was 98 cc to final expansion in the Botulinum toxin A versus 5.8 fills of 54 cc in the placebo group. There were no complications associated with the use of Botulinum toxin A in the pectoralis major muscle. There was a significant difference between the two groups in the VAS score, demonstrating decreased pain in the Botulinum Toxin A group from 7 to 45 days \((p < .05; \text{Figure 5})\).

**Figure 1.** (A) With adequate retraction of the mastectomy flaps, 40 units of Botulinum toxin A was injected within the pectoralis major muscle, first at the tail of muscle, where the nerve enters, and in subsequent passes toward its inferior attachment. The toxin was injected retrograde upon removal of the 25-gauge needle to confirm accurate intramuscular infiltration. (B) Retrograde infiltration of Botulinum toxin A helped in targeting only the pectoralis major muscle for relaxation and spasm reduction. The tissue expander was subsequently placed underneath this muscle. The pectoralis minor muscle was not injected and remained adherent to the chest wall.

**Figure 2.** Narcotic usage postoperatively on days 7-45. Although there was no difference in immediate postoperative pain between the Botulinum toxin A (BT) and the placebo group (NON-BT), the graphs show that significantly less oxycodone and valium were required by the treatment group between 1 and 6 weeks postoperatively.

**Figure 3.** Anti-inflammatory usage postoperatively on days 7-45. Unlike oxycodone and valium, there was no statistical difference between the Botulinum toxin A (BT) and the placebo group (NON-BT) between between 1 and 6 weeks postoperatively.
DISCUSSION

This study provides evidence related to the efficacy of Botulinum toxin A in the pectoralis major muscle for the improvement of pain and enhanced tissue expansion in patients undergoing immediate breast reconstruction. This observation aligns well with previous observations of the efficacy of Botulinum toxin A in reduction of pain in several disease processes. Several patients had sustained pain relief and an improved experience with tissue expansion after Botulinum toxin A. Pain relief was especially noticeable in the postoperative period after 3 days and up to day 45, with a significant difference in the amount of narcotics and muscle relaxants and anxiolytics necessary to provide adequate pain control. No data was collected beyond 45 days for pain control, as all patients had already completed expansion and were no longer on narcotics. Although there may be little data to support our follow-up observations, following un-blinding of the patients we observed fewer complaints from patients regarding chest tightness in the neurotoxin group. In our view, the pain relief started early and was sustained in these patients. Extended effects of local anesthesia (rib blocks) and hospital care with nursing support and physical therapy may explain the absence of any difference in pain medications in the immediate postoperative period (0-3 days). Also, the onset of effect of Botulinum toxin A varies between 3-7 days, and may also explain the absence of any difference in the early days following surgery. However, it is very intriguing that Layeeque et al. showed significantly reduced postoperative pain within 24 hours of administration. Even though not discussed, this clinical finding may be explained by the in vitro finding of the effect of substance P inhibition by Botulinum toxin A in embryonic rat dorsal neurons.11

It is also important to understand the anatomy of the muscle and ensure that the tail of the pectoralis major is injected, followed by at least 3 other locations, for maximum effect (Figure 6).23

This study supports the efficacy of Botulinum toxin A in expediting tissue expansion in breast reconstruction. By relaxing the muscle and decreasing the pain associated with stretch, more fluid was inserted into the tissue expander in each visit, reaching the expansion volume goal sooner and decreasing the number of visits to reach the volume goal (Figure 7). Even with high-volume fill expansions, there was no need for fluid removal due to pain or discomfort. All patients returned to their baseline activity the following day after expansion. The only medication required was oral NSAIDS, due to the expander stiffness that caused tenderness to the surrounding tissues, such as the serratus anterior muscle. Ideally, if an additional neurotoxin was available, injection into the serratus anterior muscle would be beneficial. At the time of this study, tabbed expanders were not available; currently, with the use of tabbed expanders and the availability to anchor to the chest at the 4 or 8 o’clock positions, some neurotoxin is injected into the serratus anterior muscle to minimize the long-term discomfort when sutures are placed in the serratus anterior fascia or muscle. Pain tolerance per patient varies, and as tissue expanders can be firm and uncomfortable when fully expanded, we believe that by relaxing the muscle, the discomfort of this area is minimized. Furthermore, a core finding of this was a shorter span of time necessary to complete the expansion phase of breast reconstruction, thereby shortening the entire reconstructive timeline, all the while providing maximal comfort for the patient. We believe that the improved pain control translated into better function and mobility. In the end, we believe patients who underwent

Figure 4. Expansion volume per visit. There was a significant increase in the volume of expansion per visit in the Botulinum toxin A (BT) versus the placebo group (NON-BT; p < .0001).

