Donor Site Aesthetic Enhancement With Preoperative Botulinum Toxin in Forehead Flap Nasal Reconstruction

Jonathan Zelken, MD, Shih-Yi Yang, MD, Chun-Shin Chang, MD, Cheng-Jen Chang, MD, PhD, Jui-Yung Yang, MD, Shiow-Shuh Chuang, MD, Hung-Chang Chen, MD, and Yen-Chang Hsiao, MD

Background: Donor site scarring after forehead flap nasal reconstruction is acceptable. However, as aesthetic outcomes standards for cosmetic and reconstructive surgery merge, we aim to enhance results. We recently demonstrated the cosmetic benefit of botulinum toxin type A (BTX-A) for cleft lip cheiloplasty outcomes. We hypothesize that similar mechanism(s) benefit forehead flap donor scars.

Methods: A single surgeon performed 26 forehead flap reconstructions. Indications were cancer ($n = 17$), trauma ($n = 3$), and congenital deformity ($n = 6$). In this split-scar study half the forehead was pretreated with BTX-A and half with normal saline after random assignment. Photographs were evaluated at most recent follow-up. Scar evaluation was based on photographs by 3 plastic surgeons using a composite subjective visual analogue score (VAS).

Results: Photographic follow-up was 27 months (range, 10–60 months). Botulinum toxin type A was assigned to the upper forehead in 16 cases and lower forehead in 10 cases. Intrarater reliability among 4 evaluators of 104 VAS scores was 78.1%. Upper forehead VAS (7.9 ± 1.2) was not different than lower forehead VAS (7.9 ± 1.2) regardless of treatment ($P = 0.62$). The VAS score of BTX-A–treated scars (8.5 ± 1.0) was significantly higher than the control (7.3 ± 1.1; $P < 0.0001$). Among 104 individual comparisons (26 patients × 4 observers), there were 73 instances (70.2%) where the experimental VAS score was higher than the control.

Conclusions: Preoperative BTX-A injection is feasible and enhances donor site scar appearance after forehead flap nasal reconstruction in an Asian population.

Key Words: botulinum toxin, wound, rhinoplasty, scar, forehead flap, Asian, reconstruction

(*Ann Plast Surg* 2015;00: 00–00)

The nose is a psychologically significant central facial structure that can be challenging to reconstruct due to the quality and quantity of tissue required. When local flaps and grafts are inadequate, the forehead is a superb option for dorsal resurfacing because of its reliability and likeness to dorsal skin. Judicious forehead tissue harvest is advocated; despite its status as a privileged healing site,[1] unfavorable scarring is common after both primary and secondary healing.[2,3] Excellent forehead healing can be achieved in Asian patients,[4] but we have observed poor results as well.

At this center, the reconstructive goal is restoration of normal appearance. We routinely draw from our cosmetic armamentarium as aesthetic and reconstructive standards merge. For example, scar prevention and management strategies are the same whether elective surgery or reconstruction was performed, and include silicone gel sheeting, pressure therapy, and laser therapy. Botulinum toxin is a historically lethal neurotoxin produced by *Clostridium botulinum* that is widely marketed as a cosmetic paralytic agent.[5] Botulinum toxin type-A (BTX-A) has been extensively studied and is routinely used in aesthetic medicine. Its role in reconstructive scar prophylaxis, such as for the donor site of a forehead flap, has yet to be determined.

Galárraga and Tollefson et al[6,7] injected BTX-A before and during cleft lip repair and demonstrated its feasibility and efficacy. In 2014, Chang et al[8] demonstrated subjectively noticeable cleft lip scar width reduction at this center when perioperative, periwound BTX-A was injected. The same year, Kim et al[9] demonstrated the benefit of BTX-A for fresh thyroidectomy scars. Wound tension, fibroblast proliferation, and transforming growth factor-β_1 expression are likely contributors to fibrosis and hypertrophic scar formation. Botulinum toxin type A modulates these processes and has demonstrated improved cosmetic outcomes animal and human models.[10–17] We aim to investigate the role of selective paralysis by BTX-A on the forehead donor site before forehead flap nasal reconstruction.

PATIENTS AND METHODS

This blinded, randomized, prospective, comparative split-scar study was designed to investigate the effect of frontalis chemodenervation by BTX-A before forehead flap nasal reconstruction affected the quality of the scar. The Institutional Review Board approved the study. Twenty-six ethnically Asian patients (mean age, 53.5 years, range, 9–82 years; Fitzpatrick skin Type II–IV) were enrolled. Table 1 summarizes patient demographics. There were 10 men and 16 women. The senior author performed every reconstruction in this series with consistent harvest and closure technique. Indications for forehead flap nasal reconstruction included post-extirpative reconstruction for malignancy (n = 17), post-traumatic reconstruction (n = 3), and congenital nasal deformity (n = 6). Four of the patients (15.4%) had preoperative radiation therapy. Thirteen patients (50%) had wounds that were closed in part by secondary intention. Thirteen wounds left to heal by secondary intention were 4.3 ± 3.0 cm long and 4.6 ± 2.8 cm wide.

