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. 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 spasm, 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.

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.

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that an intraoperative injection of BTX-A in the pectoralis
being during the postoperative period. We hypothesized
BTX-A on alleviating pain and improving physical well-
subpectoral TE placement to establish the efficacy of
ing unilateral and bilateral mastectomies with immediate
blinded randomized controlled trial of women undergo-
breast reconstruction. We present the results of a double-
study participants were blinded to the group allocation.
and study drug preparation were carried out in the hos-
tional border medially to the anterior axillary line laterally.
In the past decades, publications on the use of botuli-
potential for a therapeutic use of BTX-A as an analgesic
temporary clinical problems. There is paucity of high-level evidence assessing the effects
BTX-A in relieving pain associated with subpectoral TE
major muscle reduces pain associated with tissue expan-
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 prospec-
tively between May 2012 and May 2017. Women who are at
least 18 years old were recruited if undergoing unilateral
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 5mL. The placebo was 5mL of 0.9% sodium
chloride. The surgical team received 1 vial of study drug
directly subpectoral TE breast reconstruction. Safety end-
points included the incidence of side effects attributable
to BTX-A.

Follow-up Visits and Study Procedures
The 2 outcome measures selected to test our hypo-
thesis, a numeric pain intensity scale and the physical well-
scalae of the BREAST-Q: Reconstruction Module,14
were administered to the study participants at the preoper-
ating appointment, the first postoperative visit, and at each
expansion visit or subsequent plastic surgery appointment
until the end of the study (last plastic surgery appoint-
ment 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 pecto-
rals major muscle on pain and physical well-being in
women undergoing tissue expansions following imme-
diate subpectoral TE breast reconstruction. Safety end-
points 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 rang-
ing 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 pla-
cebo 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, α = 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
animation deformity, and lateral displacement of the
breast mound, 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 botul-
umin toxin A (BTX-A) for pain relief in a wide array of clinical
conditions have increased tremendously. Although the
surgery; (8) pregnancy or lactation; (9) breast implants
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 prog-
ress 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 hos-
pital’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 ster-
nal border medially to the anterior axillary line laterally.
The subpectoral dissection was completed in a cephalad
direction. Following pocket irrigation with antibiotic solu-
tion 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
vial of study drug was injected retrogradely into the pectoralis
major muscle with a 22-gauge spinal needle into 5 equi-
distant points in the inferior third of the pectoralis major
muscle.

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
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, $\chi^2$, 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 to 0.43), 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 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, chronic pelvic pain, chronic tennis elbow, and postoperative pain control for lower limb lengthening correction, among others.

In a systematic review of the use of BTX-A with subpectoral breast implants, Winocour et al 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\(^\text{15}\) 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\(^\text{24}\) published a pilot study on 30 women that supported the findings reported by Layeeque et al\(^\text{15}\) 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.

Valerie Lemaine, MD, MPH
3300 Edinborough Way
Suite #410
Edina, MN 55435
E-mail: valerie.lemaine@usoncology.com

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