Effects of Botulinum Toxin on Improving Facial Surgical Scars: A Prospective, Split-Scar, Double-Blind, Randomized Controlled Trial

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Background: Early intervention might improve the quality of surgical scars. Botulinum toxin type A has been shown to improve surgical scars in the past decade. The purpose of this study was to evaluate the effect of botulinum toxin type A on surgical facial scars.
Methods: In this prospective, split-scar, double-blind, randomized controlled trial, 16 consecutive patients who underwent facial surgery between June and October of 2015 were enrolled. Botulinum toxin type A was injected randomly into half of each surgical wound closure immediately after surgery. The scars were assessed independently by two plastic surgeons at a 6-month follow-up visit using the Vancouver Scar Scale and the visual analogue scale. The scar width was also measured.
Results: Fourteen patients completed the study. The visual analogue scale score and scar width measurements revealed a significant improvement in appearance and narrower scars for the botulinum toxin type A–treated halves of the scars ($p = 0.046$ and $p = 0.001$, respectively). The mean Vancouver Scar Scale score was 4.68 for the botulinum toxin type A–injected group and 5.24 for the control group ($p = 0.15$). In addition, the Vancouver Scar Scale height score was significantly different between the two groups ($p = 0.008$).
Conclusion: This study demonstrates that early postsurgical botulinum toxin injections can produce better, narrower, and flatter facial surgical scars. (*Plast. Reconstr. Surg.* 141: 646, 2018.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Facial scars associated with reconstructive and aesthetic surgery are always a great concern for patients and can have a destructive social-psychological impact.[1] Too many reports have focused on the treatment rather than the prevention of untoward surgical scars. However, early management of surgical scars is more likely to yield a better cosmetic appearance and require fewer treatments.[2]

Botulinum toxin type A is one of the most widely used medications for wrinkle reduction and facial contouring.[3] Botulinum toxin type A injections are also an effective and safe treatment for migraine headache, hyperhidrosis, blepharospasm, and strabismus.[4–7]

Recently, there has been increasing interest in the use of botulinum toxin type A for the

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management of fresh wounds and postsurgical scars.[8,9] However, significant individual differences in scar formation make it necessary to perform split-scar studies to ascertain whether botulinum toxin type A improves facial surgical scars. Therefore, we conducted this prospective, split-scar, double-blind, randomized controlled trial to investigate the safety and efficacy of early botulinum toxin type A injection into facial surgical scars.

PATIENTS AND METHODS

This prospective, split-scar, double-blind, randomized controlled study was approved by the Shanghai Ninth People's Hospital Institutional Review Board. The local ethics committee of our hospital approved this study, which conformed to the provisions of the Declaration of Helsinki.

Patient Sample Size

The sample size was calculated based on the literature published in 2014.[9] If treatment could improve the visual analogue scale score by 1.24, which was considered clinically significant, approximately 13 scars per group would have been necessary to provide a result with real significance (considering the standard type 1 α error of 0.01 and a power of 0.8). Assuming a 20 percent noncompliance rate for follow-up evaluation, the sample size was increased to 16 patients.

Patients and Randomization

Between June and October of 2015, 16 consecutive patients who underwent facial reconstructive surgery were enrolled. The original diagnoses included seven congenital melanocytic nevi, four port-wine stains, three disfiguring scars, and two arteriovenous malformations. The exclusion criteria included the following: (1) a known allergy to botulinum toxin; (2) previous injection of botulinum toxin within 6 months before enrollment; (3) myasthenia; and (4) Fitzpatrick skin type V to VI. A random-number generator was used to generate ones and zeroes, which designated left and right, respectively, or upper and lower, respectively.

Study Procedures

The postoperative scar was treated, with each side randomized to receive either botulinum toxin type A or 0.9% normal saline. Vials containing 100 U of botulinum toxin type A (Lanzhou Biochemical Company, Lanzhou City, People's Republic of China) were mixed with 2 ml of 0.9% saline. Only 0.9% saline was injected on the control side. Immediately after skin closure, the encoded vial contents (0.2 ml containing 10 U for each 1-cm scar) were injected at a distance of 5 mm on either side of the wound. The injections were intradermal during all of the procedures. All of the injections were performed by a single plastic surgeon (Y.J.).

