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# Botulinum Toxin-A and Scar Reduction: A Review

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**Abstract**

Pathologic scars remain a therapeutic enigma. Several therapeutic modalities have been described for the prevention and treatment of hypertrophic and keloid scars, but the optimal management approach has not yet been defined. This article reviews the newly emerging, off-label treatment, botulinum toxin-A (BTXA) for scar reduction. Eight in vitro, 9 in vivo animal, and 23 human clinical studies were deemed relevant to this review. Studies were conducted between 2000 and 2018. Clinical studies were of various methodologic qualities and comprised of 8 blinded randomized control trials, 7 cohort studies, and 7 case series/reports. Across all 23 human clinical studies, 521 patients were recruited, 20 studies were in favor of BTXA to reduce scars, 2 studies had equivocal results, and 1 study showed no benefit. The efficacy of BTXA to reduce scars appears promising and the clinical literature currently favors its use over placebo controls as a safe scar reduction alternative. The efficacy of this modality in comparison with other more widely accepted scar reduction methods is less clear. Further understanding of the molecular mechanism of action of BTXA upon scars and treatment modality cost-effectiveness comparisons remain to be explored. Large-scale randomized control trials of high methodologic quality, using objective measurement scales, must be produced to truly determine the efficacy of this innovative treatment.

**Keywords**

botulinum toxin, scar, hypertrophic, keloid, Botox

## Introduction

Scarring is a significant medical problem that affects more than 100 million people annually, in developed countries alone, and there are many etiologies.[1,2] For example, more than 4.4 million people are injured in motor vehicle accidents, more than 2.4 million patients are burned, and thousands of warriors are wounded in military excursions each year.[3,4] In addition, each time a surgical incision in the skin is created, a scar is inevitably produced. In many patients, the scar heals adequately and is not cosmetically disfiguring, but occasionally, pronounced hypertrophic or keloid scars can form. Following dermal injury, wound repair processes involve a cascade of events including inflammation, proliferation, and scar differentiation. A common result of this process is scarring which can lead to undesirable changes in skin mechanical function as well as cosmetic disfiguration. On the more severe end of the scarring spectrum, hypertrophic and keloid scars can develop.

Hypertrophic and keloid scars are characterized by excessive fibrosis and extracellular matrix (ECM) deposition. It has been hypothesized that hypertrophic and keloid scars can be considered as successive stages of the same fibroproliferative skin disorder, with differing degrees of inflammation that might be affected by genetic predisposition.[5] Patients with scars often experience severe physical complications[6] (eg, deformities and disfigurement, restricted range of motion, pain, and pruritus) and psychological problems[7] (eg, anxiety, lowered self-esteem, and depression). Scars can also affect quality of life and cost millions of dollars per year in medical and surgical treatments and physical therapy. In humans, scars develop throughout wound healing over 6 to 12 months.[8]

Despite the high consumer demand for therapeutics that promote healing, there is no universally accepted treatment resulting in permanent hypertrophic or keloid scar ablation.[9] Hence, alternatives are needed. A promising new treatment for scars is botulinum toxin-A (BTXA) which is a potent neurotoxin derived from *Clostridium botulinum* that causes

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flaccid paralysis of striated muscle by inhibiting acetylcholine release at the neuromuscular junction.[10] In addition to producing a flaccid paralysis of striated muscle for 2 to 6 months, studies have indicated that BTXA can improve the symptoms and appearance of scars. In this article, we present a summation of the in vitro, in vivo animal, and human-based clinical evidence investigating the use of BTXA to reduce scars.

## Methods

A review protocol was prepared in March 2018. We searched the PubMed and Cochrane databases for literature published between January 2000 and March 2018. Studies that are not PubMed indexed were not included for review. Our aim was to summarize the published literature available between these dates to provide a succinct overview of the evidence in relation to BTXA administration and scar reduction. The following keywords were used when searching the literature databases: abobotulinum, abobotulinumtoxinA, incobotulinumtoxin, onabotulinumtoxin, botulinum toxin, Dysport, Botox, Xeomin, scar, hypertrophic and keloid. A total of 80 articles were identified and initially screened by the main author and 40 were found to be relevant to this study.