Treatment Randomization and Protocol

Before the 26 consecutive reconstructions, patients were enrolled with the following criteria: forehead flap reconstruction, and valid written informed consent provided for surgery and trial inclusion. Exclusion criteria were nonconsenting patients or legal guardians, and egg allergy. Patients included in this study had at least 6 months' photographic follow-up. Every operation was performed at this hospital. A qualified nurse who was independent of this study randomly assigned which half of the wound would receive experimental (BTX-A) or control (saline placebo) treatment using secure randomization envelopes. Patients, investigators and other study personnel were blinded to which half of the scar was treated with BTX-A or saline treatment (Fig. 1). The frontalis muscle was injected accordingly 10 days before the first stage of forehead flap surgery. Encoded treatment vials were prepared. Experimental group vials contained BTX-A in preservative-free normal saline (100 units of BTX-A [BOTOX; Allergan, Irvine, CA] per 2.5 cc saline). Vehicle-control group vials contained the same volume of normal saline. Each treatment half had 10 injection sites of 0.05 cc/site, amounting to 2 units BTX-A per site or 20 units overall in the experimental half.

Operative Technique

Forehead flap reconstruction was performed under general anesthesia. Conventional methods were followed after appropriate oncologic,

Received May 6, 2015, and accepted for publication, after revision July 21, 2015.
From the Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taipei, Taiwan.
Conflicts of interest and sources of funding: none declared.
Reprints: Yen-Chang Hsiao, MD, Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital, 5, Fu-Hsing Street, Kweishan, Taoyuan 333, Taiwan. E-mail: nosehsiao@gmail.com.

ISSN: 0148-7043/15/0000–0000
DOI: 10.1097/SAP.0000000000000625

TABLE 1. Patients' Information

		Distribution		
	Overall	BTX-A: Upper	BTX-A: Lower	P*
No. patients, *n* (%)	26	16 (61.5)	10 (38.5)	
Age, y	53.5 ± 20.4	54.1 ± 23.2	52.6 ± 15.9	NS
Virgin forehead, *n* (%)	24 (92.3)	15 (93.8)	9 (90)	NS
Indication, n (%)				
Neoplasm	17 (65.4)	11 (68.8)	6 (60)	NS
Trauma	3 (11.5)	2 (12.5)	1 (10)	NS
Congenital	6 (23.1)	3 (18.8)	3 (30)	NS
Radiation, n (%)	4 (15.4)	2 (12.5)	2 (20)	NS
Secondary healing, n (%)	13 (50)	8 (50)	8 (50)	NS

*P value < 0.05 was considered significant.

Virgin forehead indicates no previous forehead flap; NS, no significant difference.

and wound control was obtained. Donor sites followed the supratrochlear arterial axis and were closed primarily in the first stage when possible; resultant open wounds healed by secondary intention. The base of the pedicle was less than 1.5 cm wide in all cases, often closer to 1.2 cm, allowing for easy closure in the lower forehead. In subsequent stages soft tissue refinement was supplanted by cartilaginous reconstruction. Pedicle division was accomplished in the final stage. Primary wound closure was consistent in each case, and included: adequate undermining, three-layer closure with 3-0 and 4-0 polyglycolic acid suture (Dexon) and 6-0 Nylon. Nylon sutures were removed on postoperative day 5 and replaced with porous medical-grade paper tape (Micropore; 3M, St. Paul, MN). Scar massage was encouraged but not enforced. For the purposes of this study, silicone gel and sheet application was prohibited. Complications including wound dehiscence, infection, necrosis, and hematoma were documented if they occurred.

Evaluation

Photographs were taken using same patient positioning, camera setting, and lighting conditions at every visit by a professional medical photographer. Four independent, blinded, and qualified nontreating plastic surgeons evaluated the cosmetic outcome obtained at the most recent follow-up examination. Patients with less than 6 months of follow-up were not included. Scars were scored using a subjective scale (visual analogue scale, VAS) ranging from 0 (worst possible) to 10 (best possible) and evaluators were instructed to account for pigmentation, width, and contour in their score. The vertical midpoint of the forehead was the interface of the treatment and control areas. Evaluators were instructed evaluate 5 mm above and below the midpoint of the linear scar. In wounds that healed partially by secondary intention, only the linear scar component that resulted from primary closure was evaluated (Fig. 2).