Evaluation of Clinical Effect

At the 6-month follow-up appointment, two blinded plastic surgeons (Y.Q. and H.C.) were asked to separately make objective clinical assessments using the Vancouver Scar Scale and the visual analogue scale (from 0 to 10, with 0 = worst and 10 = best) score. At this visit, the surgeon (Y.Z.) recorded the scar width, which was measured as the mean of the widest and narrowest value, and patient-reported adverse events. Standardized digital photographs were taken at the same time.

Statistical Analysis

Continuous variables are reported as the mean ± SD. We longitudinally analyzed each aspect of the Vancouver Scar Scale score, visual analogue scale score, and width for each scar half between the botulinum toxin type A–treated and control groups using the paired t test. The interrater consistency was evaluated using the Spearman rho. All analyses were performed with IBM SPSS Version 23.0 (IBM Corp., Redmond, Wash.). A value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Fourteen of the 16 enrolled subjects (seven male patients and seven female patients) with 19 facial surgical scars completed this study, and the other two were lost to follow-up. The mean subject age was 12 years (range, 6 to 49 years). The mean scar length was 6.74 cm (range, 3 to 16 cm), and the average amount of botulinum toxin type A injected was 33.7 U (range, 15 to 80 U). (**See Table, Supplemental Digital Content 1**, which shows patient characteristics and treatment records. *BTA*, botulinum toxin type A, ***http://links.lww.com/PRS/C627***.) The interrater consistency showed that the Spearman rho was 0.713 for the Vancouver Scar Scale ($p < 0.001$) and 0.642 for the visual analogue scale ($p < 0.001$), which indicates high consistency between the two raters.

At the 6-month follow-up, the mean Vancouver Scar Scale score was 4.68 ± 2.34 for the botulinum toxin type A–treated half of the scar and 5.24 ± 2.55 for the control half; this difference was not statistically significant ($p = 0.146$). In the subset analysis, there was a significant difference in the Vancouver Scar Scale height score between the experimental

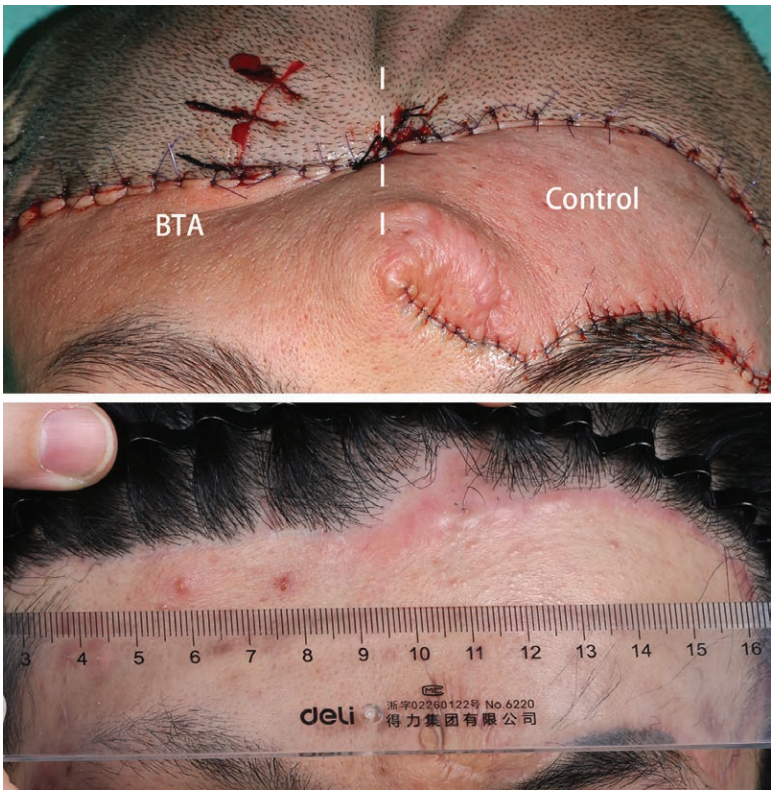

Fig. 1. Forehead hairline scar at baseline (*above*) and at 6-month follow-up (*below*). The right half of the scar was treated with botulinum toxin type A (*BTA*) and the left half was treated with 0.9% normal saline.