## In Vitro Studies

Eight in vitro studies were discovered, published between 2008 and 2016, which focused on various aspects of BTXA administration and scar reduction. These studies have demonstrated that BTXA can affect the cell cycle distribution of fibroblasts derived from hypertrophic scars[11] and fibroblast-to-myofibroblast differentiation is decreased after BTXA treatment.[12] Studies have also demonstrated that BTXA can decrease the expression of transforming growth factor β1 (TGF-β1),[13] connective tissue growth factor (CTGF),[14] and α-smooth muscle actin (α-SMA) and myosin II expression[15] which could provide theoretical explanations as to why BTXA may result in fibroblast inhibition and therefore visual improvement of scars. Xiaoxue and colleagues also found that BTXA altered the gene expression levels of vascular endothelial growth factor (VEGF), matrix metalloproteinase-1 (MMP-1), platelet-derived growth factor subunit A (PDGFA), and S100A4 and TGF-β1 genes in keloid fibroblasts which provides further clues as to the mechanism of action of BTXA upon scars. Conversely, Haubner and colleagues[17,18] found in 2 separate studies that BTXA administration to cell culture models had no effect on cell proliferation and expression of VEGF, TGF-β1, interleukin-6 (IL-6), macrophage colony-stimulating factor (M-CSF), fibroblast growth factor (FGF), and monocyte chemoattractant protein 2 (MCP2). At this stage, the exact mechanism of BTXA on scars is still not fully understood and further in vitro studies that include patient-specific cells of hypertrophic or keloid scars are required to better understand what role BTXA can play in the treatment of mature scar tissue.

## In Vivo Animal Studies

Nine animal studies were published between 2000 and 2017, with results largely in favor of BTXA for the treatment of scars. Xiao and Qu showed that hypertrophic scars treated with BTXA had significantly reduced scar thickness and collagen fibers were thinner with a more orderly arrangement compared with controls in a rabbit ear model.[19] Wang et al illustrated that BTXA can inhibit the activity of fibroblasts and decrease the expression of collagen I and III in hypertrophic scars, also in a rabbit ear model.[20] Lee and colleagues demonstrated that BTXA treatment significantly decreased the wound size, infiltration of inflammatory cells, fibrosis, and expression of TGF-β1 as well as increasing collagen synthesis in a rat model when compared with controls.[21] Sahinkanat et al examined BTXA and urethral wound healing in a rat model and found that BTXA prevented increases in collagen content during urethral wound healing.[22] Chen and colleagues implanted human hypertrophic scar fragments into the backs of 12 nude athymic mice and performed comparisons between negative controls, triamcinolone alone, BTXA alone, and a combination of triamcinolone and BTXA. The authors found that BTXA or triamcinolone intralesional monotherapy had significant therapeutic efficacy compared with the control group; however, combined therapy further exhibited a significant therapeutic effect compared with monotherapy alone.[23] Wang et al revealed, in a rat model, that BTXA can decrease the expression of substance P (SP), calcitonin gene-related peptide (CGRP), TGF-β1, and α-SMA in a dose-dependent manner.[24] Gassner et al performed a randomized, double-blind, placebo-controlled primate study by making symmetric pairs of standardized excisions on either side of the forehead of 6 primates. The half foreheads were randomized to a single BTXA treatment side versus a placebo 0.9% saline injection side and a panel of 3 blinded facial plastic surgeons assessed the cosmetic appearance of the mature scars 3 months postoperatively. The wounds that had been immobilized with BTXA were rated as significantly better in appearance than the control wounds ($P = .01$).[10]

Although there is a growing body of animal-based literature supporting the use of BTXA, there are some animal studies that are equivocal or do not support BTXA as an effective scar reduction therapy. Liu and colleagues demonstrated that BTXA improved the appearance of hypertrophic scars and inhibited the formation of collagen fibrils and fibroblasts in a rabbit ear model and the higher dose of 2 U showed improved results compared with triamcinolone acetonide; however, at the mid doses of 1 U and 1.5 U, there was similar efficacy.[25] Çaliskan and colleagues compared triamcinolone acetonide, 5-fluorouracil, BTXA, and controls in a rabbit ear model and found that triamcinolone acetonide and 5-fluorouracil injections decreased hypertrophic indexes significantly compared with BTXA and the control group and the study concluded that triamcinolone acetonide

and 5-fluorouracil were comparatively effective as monotherapy, but BTXA was not effective on established hypertrophic scars.[26]

## Human Clinical Studies

Twenty-three human clinical studies have been performed between 2003 and 2018. These studies are summarized in Table 1. Twenty studies were overall in favor of BTXA for the treatment of scars, 2 studies had equivocal results, and 1 study showed no benefit of BTXA to improve scars. The studies were of various qualities and comprised of 8 blinded randomized control trials, 7 cohort studies, and 7 case series/reports. Across all 23 clinical studies, 521 patients were recruited. The largest study sample size was 80 patients with a mean sample size of 22.65 patients per study.