Comparisons and Analysis

Upper and lower scores for every patient were obtained for 4 evaluators and inter-rater reliability was estimated with the 2-way random intraclass coefficient (ICC) for consistency (Cronbach α). All analyses were performed using SPSS Version 22.0 (SPSS, Inc., Chicago IL), and significance was established at P less than 0.05. The VAS scores for the upper and lower forehead were compared, and for the control and experimental forehead using the paired samples, t test. The independent samples t test was used to determine if there was a significant difference in VAS score for patients treated with radiation therapy and who healed by secondary intention, or if there was a difference in treatment benefit. A 1-way analysis of variance was calculated on ratings. All data were evaluated using SPSS software (SPSS, Inc., Chicago, Ill. Version 22.0). Statistical significance was established with values of P less than 0.05.

RESULTS

Average photographic follow-up for 26 patients was 27.0 ± 15.4 months (range, 10–60 months). No hematoma, wound dehiscence, or infection was reported. Cronbach α for the ICC, an estimate of inter-rater reliability for the 4 raters, was 0.781. Table 2 summarizes the results of scar evaluation. The average upper forehead VAS score (regardless of treatment) was 7.9 ± 1.2, the average lower forehead score was 7.9 ± 1.2; there was no difference (P = 0.62). The average VAS score of experimentally pretreated scars (8.5 ± 1.0) was significantly higher than the VAS score of scar tissue pretreated with saline (7.3 ± 1.1, P < 0.0001). There were 104 comparisons made between experimental and control groups (26 patients × 4 scores). Overall, 73 comparisons (70.2%) favored experimental regions pretreated with neurotoxin, 10 comparisons favored the control group (9.6%), and ratings were no different between groups in 21 (20.2%). Average VAS score was not different in patients treated with radiation (P = 0.402) or left to heal by secondary intention (P = 0.383). Patients with wounds closed primarily demonstrated a slightly higher improvement (1.3 point difference) than those with

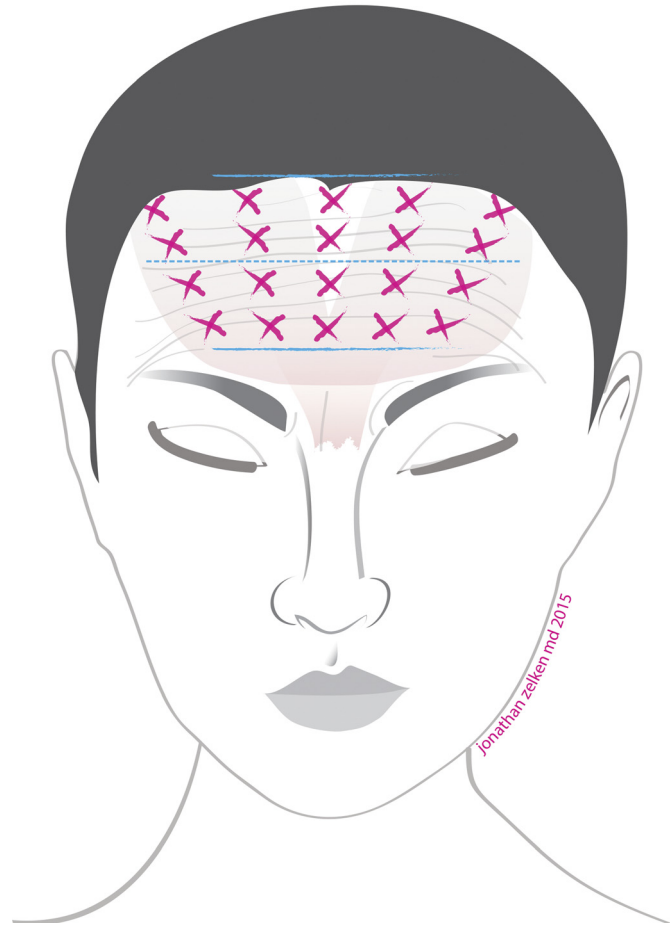

FIGURE 1. In each case, BTX-A pretreatment is randomly assigned to the upper or lower half of the forehead. The vertical extent of the frontalis (blue solid lines) and the midpoint (blue dashed line) was marked along the width of the frontalis. Ten aliquots of BTX-A (experimental) or normal saline (control) were evenly injected into the appropriate region (pink x marks) preoperatively. The technique is just as we would do for elective frontalis chemodenervation. Figure 1 can be viewed online in color at www.annalsplasticsurgery.com.

