Chapter 9
Use of Botulinum Toxin A in Postmastectomy Breast Reconstruction

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Abstract 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. This chapter describes the use of botulinum toxin A in managing pain and discomfort in the breast reconstruction patients.

Keywords Breast reconstruction · Botox · Neurotoxin · Botulinum toxin A · Pain · Tissue expanders · Breast implants · Breast cancer

Introduction

Implant-based breast reconstruction is the most frequently performed reconstructive technique following breast ablative surgery. Breast reconstruction with tissue expanders (two-stage) and direct to implant (DTI) offers patients satisfying aesthetic results with minimal donor site morbidity. Each year, the number of breast cancer survivors who choose postmastectomy breast reconstruction keeps rising, and a majority will choose expander/implant reconstruction [1]. Evolved over the past few decades into a highly successful and rewarding method of reconstruction, implant-based breast reconstruction is a precise and demanding method.

Postmastectomy reconstruction with a tissue expander and implant can involve a staged approach. The first stage consists of the placement of a tissue expander deep

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B. Jabbari (ed.), *Botulinum Toxin Treatment in Surgery, Dentistry, and Veterinary Medicine*, https://doi.org/10.1007/978-3-030-50691-9_9

to the pectoralis major muscle or into the prepectoral space. 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. The expander during immediate reconstruction is not for expansion purposes but rather a pocket-creating device (PCD). This is followed by a period of weekly tissue expansions that can sometimes last months depending on the patient. 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. Pectoralis major muscle spasm is a frequently reported problem during tissue expansion and in certain instances has led to premature removal of expanders [2]. Legeby et al. showed that women who underwent prosthetic breast reconstruction had higher pain scores and took more analgesics than those who did not choose postmastectomy reconstruction [3]. Therefore, numerous methods and technical variations have been attempted to decrease pain associated with subpectoral placement of tissue expanders and implants, all with questionable success [4–9].

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 and modulates the release of neuropeptides such as substance P and calcitonin gene-related protein and inhibits neurogenic inflammation, which likely underlies its independent antinociceptive effect [10]. 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 [11]. 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 [12], chronic pelvic pain [13], chronic tennis elbow [14], and postoperative pain control for painful joint arthroplasty [15], among others. Furthermore, botulinum toxin A has been used to treat various painful muscle spasms, such as paravertebral muscle spasm [16], fibromyalgia-myofascial pain [17], and temporomandibular joint pain [18]. 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 fully utilized. Layeequee 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 [19]. 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 [20]. Others have also demonstrated objectively some pain relief with the use of botulinum toxin into the pectoralis major muscle [21, 22]. All of these studies have used a dose range of 75–100 units per pectoralis major or latissimus dorsi muscle groups. In our study, we evaluated 30 patients following mastectomies with immediate expander/ADM reconstruction and divided them into two groups [23]. The neurotoxin group ($n = 15$) received 40 units of neurotoxin (botulinum toxin A, Allergan, Inc., Irvine, CA) into each pectoralis major muscle through four serial injections, and the placebo group ($n = 15$) received four serial injections of 0.9% NaCl. We found no significant difference between the two groups in terms of age, laterality, expander size, and complications ($p = 0.46$–0.66). However, there was a significant difference between the two groups in the VAS (Visual Analog Scale) score demonstrating decreased pain in the neurotoxin group ($p < 0.05$). In addition, there was a significant increase in the volume of expansion per visit in the neurotoxin group as compared to the placebo group ($p < 0.05$). 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 ($p < 0.05$). There were no complications associated with the use of neurotoxin [23].

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 [24], 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 [25] and headache studies [26]. The antinociceptive effect is likely due to inhibition of neurogenic inflammation [10], which is mediated by CGRP and substance P and blockade of local glutamate release that leads to local edema [27]. 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 [28].

Discussion

Noninvasive aesthetic procedures are continuously on the rise, and every year there is an increase in uptake of botulinum toxin as one of the most popular procedures performed in the United States and perhaps the world. In addition to the well-known anticholinergic effect (responsible for muscle-relaxation action), there is also increasing evidence of the antinociceptive effect, likely due to inhibition of neurogenic inflammation [10], which is mediated by CGRP and substance P and blockade of local glutamate release that leads to local edema [27]. It is difficult to quantify the utilization of botulinum toxin for its therapeutic uses as currently there is no

tracking method of this modality and one may be surprised that the therapeutic utilization may be as high as the aesthetic market growth.

In breast reconstruction, our study provides the 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 [23]. This observation aligns well with previously observed efficacy of botulinum toxin A in reduction of pain in several disease processes. Several patients had a sustained pain relief and improved experience with tissue expansion after botulinum toxin A treatment. 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/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. It is very intriguing that Layeequee et al. showed significantly reduced postoperative pain within the 24 hours of administration [19]. 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 three other locations, for maximum effect [29] (Fig. 9.1).