## Systematic Reviews and Metanalyses

A systematic review was performed by Prodromidou and colleagues in 2015 which included 10 clinical studies (225 patients), published between 2006 and 2014.[50] This systematic review noted improved outcomes among certain studies using the visual analog scale (VAS) (BTXA experimental group: median score 8.25 [range 6-10] vs control group: median score 6.38 [range 2-9]; $P < .001$) and the Stony Brook Scar Evaluation Scale (BTXA experimental group score: 6.7 vs control group score: 4.17; $P < .001$) assessments. However, the methodological heterogeneity of the included studies, the lack of a control group in the majority of studies, the use of subjective scales of measurement, and the frequent use of patient self-assessment, precluded unbiased results.[50] Therefore, the study group concluded that although current literature does seem to suggest BTXA may be beneficial for the treatment of scars, it is not sufficiently demonstrated in the human clinical literature to support its use as a new alternative treatment option for scars.

In 2016, Zhang and colleagues published a metanalysis evaluating BTXA and the reduction of hypertrophic scars involving the maxillofacial area and neck.[51] This study pooled 9 studies (total of 539 patients), including 2 Chinese studies that were not included in this study as they are not PubMed indexed. The effects of BTXA were evaluated by comparing scar widths, patient satisfaction, and visual analysis scores (VAS), respectively. Pooled weighted mean differences (WMDs), pooled odds ratios (ORs), and 95% confidence intervals (CI) were calculated. Statistically significant differences between BTXA and the control group were noted in relation to scar width (WMD = −0.41, 95% CI = −0.68 to −0.14, $P = .003$), patient satisfaction (OR = 25.76, 95% CI = 2.58 to 256.67, $P = .006$), and VAS scores (WMD = 1.30, 95% CI = 1.00 to 1.60, $P < .00001$). Thus, in contrary to the systematic review performed by Prodromidou et al, this study group concluded BTXA is a suitable potential therapy for the reduction of hypertrophic scars in the maxillofacial and neck areas.[51]

## Ongoing Clinical Studies

Seven early phase clinical trials to evaluate the efficacy of BTXA administration and scar reduction were listed on ClinicalTrials.gov in March 2018 (Table 2). Most of the results of these studies should be available within the next 12 to 18 months.

## Discussion

Wound healing with subsequent scar formation is a complex and dynamic process that is dependent on the coordinated activities of multiple cell types in the epithelium, connective tissue, and vasculature.[52] The process consists of 3 overlapping phases.[53-55] Initially, the inflammatory, or migration phase, which lasts a few days, occurs during which an array of potent cytokines and growth factors recruit inflammatory cells such as macrophages, neutrophils, and fibroblasts for use in the second phase. The proliferative, or mitotic, second phase typically lasts for weeks and is characterized by the formation of granulation tissue. Recruited fibroblasts synthesize a scaffold of ECM which builds a structural framework on which to bridge the wound and allow vascular ingrowth. Myofibroblasts help to initiate wound contraction. The final phase in the process is maturation, which starts once the wound is closed and typically lasts for approximately 7 months. During this phase, the scar begins to shrink and swelling diminishes. The inflammatory cells gradually diminish in number, ECM is degraded, angiogenesis and fibroplasia cease, and immature type III collagen is modified into mature type I collagen.[54,55] Wound healing is frequently an imperfect process and inevitably leaves patients with scars and potential disfigurement.[52] The interruption of any of these 3 phases can result in pathologic wound healing complications. This may be influenced by the location of the wound, prolonged inflammation, wound infections, and delayed epithelialization (longer than 10 days).[14,39,53,55]

Every discontinuity of the skin can influence its architecture and leave a scar.[50] The outcome of wound healing and scar formation is of great importance for both physicians and patients as such deformities can result in functional and cosmetic defects, cause psychological stress, pain and itching, as well as reduce the quality of life of an individual.[56] Many scars heal pathologically, resulting in hypertrophic scars or even keloid scars. It has been suggested that their pathogenesis is synergistic, involving topographical, metabolic, circulatory, immunological, and nutritional factors combined with age and genetic predisposition.[57] Further variations in surgical techniques to include undermining, sutures utilized, and the actual closure technique as well as postoperative factors such as infections and trauma can also affect scar formation.[10] Clinically, hypertrophic scars seem to be more related to tension adjacent to the wound, whereas keloids seem to be more related to the ethnic background of the patient and the anatomic location. Attempts to differentiate these 2 entities have led to conflicting results.[10,58]