Figure 5. Pain score, assessed at each postoperative visit. There was a significant decrease the pain level in the Botulinum toxin A (BT) versus the placebo group (NON-BT; p < .0001).
Botulinum toxin A injection had a superior breast reconstruction experience—one that was shorter and that had minimal discomfort.

Botulinum toxin A has not been approved by the US Food and Drug Administration for paralysis of the pectoralis major muscle in breast reconstruction. Therefore, this constitutes an “off-label” use and should be considered only after a full understanding of the risks and benefits by both the patient and care providers. To our knowledge, this is the only randomized study of breast reconstruction patients undergoing tissue expander-based reconstruction with the use of Botulinum toxin A in the pectoralis major muscle. In the systematic review of the literature, only four studies researching the effect of Botulinum toxin A on pain during expander-based reconstruction have been published, and by design all were retrospective cohort studies. Altieri et al showed improved pain control starting at day 7 in the neurotoxin cohort, which is consistent with our findings, but the amount of Botulinum toxin A was not specified. Layeeque et al also showed improved pain control in the neurotoxin group, but this was observed immediately at postoperative day 1 with decreased narcotic use. The same group described the safety of nipple-sparing mastectomy in 2011 and revealed that all 293 patients received neurotoxin into the pectoralis major muscle to reduce postoperative pain, decrease the hospital stay, and facilitate expansion. Our data does not support a decrease in hospital stay but rather supports decreased pain and ease of expansion. These investigators, much like our group, have incorporated neurotoxin injection into the reconstructive algorithm in all patients undergoing expander-based reconstruction.

Figure 6. (A) Intraoperative portrayal of proper injection into the pectoralis major muscle in a 55-year-old woman with left breast cancer undergoing skin-sparing mastectomy. Botulinum toxin A is first injected into the tail of the pectoralis major muscle to maximally paralyze the muscle where the nerve enters it. (B) After injection into the tail, further injections are placed throughout the pectoralis major muscle, often with a bent needle to accurately infiltrate thin muscle.

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The early significant pain control with the neurotoxin, as documented by Layeeque et al, can be explained by the antinociceptive effect of the drug. Botulinum toxin A injections have an independent antinociceptive effect, in addition to the well-known anticholinergic effect (responsible for muscle-paralyzing action), which has been utilized to treat several syndromes associated with painful muscle spasms. This dual action was noted in cervical dystonia and headache studies. The antinociceptive effect is likely due to an inhibition of neurogenic inflammation, which is mediated by CGRP and substance P, and a blockade of local glutamate release that leads to local edema. A recent systematic review summarized evidence from randomized clinical control trials that supports the antinociceptive effect of Botulinum toxin A in osteoarticular pain, including patients with tennis elbow, low back pain, temporomandibular joint pain, carpal tunnel syndrome, and plantar fasciitis.

Our study has several limitations. Pain assessments were done in the hospital and at clinical follow-ups, which led to a range of follow-up periods for this study, rather than fixed time-points. The length of the follow-ups varied, and some patients did not return for follow-up after 12 months. Furthermore, our sample size was relatively small, with only 30 patients; the goal was to enroll 50 subjects, but patients declined randomization once the potential benefit of the study was discussed. However, a power analysis revealed a sufficient number of patients to perform statistical analyses. Botulinum toxin A effect is dose dependent, and the dosage used for injection (40 units intramuscular) may not have been sufficient for adequate nociceptive and muscle relaxation effect. It is unclear what dose of the neurotoxin is required to temporarily relax the pectoralis major muscle. As other studies have demonstrated, there is some pain control that is associated with the use of the neurotoxin in the pectoralis major muscle, but the doses all varied. These results should be interpreted with caution, as patients may respond differently to different doses of Botulinum toxin A. Our study used a more concentrated dose with targeted placement within the pectoralis major muscle, instead of a
CONCLUSION

Despite its simplicity, implant-based breast reconstruction requires integration of several variables, the most important being careful postoperative management to minimize complications and maximize patient satisfaction and the end result. Intramuscular injection of Botulinum toxin A is a potential clinical tool for plastic surgeons to navigate successful postoperative management. This study adds to the growing body of literature supporting the antinociceptive effects of Botulinum toxin A and its potential benefits in reducing postoperative pain, a challenging clinical problem for reconstructive plastic surgeons in implant-based breast reconstruction. Use of this neurotoxin can be utilized in both aesthetic and reconstructive procedures involving the pectoralis major muscle, and can be further expanded in other areas of the body that require relaxation of muscle for pain control. Nevertheless, the investigators recommend further investigations be undertaken to further validate these findings with a larger cohort of patients and to more closely assess the potential benefits and harms of this treatment.

Disclosures

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