and control half scars (0.47 ± 0.56 versus 0.76 ± 0.77; $p = 0.009$). There was no significant difference in pigmentation, pliability, or vascularity between the two halves. (**See Table, Supplemental Digital Content 2**, which shows the Vancouver Scar Scale score, visual analogue scale score, and scar width for the botulinum toxin type A–treated side and the control side. *VSS*, Vancouver Scar Scale; *VAS*, visual analogue scale; *BTA*, botulinum toxin type A, ***http://links.lww.com/PRS/C628***.) At the 6-month follow-up, the mean visual analogue scale score was 5.76 ± 1.48 for the botulinum toxin type A–treated half of the scar and 4.97 ± 1.78 for the control half; this difference was significant ($p = 0.046$).

The scars were significantly narrower in the experimental group than in the control group at the 6-month follow-up (0.32 ± 0.15 mm versus 0.43 ± 0.15 mm; $p = 0.001$). Figures 1 and 2 are photographs of representative patients at the 6-month follow-up visit. No obvious adverse events were observed.

DISCUSSION

Multiple factors contribute to an undesirable scar, including the patient's ethnic background, the anatomical location of the incision, surgical techniques, and postoperative infections.[10] The present split-scar, double-blind, randomized controlled study demonstrated that the immediate postsurgical injection of botulinum toxin type A could improve the appearance of facial surgical scars and reduce their width and height. Our results prompted further questions about the use and efficacy of botulinum toxin type A for facial surgical scars, which we address below.

Injection Time and Dose

The surgical wound healing process involves multiple stages, including inflammation (immediate to 2 to 5 days), proliferation (2 days to 3 weeks), and tissue remodeling (3 weeks to 2 years).[2] In previous studies, botulinum toxin type A was injected at times that ranged from immediately before or after skin closure to 9 days after surgery.[8,9,11] Although Kim et al. presented excellent results for thyroidectomy scars on injection of botulinum toxin type A 6.6 days after surgery, botulinum toxin type A may be more beneficial in the very early stages of wound healing.[11] Therefore, we choose to inject botulinum toxin type A right after wound closure.

There is no consensus in the literature regarding the dosage of botulinum toxin type A for scars