**Table 1.** Summary of the Human Clinical Evidence for BTXA and Scar Reduction.

| Source, year | Trial design | Inclusion criteria | Number of patients, Study duration | Therapy/dose | Timing of BTXA injection/s | Measurement scale | Results |
|---|---|---|---|---|---|---|---|
| Lin et al (2018)[27] | Blinded, prospective, randomized control trial | Patients planned to undergo facial reconstructive surgical procedures | 14, 6 months | Split scar study with each side of the scar randomized to receive; BTXA 10 U for each 1 cm length of the incision injected at a distance of 5 mm on either side of the wound or 0.9% normal saline (control) | Single injection immediately following wound closure by a single plastic surgeon | Photography<br>VSS<br>VAS<br>Mean scar width measurement | Significantly improved VAS, $P = .046$, and mean scar width, $P = .001$<br>Mean VSS was 4.68 for the BTXA group and 5.24 for the control group, $P = .15$<br>VSS height score also favored the BTXA group, $P = .008$ |
| Lee et al (2017)[28] | Blinded, prospective, randomized control trial | Vertically orientated traumatic forehead lacerations | 36, 6 months | 18 patients BTXA arm (30 U BTXA); 18 patients negative control arm<br>Note: An additional 10-20 U was injected when complete muscle paralysis was not observed within 5 days of the initial injection | Single injection within 5 days after repair | Photography<br>VSS | Improved VSS scores, reduced wound width, and less scar discoloration in the BTXA arm<br>Differences were observed at the 6-month visit, but not at the 1-month visit |
| Zelken et al (2016)[29] | Blinded, prospective, randomized control trial | Patients planned to undergo forehead flap nasal reconstruction | 26, >6 months | BTXA pretreatment randomly assigned to the upper or lower half of the forehead<br>20 U BTXA in the experimental site; 0.9% saline in the control site | Single injection 10 days prior to surgery | Photography<br>VAS | VAS score of BTXA treated scars (8.5 ± 1.0) was significantly higher than the control (7.3 ± 1.1; $P < .0001$) |
| Elhefnawy et al (2016)[30] | Cohort study | Patients with hypertrophic scars >1 year and patients more than 18 years | 20, 6 months | 2.5 U/cm$^3$ BTXA (not exceeding 100 units per session) | Once a month for a total period of 3 months | Photography<br>5-point scale | Therapeutic satisfaction was "good" in 14 patients and "excellent" in 6. Mean erythema score decreased from 3.2 to 1.0 ($P = .000$), mean pliability score from 3.3 to 0.8 ($P = .000$), and mean itching score from 2.7 to 0.7 ($P = .000$) |
| Lee et al (2015)[31] | Case series/report | Traumatic scars that occurred on the chin | 2, 8 weeks | Combined therapy with 595-nm PDL and BTXA<br>Patient 1: 8 U BTXA into mentalis muscle combined with PDL at 2-week intervals (total 5 treatments)<br>Patient 2: 6 U BTXA into mentalis muscle combined with PDL at 3-week intervals (total 3 treatments) | Single injection immediately after first laser treatment | Photography | Subjective improvement after 8 weeks |
| Shaarawy et al (2014)[32] | Blinded, prospective, randomized control trial | Female patients with posttraumatic or idiopathic keloid scars | 24, 7 months | Twelve patients intralesional triamcinolone acetonide 10 mg/cc; 12 patients intralesional BTXA injection 5 U/cm$^3$ | Injections repeated every 8 weeks for three sessions/or complete improvement of the keloid | Blinded clinical assessment<br>Patient satisfaction | Decrease in volume of the scars after treatment ($P < .01$) in both groups. Softening of lesions vs baseline with triamcinolone ($P < .01$). Decrease in height of lesions and redness compared with baseline ($P < .01$) with no difference between groups. All patients had reduction in subjective complaints ($P < .01$) that were more significant in BTXA treatment group |
| Chang et al (2014)[33] | Blinded, prospective, randomized control trial | Patients with unilateral cleft lip undergoing primary cheiloplasty at approximately 3 months of age | 59, 6 months | BTXA; 30 patients received 2.5 U BTXA adjacent to the wound, 29 patients received 0.9% saline placebo control | Single injection immediately after cheiloplasty | VSS<br>VAS<br>Objective photography | VSS scores in the BTXA and placebo groups were similar (2.70 ± 1.29 vs 2.76 ± 1.44)<br>VAS scores favored BTXA (8.43 ± 0.56 vs 7.19 ± 0.95; $P < .001$)<br>Widths of scars in the experimental group were significantly better $P < .001$ |
| Kim et al (2014)[34] | Blinded, prospective, randomized control trial | >18 years of age with a thyroidectomy (neck) scar of <10 days | 15, 6 months | Split scar study; mean of 32.3 U BTXA (range 20-65) injected into the experimental side and 0.9% saline to the control side | Single injection of BTXA at a mean of 6.6 days post surgery (range 5-9 days) | Photography<br>SBSES<br>Patient subjective evaluation | At 6-month follow-up, the BTXA arm showed significant improvement in SBSES compared with controls (6.70 ± 1.52 vs 4.17 ± 1.44 ($P < .001$) |

