RESEARCH LETTERS

Botulinum toxin for depression: Does patient appearance matter?

To the Editor: Three prospective studies have now shown that onabotulinumtoxinA (BTA) injection to the corrugator and procerus forehead muscles can improve the symptoms of major depression.[1-3] A range of theories have been proposed to explain these effects, including:

1. BTA yields a cosmetic effect, which indirectly leads to improved mood;
2. More pleasant facial expression leads to positive social feedback with resultant mood improvement;
3. Decreased glabellar muscle activation decreases afferent nerve signals back to the brain, thereby decreasing "negative emotional feedback";
4. BTA itself reaches the brain, causing direct effects on emotional processing.

We hypothesized that if theories 1 or 2 were correct, that patients with more severe frown lines would have a greater response to BTA intervention.

We used deidentified data from the 3 randomized, double-blind, placebo-controlled trials on the treatment of depression using BTA (n = 134, 59 BTA and 75 placebo).[1-3] In each, the severity of maximum frown lines was measured on a 0-to-3 scale using the Clinical Severity Score of Glabellar Frown Lines (CSS-GFL), and depression was scored with the Beck Depression Inventory (BDI) before randomization occurred. These trials received prior approval from their hospital institutional review boards, which had been aware they planned to combine the data for this study in a deidentified manner. Each trial was registered under clinicaltrials.gov. Patients were prospectively recruited into these studies based on a history of depression, not for the cosmetic treatment of wrinkles. The severity of frown lines at baseline varied across the 3 studies.

Our primary outcome was looking for an association between baseline CSS-GFL score and a change in BDI score (model 1). This was analyzed using a regression coefficient of analysis of covariance linear mixed model with both continuous and discrete variables. A random effect was added to account for the data coming from a meta-analysis of 3 different studies. Our secondary outcomes were comparing baseline CSS-GFL score and baseline BDI score (model 2), and change in CSS-GFL score with change in BDI score (model 3). Each model was performed on both placebo and BTA-treated subjects, and adjusted for age, sex, initial CSS-GFL scores, initial depression scores, and treatment.

Results are shown in Table I. Detailed regression results are available online in Supplemental Table I (available at http://www.jaad.org). Our findings for model 1 contradict the initial hypothesis proposed: pretreatment frown line severity (CSS-GFL) was inversely correlated with improvement in depression after treatment (on BDI). More severe frown lines at baseline were not predictive of having better antidepressive response to BTA.

Model 2 revealed that more severe frown lines at baseline was not predictive of having worse

Table I. Correlation between Clinical Severity Score of Glabellar Frown Lines scores and Beck Depression Inventory scores for both placebo and onabotulinumtoxinA after adjusting for age, sex, and initial Beck Depression Inventory score

Model	Coefficient	*P* value	95% CI
1: Baseline CSS-GFL compared with change in BDI score; regression coefficient of ANCOVA linear mixed model	−1.91	.024	(−3.57 to −0.25)
2: Correlation coefficient of baseline CSS-GFL score compared with baseline BDI score	−0.21	.015	(−0.37 to −0.04)
3: Correlation coefficient of change in CSS-GFL score compared with change in BDI score	−0.13	.19	(−0.33 to 0.07)

Change in BDI score for every 1-U increase in baseline CSS-GFL score, after adjusting for other factors. Statistical analysis done using linear regression models with random effects.

ANCOVA, Analysis of covariance; *BDI*, Beck Depression Inventory; *CI*, confidence interval; *CSS-GFL*, Clinical Severity Score of Glabellar Frown Lines.

depression at baseline; the presence or absence of frown lines cannot be used as a measure of baseline depression severity. Model 3 showed no significant association between visible improvement in frown scores and improvement in depression scores.

These findings debunk theories 1 and 2 above. This is in line with studies that have shown that patients without any baseline frown lines can have remission of depression after BTA,[1] depression improvement from BTA outlasts the cosmetic effects,[2] and that antidepressive effects are present even in individuals who dislike the cosmetic effects of BTA.[3] Simply put, people do not feel better solely because they look better.

Magnetic resonance imaging studies have shown that BTA treatment of corrugators impacts brain areas involved with emotion-processing by decreasing afferent signals from facial muscles.[4]

A recent study showed that patients who received BTA in crow's feet (ie, suppressing "smile muscles") had worsening depression scores.[5] In this case, perhaps, nerve feedback affected the brain in the opposite manner. In addition, the study argues against theory 4, because patients treated with BTA in the glabella and crow's feet had opposite effects on their depression scores. Or perhaps, BTA injected at different peripheral regions may reach different areas of the brain, which may be crucial in the direction of mood change. In rat models, BTA injected into the whisker pad was found in the facial nucleus of the brain, whereas BTA into the optic tectum was found in the retina and striate cortex. No human studies tracing peripheral BTA to its final destination have been done.[6]

This study suggests that an individual with major depression may not need visible frown lines to experience antidepressive benefit from glabellar BTA therapy, although a placebo-controlled trial is needed to confirm. In addition, the improvement in frown lines (or lack thereof) does not predict degree of depression response.