By relaxing the muscle, and decreasing the pain associated with stretch of muscle, more efficient expansions can be performed. With the advent of tabbed expanders in early 2011, the need for injection of serratus anterior muscle was introduced

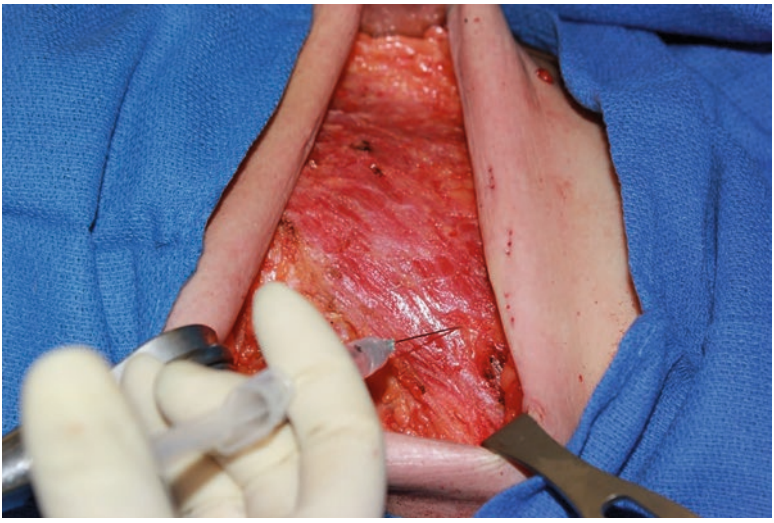

Fig. 9.1 Intraoperative portrayal of proper injection into the pectoralis major muscle in a 55-year-old female with left breast cancer undergoing skin-sparing mastectomy. Botulinum toxin A is first injected into the tail of the pectoralis major muscle to maximally paralyze the muscle, where the nerve enters the muscle

to minimize the long-term discomfort when sutures are placed in the serratus anterior fascia or muscle [23]. Of course, 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 shorter span of time necessary to complete the expansion phase of breast reconstruction can shorten the entire reconstructive timeline, all the while providing maximal comfort for the patient.

For the past 20 years, implant-based breast reconstruction has been performed primarily with subpectoral implant placement via the dual-plane approach. The coverage and support provided by the pectoralis major muscle has not only minimized implant-related complications but has mitigated the risk of capsular contracture and produced a more natural-looking breast. However, a concern with this approach is the risk of functional impairment of the pectoralis muscle and animation deformities, both of which are a direct consequence of muscle elevation [30]. The muscle discomfort can be at times controlled with neurotoxin injection into the tail of the pectoralis major muscle, but this is not a sustainable solution long term. Therefore, in the last 6 years, the trend has been to change the implant site to a prepectoral placement to help resolve some of these concerns [30].

Even though the pectoralis major muscle is not included in prepectoral reconstruction, neurotoxin injection into serratus anterior and pectoralis major muscles should still be considered. This can be beneficial, since numerous tacking sutures are placed in these muscles. These tacking sutures can lead to severe muscle spasms in the postoperative period and sometimes until the expander is replaced with an implant. In addition, in the site where the axilla is violated, the injection of neurotoxin into the pectoralis major can help with postoperative discomfort.

Botulinum toxin A has not been approved by the US Food and Drug Administration for paralysis of pectoralis major muscle in breast reconstruction. Therefore, this constitutes an "off-label" use and should be considered only after a full understanding of risks/benefits by the patients and care providers. In the systematic review of the literature, limited studies researching the effect of botulinum toxin A on pain during expander-based reconstruction have been published [19, 21]. 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 [31]. Layeeque et al. also showed improved pain control in the neurotoxin group, but this was observed immediately at postoperative 1 with decreased narcotic use [19]. 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 hospital stay, and facilitate expansion [32]. 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.

The role of botulinum toxin is expanding every year in aesthetic and therapeutic markets. There are many benefits of its use that have been well described [11–18, 23–26, 28].

We believe that as more surgeons are innovative and understand the potential benefits of botulinum toxin, the more clinical applications will be identified. Even though many of these therapeutic treatments are "off label," the use and advantages cannot be overlooked. Unfortunately, industry will not be able to obtain an "on-label" use of an existing FDA-approved product for every clinical scenario, given the stringent government study requirements for an on-label approval. It will be up to every physician to describe the potential benefit of its use and have the patient consent to the procedure. One example is the rapidly expanding use of botulinum toxin in management of large hernias [33].

Despite its simplicity, implant-based breast reconstruction requires integration of severable variables, the most important being careful postoperative management to minimize complications and maximize patient satisfaction and end result. Intramuscular injection of botulinum toxin A is a potential clinical tool for plastic surgeons to navigate successful postoperative management. The 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.

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