*(continued)*

**Table 1. (continued)**

| Source, year | Trial design | Inclusion criteria | Number of patients, Study duration | Therapy/dose | Timing of BTXA injection/s | Measurement scale | Results |
|---|---|---|---|---|---|---|---|
| Chang et al (2014)[35] | Blinded, prospective, randomized control trial | >16 years with moderate to severe secondary scar deformity following primary cleft lip repair that warranted revision surgery | 60, 6 months | Thirty patients injected with BTXA to subjacent orbicularis oris; 30 patients injected with 0.9% saline control | Single injection immediately following cleft lip scar revision wound closure | Photography<br>Ultrasonography<br>VSS<br>VAS | Lower VSS score for the experimental group (2.45 ± 1.52 vs 3.50 ± 1.88; $P = .023$)<br>Lower VAS score in the experimental group (7.47 ± 0.64 vs 6.10 ± 1.06; $P = .001$)<br>Narrower scar according to photographic measurement, $P = .001$, and ultrasonographic measurements, $P = .001$ |
| Wilson (2013)[36] | Cohort study | Persistent keloids (1-4 years) | 80, 17-24 months (mean 19.6 months) | Surgical excision followed by BTXA (20 U/cm³) and 5-FU (50 mg/mL with 0.4 mL/cm³) injection on day 9. Total dose of BTXA and 5-FU < 140 IU and 500 mg, respectively | Single BTXA and 5-FU injection on day 9 post scar excision | Subjective patient assessment | 67 (83.75%) patients rated the improvement as significant, 10 (12.5%) as slight, and 3 (3.75%) as unchanged |
| Robinson (2013)[37] | Case series/report | Keloid scars | 12, mean 11 months (range 2-43 months) | BTXA dose between 20 and 100 U depending on the size and location of the keloid<br>Eight patients had concurrent alternating intralesional triamcinolone | No standardized injection timing | VSS | Complete flattening of the keloid scar in an average of 11 months (range 2-43 months) in 9 patients. Two patients developed recurrences adjacent to previously treated areas |
| Ziade et al (2013)[38] | Blinded, prospective, randomized control trial | >18 years of age with a facial wound without tissue loss | 30, 1 year | Fifteen patients injected with BTXA dose based on what physician considered necessary to induce paresis in facial muscles directly or indirectly involved in scar widening; 15 patients were not given injections (control) | Single BTXA injection within 72 hours after wound closure | Photography<br>PSAS<br>OSAS<br>VSS<br>VAS | PSAS: 9 (6-18) vs 8 (6-26)<br>OSAS: 8 (6-13) vs 9 (5-24)<br>VSS: 3 (1-4) vs 2 (1-9)<br>VAS: 8.25 (6-10) vs 6.38 (2-9) ($P < .001$) |
| Gauglitz et al (2012)[39] | Case series/report | Keloids resistant to any previous therapy for >2 years | 4, >6 months | BTXA intralesional injection (doses varying from 70-140 U per session) | BTXA injection every 2 months for up to 6 months | Three-dimensional optical profiling | No changes to the macroscopic appearance, morphology or size of keloid scars<br>No differences to ECM markers, collagen synthesis, cell proliferation, TGF-β, or metabolism of keloid fibroblasts after BTXA treatment |
| Uyesugi et al (2010)[40] | Case report | Single patient with a painful chest wall scar | 1, 5 weeks | 100 U BTXA to a chest wall keloid scar | Single injection | Subjective patient assessment | Subjectively improved pain. No change in pruritus. No change in scar appearance. |
| Flynn (2009)[41] | Cohort study | Patients with Mohs surgical defects | 18, 3 months | BTXA (dose range 6-24 U) or BTXB (dose range 12-3550 U) | Single injection immediately following surgery | Photography<br>Subjective patient assessment | No difference in patients treated with BTXA and BTXB<br>Excellent apposition of wound edges and smooth skin overlying soft tissue |
| Xiao et al (2009)[42] | Cohort study | Single hypertrophic scar that persisted for >2 years | 19, 6 months | BTXA 2.5 U/cm³ (did not exceed 100 U BTXA per injection session) | BTXA once monthly for a total duration of 3 months | Subjective patient assessment<br>Subjective unblinded physician assessment<br>5-point scale | Patient assessment: 12 good, 7 excellent<br>Physician assessment: 15 good, 4 excellent<br>Mean erythema score (3.41 ± 1.23), mean pliability score (3.85 ± 0.78), mean itching score (3.50 ± 0.83) |
| Zhibo et al (2009)[43] | Cohort study | Keloids of any duration | 12, 1 year | BTXA (dose range between 70-140 U per session) | Three-month interval injections for a maximum of 9 months | Photography<br>5-point scale<br>Patient satisfaction | 3 patients excellent, 5 good, 4 fair. None of the patients showed failure of therapy. Peripheral regression of lesions was noted in addition to flattening in all cases, and there was no evidence of recurrence after 1 year. |
| Gassner et al (2009)[44] | Case report | Perioral wounds | 2, 6 months to 1 year | Patient 1: 40 U BTXA injected into orbicularis oris immediately prior to lip repair<br>Patient 2: 30 U BTXA injected into buccinator and zygomatici muscles | Single injection | Photography | Excellent subjective healing of perioral wounds based on photographic assessment |