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Preliminary data from this paper were presented at the Texas Dermatological Society Meeting in Austin, Texas on May 1, 2015.

The studies upon which the data used in this article are based was approved by the Seton Family of Hospitals institutional review board (IRB) (Dr Magid), the Quorum Review IRB (Dr Finzi), and the Ethics Committee of Basel (Dr Wolmer). Each trial was registered under clinicaltrials.gov under study numbers NCT01392963, NCT 01556971, and NCT00934687, respectively.

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A randomized, controlled, prospective clinical study comparing a novel skin closure device to conventional suturing

To the Editor: A novel wound closure device (Zipline 3 system, ZipLine Medical, Inc, Campbell, CA) is a noninvasive surgical skin closure device designed to provide a faster but reliable closure of surgical incisions with comparable aesthetic results to conventional suturing. The system is an adhesive, single-use, sterile closure device applied after placing dermal sutures. A releasable, ratcheting device tightens to reapproximate the wound edges for optimal healing (Fig 1).

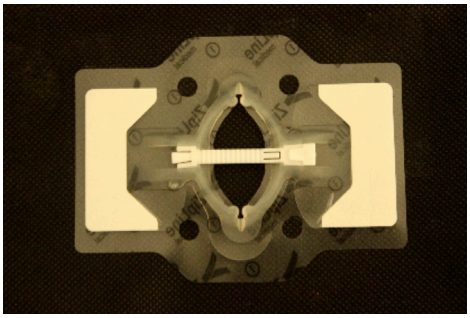

Fig 1. The Zipline 3 System.

An IRB-approved, evaluator-blinded, randomized, prospective study was performed at the Mt Sinai School of Medicine Division of Dermatologic Surgery of patients undergoing excision for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or dysplastic nevi of the trunk or extremities. The study was divided into 3 arms: 2 treatment arms of the closure device with and without dermal suturing, as well as a control group of nylon suturing in interrupted fashion with dermal suturing. Patients with facial or high-tension incision sites and those with comorbid conditions, taking medications, or with skin disorders affecting wound healing were excluded.

Twenty patients (mean age, 51.17 ± 14.9 years) with BCC, SCC, or dysplastic nevi of the trunk (n = 14) or extremities (n = 6) were enrolled in the study. Seventeen patients (11 males, 6 females) completed all study end points; 3 patients withdrew before the 3-month follow-up. Patients were randomized to the control (n = 8) or treatment group (n = 9). All surgeries were performed by 1 investigator (HK). The mean final incision length was 3.06 ± 0.38 cm (range 2 to 3.5 cm). The primary aesthetic outcome was the average rating of 3 investigators using a 10-point visual analog scale and high-resolution photographs at 3 months postoperatively.[1,2] The mean cosmetic rating for the suture-repaired defects equaled 8.5 ± 1.02 (n = 8) compared with 8.5 ± 1.14 (n = 9) for device-repaired defects; the difference was not statistically significant (P = 1). Secondary outcomes were time required for wound reapproximation and time required for device or suture removal. Time required for device placement equaled 1.83 ± 1.05 minutes compared with 3.88 ± 1.3 minutes for epidermal suturing the defects (P = .001). Device removal required 8.2 ± 1.16 seconds compared with 58.1 ± 14.9 for suture removal ($P < .001$). In the first arm, no adverse events were reported. The second arm was dropped after dehiscence in the first patient, deeming closure with the device alone unreliable. We found no significant difference in the cosmetic appearance of the scar at the 3-month follow-up (Fig 2). Finally, reapproximating the epidermis with the device took less time than suturing, as did device removal compared to suture removal. The device may also be removed by the patient, obviating the need for a return visit.

In conclusion, this novel wound closure device may be used for epidermal approximation of low-tension, linear wound closures on the trunk or extremities after dermal suturing. The device plus dermal suturing is more efficient with equivalent aesthetic results compared to conventional suturing, without increasing complication rates in this small sample.[3] Cost benefit analysis was not performed; the retail price is $40 with a comparable shelf life to suture.

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Supplemental Table I. Detailed regression results of linear mixed model for Beck Depression Inventory score change

Fixed effects	Estimate	SE	*t* value	*P* value
(Intercept)	3.98	4.75	0.84	.4027
Intervention	7.59	1.37	5.55	<.0001
Baseline BDI	0.48	0.08	6.35	<.0001
Age	−0.14	0.07	−2.03	.0424
Male	−5.25	2.20	−2.39	.0168
Baseline CSS-GFL score	−1.91	0.85	−2.26	.0239
Random effects	Variance			
Study	1.69	1.30		
Residual	57.35	7.57		

BDI, Beck Depression Inventory; *CSS-GFL*, Clinical Severity Score of Glabellar Frown Lines.