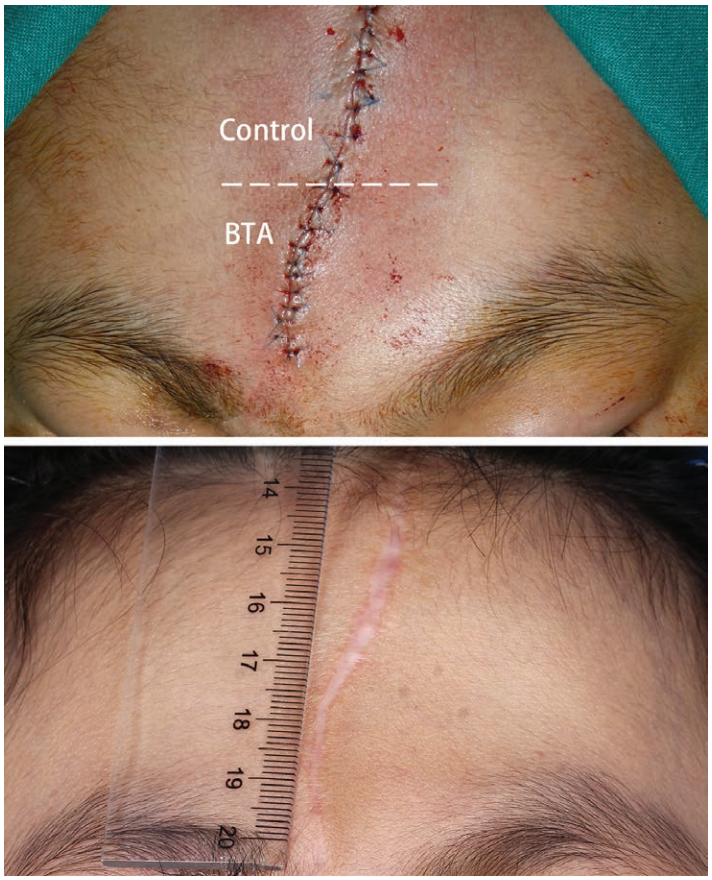

Fig. 2. Forehead longitudinal scar at baseline (*above*) and at 6 month follow-up (*below*). The lower half of the scar was treated with botulinum toxin type A (*BTA*) and the upper half was treated with 0.9% normal saline.

or wounds. We referred to a prospective, blinded, placebo-controlled trial that described a mean dose of 30 U for 2- to 4- cm forehead wounds, and simplified the dose to 10 U for each 1-cm scar.[8] Pascual-Pascual and Pascual-Castroviejo studied the safety of botulinum toxin type A in young children (younger than 2 years) and concluded that 6.55 U/kg was safe for obstetric brachial plexus palsy and cerebral palsy.[12] In our study, a much lower maximum dosage was used: 2.6 U/kg in patient 2, who was 7 years old.

Effect and Evaluation

In 1997, Choi et al. first reported that botulinum toxin type A prevented wound complications following eyelid reconstruction in 11 patients.[13] In 2006, a prospective, blinded, placebo-controlled study showed that botulinum toxin type A injection within 24 hours after closure of a forehead wound improved the eventual appearance of the scars.[8] Ziade et al. also reported similar results for botulinum toxin type A treatment of facial wounds.[1]

With regard to surgical scars, Wilson found that the outcome for facial scars after botulinum toxin type A injection during revision surgery was highly satisfactory.[14] Chang et al. demonstrated that botulinum toxin type A injections produced more aesthetic and narrower cheiloplasty scars at the 6-month follow-up assessment.[9] In 2014, Kim et al. published the first split-scar, double-blind, randomized controlled trial of botulinum toxin type A injection in 15 thyroidectomy scars. At the 6-month follow-up, a significant improvement was noted for the botulinum toxin type A–treated halves, with minimal changes in the control halves.[11] Our results are consistent with those of the previously mentioned studies.

In our study, the Vancouver Scar Scale score failed to detect a significant objective difference between the two groups, which was similar to that of the study by Chang et al.[9] This could be attributed to the fact that the traditional use of the assessment scale is for evaluating burn scars.

Potential Mechanism

The tension acting on the wound edges is a major factor in the unsightly appearance of scars.[1,3] Temporary muscular paralysis induced by

botulinum toxin type A could decrease movement and stress around a healing wound. This relief of tension may help prevent facial scar widening, hypertrophy, and hyperpigmentation.

Experimental studies revealed a greater population of botulinum toxin type A–treated fibroblasts in the G_0 to G_1 phase, and botulinum toxin type A could inhibit the expression of transforming growth factor-β1, a key component in the formation of hypertrophic scars.[15,16] Therefore, we speculate that the tension-relieving properties of botulinum toxin type A, together with its direct inhibitory effects on fibroblasts and transforming growth factor-β1 expression, finally contribute to a better appearance of facial surgical scars.

Limitations

There are several limitations to our study. First, the trial was small, with only 14 participating patients; studies with a larger sample size are necessary to confirm the results. Second, because the scar width may not be uniform throughout its length, we analyzed the mean value of the minimum and maximum widths, which may not have been an accurate representation of the entire scar.[17]

CONCLUSIONS

This study indicates that early postsurgical injection of botulinum toxin produces a better and narrower facial surgical scar. Our further studies may focus on the comparison of the effects of botulinum toxin type A on surgical scars in different injection planes and at different facial anatomical locations.

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