*(continued)*

**Table 1. (continued)**

| Source, year | Trial design | Inclusion criteria | Number of patients, Study duration | Therapy/dose | Timing of BTXA injection/s | Measurement scale | Results |
|---|---|---|---|---|---|---|---|
| Mahboub et al (2006)[45] | Cohort study | Traumatic facial scars (maturity ranged between 8 months and 9 years) | 11, 6 months | BTXA (dose range 6-49 U) pretreatment to adjacent facial muscles followed by surgical excision after muscle paralysis obtained based on EMG after 2 weeks | Single injection. Note: A second dose was indicated whenever EMG hypertonicity persisted at 2 weeks | Photography<br>Subjective patient assessment<br>Subjective unblinded physician assessment | Good outcome in 6 patients, acceptable outcome in 3 patients, and unacceptable outcome in 2 patients |
| Gassner et al (2006)[46] | Blinded, prospective, randomized control trial | >18 years with traumatic forehead lacerations or undergoing excision of forehead neoplasms | 31, 6 months | 15 patients injected with BTXA (15 U injected adjacent to wounds <2 cm in length, 30 U to wounds 2-4 cm, 45 U to wounds >4 cm); 16 patients injected with placebo 0.9% saline (control) | Single injection within 24 hours after wound closure | Photography<br>VAS | BTXA treatment group was 8.9 compared with 7.2 for the placebo group ($P = .003$) |
| Tollefson et al (2006)[47] | Case report | Infants planned to undergo surgical cleft lip repair | 3, NA | BTXA (dose 1-2 U/kg at 25 U/mL) | Single injection into orbicularis oris via 4 superficial injection sites 7 days prior to surgical repair | Photography | Early aesthetic results were satisfactory, with no BTXA complications |
| Wilson (2006)[48] | Cohort study | Persistent hypertrophic facial scars | 40, 12 to 16 months (mean 15.3 months) | BTXA injection 1.5 U/cm$^3$ of wound length | Single injection into adjacent musculature immediately following revision surgery<br>Note: Eight patients had residual muscle contraction 48 hours after initial injection and additional BTXA was administered | Objective photography<br>Subjective patient assessment (5-point scale) | Photography: 36 satisfactory outcome, 3 no difference, 1 residual scar depression<br>Patient assessment: 30 marked improvement, 6 significant improvement, 4 unchanged |
| Gassner et al (2003)[49] | Case report | Facial scars requiring surgical revision | 2, 1 and 3 years | BTXA (dose of 17.5 U and 40 U in each respective patient) | Single injection into adjacent musculature at time of revision scar excision | Photography | Revised scar compared favorably to original scar<br>Better healed scars over immobilized areas than over non-immobilized areas |

*Note*. BTXA = botulinum toxin-A; BTXB = botulinum toxin-B; EMG = Electromyography; VSS = Vancouver Scar Scale; VAS = Visual Analog Scale; PDL = pulsed dye laser; 5-FU = 5-fluorouracil; SBSES = Stony Brook Scar Evaluation Scale; PSAS = Patient Scar Assessment Scale; OSAS = Observer Scar Assessment Scale; ECM = extracellular matrix; TGF-β1 = transforming growth factor-β1.

**Table 2.** Clinical Trials Currently in Progress Evaluating the Efficacy of BTXA Administration and Scar Reduction.

| ClinicalTrials.gov ID | Study title | Estimated enrollment | Details | Status |
|---|---|---|---|---|
| NCT02168634 | The Use of Botulinum Toxin in the Treatment of Itching From Hypertrophic Scar—A Randomized Controlled Trial | 40 participants | Randomized, placebo-controlled trial to evaluate relief of itching in adults with hypertrophic scars due to laparotomy or thyroidectomy | Recruiting (Taiwan) |
| NCT02623829 | Botulinum Toxin Is a Potential Prophylactic Therapy for Minimizing Post-Excisional Scarring | 60 participants | Randomized, placebo-controlled trial to evaluate the efficacy of BTXA as a prophylactic treatment in post-excisional repairs | Recruiting (USA) |
| NCT02786550 | Botulinum Toxin to Improve Lower Blepharoplasty Scar | 40 participants | Randomized, placebo-controlled trial to evaluate the efficacy of immediate postoperative BTXA injection into the lateral orbicularis oculis muscles can improve scar formation for lower blepharoplasty patients | Recruiting (Taiwan) |
| NCT03294382 | Botulinum Toxin to Improve Results in Epicanthoplasty | 42 participants | Randomized, placebo-controlled trial to evaluate the efficiency of BTXA injection on improving hypertrophic scarring after epicanthoplasty | Recruiting (China) |
| NCT01459666 | Forehead Scars Following Mohs Micrographic Surgery and Reconstruction for Skin Cancer | 50 participants | Randomized, placebo-controlled trial to evaluate the efficacy of BTXA in improving forehead wounds after Mohs reconstruction for skin cancer | Recruiting (USA) |
| NCT02247193 | Improvement of the Appearance of Cleft Lip Scars Using Botox | 40 participants | Randomized, placebo-controlled trial to evaluate if the use of BTXA during primary cleft lip repair improves the cosmetic appearance of scars in infants | Recruiting (USA) |
| NCT02886988 | Early Postoperative Prevention and Treatment of Median Sternotomy Scars With Botulinum Toxin Type A Injection | 17 participants | Randomized, placebo-controlled trial to evaluate the efficacy of BTXA in prevention of hypertrophic scar development in median sternotomy wounds | Completed (January 25, 2018) |

*Note.* BTXA = botulinum toxin-A; ID = Identificiation Number.

Mechanical tension applied to a wound during the healing process represents a potential factor predisposing to aberrant scar formation. When tension is exerted perpendicular to a wound, this can result in ongoing microtrauma to the lesion, which exacerbates inflammation, leading to overproduction of collagen and glycosaminoglycans, and delayed healing.[35,39,53,55] This leads to the formation of raised and often hyperpigmented scars, which frequently are in prominent positions on the face.[52] Brody et al offered an elegant theory for hypertrophic scar formation and scar contracture as a consequence of compression exerted on a wound during maturation.[59] Reiffel believed that the deleterious force that caused pathologic scar formation was tension, not compression. Nevertheless, his solution was to eliminate all forces by immobilizing the scar with paper tape.[60] Atkinson et al conducted a high-quality randomized control trial assessing the benefit of taping scars and she confirmed Reiffel's recommendation and concluded that the odds of a hypertrophic scar developing were 13.6 times higher without tape than with tape (95% CI = 3.6 to 66.9).[61] Thus, regardless of the exact mechanism, the solution was the same, scar immobilization.[62]

Unfortunately, the precise mechanisms underlying the formation of pathologic scars are not fully understood, and this makes their management difficult.[2] To reduce scarring, several surgical concepts have been utilized such as the use of deep sutures, undermining skin edges, flap reconstruction, and orienting the incision along relaxed skin tension lines.[63] Although such techniques reduce tension, they do not completely eliminate it.[64] Furthermore, mast cell function, VEGF, TGF-β1 along with various other cytokines in addition to alterations in fibroblast concentration are suggested to be of great importance in the process of wound healing.[13,65,66]

Many therapeutic strategies have been employed to improve the aesthetic result of scars.[66] Conventional management options include corrective surgery, intralesional corticosteroids and chemotherapeutic agents, topical applicators, cryotherapy, compression therapy, radiotherapy, topical silicone products, and laser/energy-based therapies.[15,54] To date, no consensus has been reached regarding the single best treatment due to an overall shortage of evidence-based information and a lack of understanding of the molecular mechanism of scar formation in addition to how each treatment modality can affect the process of scar formation.

BTXA is a potent neurotoxin derived from *C botulinum* that causes flaccid paralysis of striated muscle by inhibiting acetylcholine release at the neuromuscular junction and has been proposed as potential new therapy for scars. In 1973, ophthalmologist Dr Alan Scott pioneered the use of BTXA in humans with his first publication detailing the effects of the biochemical agent on rhesus monkeys.[67] Soon afterward, he published an article in 1980 concerning the injection of the toxin into humans.[68] In 1992, a team of ophthalmologists and dermatologists, known as the Carruthers, published the first comprehensive report detailing the cosmetic applicability of BTXA,[69] and today, it is the most commonly utilized cosmetic injectable for facial rejuvenation worldwide. For more than 30 years, its application has proven safe and effective for the treatment of a variety of disorders, including hyperfunctional facial lines and rhytids.[70] BTXA immobilizes local muscles and reduces skin tension caused by muscle pull, thus decreasing microtrauma and subsequent inflammation on the healing wound.[56] The reduction of the tensile force during the course of cicatrization and the potential regulation of the balance between fibroblast proliferation and cellular apoptosis may represent a novel therapeutic option for the aesthetic improvement of scars.[71] One goal of therapy in all patients with scars has been to eliminate dynamic tension on the healing tissues, to both improve wound healing and minimize scarring for optimal aesthetic results.[72] Dynamic tension caused by local muscle pull may be addressed by denervating the muscles pulling on a wound through a concept known as chemoimmobilization.[55]

As Gassner and colleagues previously discussed, the concept of immobilization in medicine is ancient and is firmly established for the treatment of fractures and soft tissue injuries.[55] A variety of devices have been developed for this purpose such as splints and casts, among others with the common objective of minimizing the effect of muscular contraction on healing tissues. Therefore, BTXA may eliminate unwanted muscle contraction adjacent to a healing wound to provide an ideal tension free environment.[55] Chemoimmobilization can be performed in a prophylactic manner prior to, or at the time of, an elective incision, or it can be employed to reduce tension adjacent to a partially or fully healed wound. As such, authors hypothesize that BTXA may assist in a prophylactic manner to prevent scar formation, but it may have an inhibitory effect on scar formation, as BTXA also appears to have an inhibitory effect on fibroblasts,[11] thereby offering another potential mechanism for producing a more satisfactory outcome for problematic scars.[73] In addition, reports have indicated that BTXA also has analgesic properties that are not yet completely understood, but may disrupt the neuropathic pain symptoms that are present in some painful scars.[74] The neurology literature has long reported successful BTXA treatment of pain, primarily attributable to the disruption of the pain-spasm-pain cycle.[75] It has been postulated that this anti-nociceptive activity may also be linked to possible anti-inflammatory effects; however, reports have been conflicting[75-78] and further studies need to be performed to determine whether BTXA does effect the modulation of pain.

As discussed in earlier sections of this paper, there are numerous in vitro and animal studies illustrating BTXA's inhibitory effects upon cytokines, growth factors, and fibroblast proliferation. Interestingly, intra-articular botulinum toxin has also been demonstrated to be useful in preventing arthrofibrosis in rabbits after transection of the anterior cruciate ligament.[79] Yet, there is also evidence to the contrary with Gauglitzs' findings of no in vitro effects of BTXA on

ECM markers, cell proliferation, TGF-β subtypes, collagen synthesis, or upon the metabolism of keloid fibroblasts. He also demonstrated no changes to the macroscopic appearance, morphology, or size of keloid scars in a human clinical study.[54] Thus, although reduction of tensile forces by prophylactic BTXA injection into the musculature adjacent to the respective wound might represent a comprehensible chemoimmobilization mechanism of action for the aesthetic improvement of scars, the suggested clinical efficiency of intralesional BTXA for the treatment of pre-existing hyeprtrophic or keloid scars remains uncertain.

As evidenced, BTXA may considered to be an innovative and efficient therapy for scars; however, its clinical effectiveness has not yet been established in large-scale randomized control trials. Although the accumulating clinical evidence is tipping the scales in favor of BTXA as a promising, safe, and relatively effective scar reduction modality, there are studies to the contrary and the evidence for its efficacy is not overwhelming. This is largely due to the heterogeneity of the current evidence with relatively low methodological quality and small, underpowered, study sample sizes. The optimal dosage, treatment timing, and frequency are also unclear. As seen in the clinical studies (Table 1), the dosage amount, frequency, and timing of BTXA injection vary significantly. Furthermore, there is uncertainty relating to the optimal injection location as some study groups focused on intralesional BTXA injection while others injected BTXA into the musculature adjacent to the wound. There are no studies that effectively evaluate BTXA dosage protocols, injection timing/frequency, and treatment efficacy based on the location of the injection, all areas that could be focused on in future studies.

The greatest obstacle to the widespread application of BTXA in preventing and controlling scars is the lack of understanding of the molecular mechanism of action of BTXA upon scars. In other words, the molecular mechanism of BTXA has not been clearly elucidated, nor has the exact molecular mechanism of hypertrophic and keloid scar development.[80] This may explain why there are numerous scar treatments available; yet, there are no accepted gold standards for the prevention and treatment of scars. Developing a better understanding of the pathophysiology of pathologic scarring holds great promise for developing novel therapeutic strategies such as BTXA. Furthermore, the cost of the scar treatment must be considered when providing treatment recommendations for an innovative therapy. For example, can BTXA provide enough perceivable benefit to a patient to warrant the additional cost over other potentially cheaper treatments such as triamcinolone acetonide? At this stage, we cannot directly answer this question based on the current literature presented, but we can offer the treatment as an option and inform our patients that 8 small blinded randomized control trials, 7 cohort studies, and 7 case series/reports have been produced and 20 of these studies were in favor of the use of BTXA.

## Conclusion and Future Directions

The efficacy of BTXA to reduce scars appears promising and the current literature favors its use over placebo controls as a safe treatment alternative; however, the degree of benefit this treatment modality provides in comparison with other accepted modalities remains to be explored. Further understanding of the molecular mechanism of action of BTXA upon scars and treatment cost comparisons should be considered in future studies. Of most importance, larger scale, randomized control trials of high methodologic quality, using objective measurement scales, must be produced to truly determine the efficacy of this innovative treatment.

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