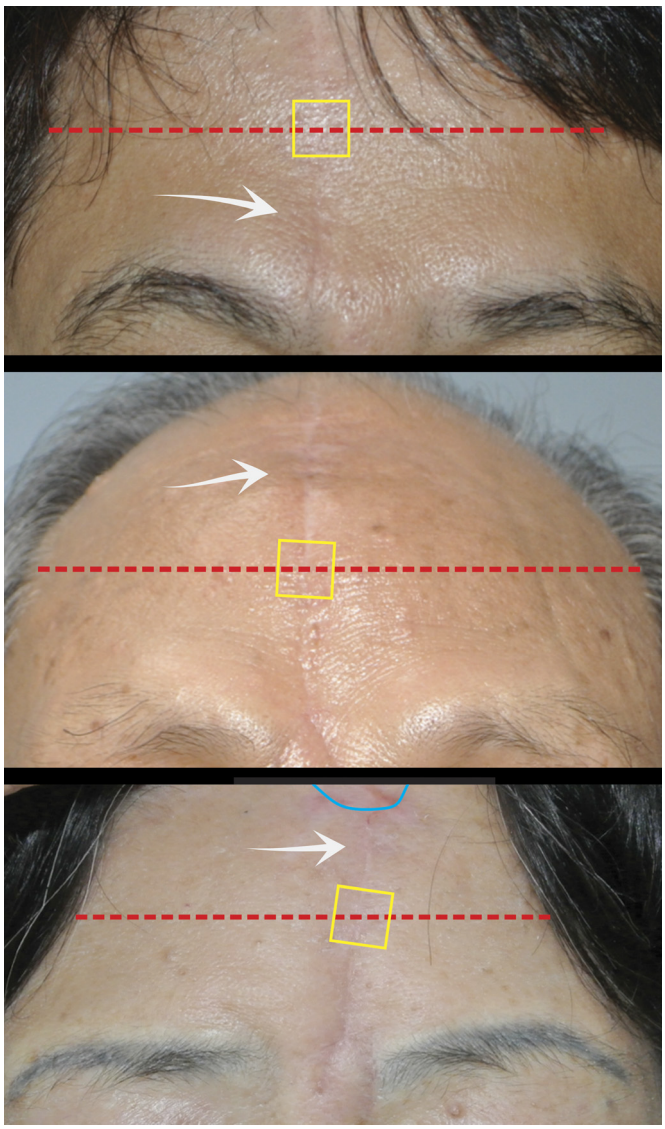

FIGURE 2. Evaluation methodology. The midpoint of the frontalis is marked (red dotted line) and a 1 cm margin is excluded from analysis at the interface (yellow boxes). Evaluators were instructed to consider width, contour, and color when scoring. The white arrows represent the area pretreated with BTX-A (lower half in upper panel; upper half in center, lower panels). In cases where primary closure was not obtained (lower panel, blue line), only the intervening linear scar was considered for evaluation. Figure 2 can be viewed online in color at www.annalsplasticsurgery.com.

secondary closure (0.9 point difference) when BTX-A was administered, although this was not significant ($P = 0.09$). Botulinum toxin type A was injected into the upper forehead in 16 cases (61.5%) and lower forehead in 10 cases (38.5%). Results of 1-way analysis of variance revealed that VAS score did not change whether the experimental group was the upper or lower scar ($F[1, 102\} = 0.533$, $P = 0.467$ [r = 0.07]).

DISCUSSION

Donor site scarring is generally acceptable after forehead flap reconstruction, but good-to-excellent outcomes should not be expected after every operation, and there may be room for improvement.[2,3] Aesthetics and donor site morbidity have become critical considerations in reconstruction; this is particularly relevant for the face. At this center, we aim to restore normal or supra-normal appearance, drawing from advances in reconstructive and aesthetic medicine. Clinically relevant cosmetic improvement in facial scars treated with neurotoxin has been demonstrated. To our knowledge, this study is the first randomized, placebo-controlled, prospective trial to investigate the effect of neurotoxin on forehead donor site wounds and the first split-scar neurotoxin study. Our data corroborate previous series by demonstrating a favorable influence on donor site cosmesis.

Botulinum toxin type A was explored in animal and human studies as a scar treatment and prophylaxis and demonstrated improved outcomes, but the mechanism is incompletely understood.[6–8,10–17] Wound tension promotes fibroblast activation, collagen expression, inflammatory cell infiltration, and transforming growth factor-β_1 expression.[18,19] It is likely that BTX-A plays a role in reducing wound tension by deactivating the underlying musculature. Alternatively, neurotoxin-induced smooth muscle relaxation might enhance periwound perfusion or minimize trophic effects and secretomotor function.[20–24] It is also possible that frontalis immobilization has a splinting effect that reduces pain, and enhances perfusion, by minimizing wound movement.

The cons of therapy are limited and include pain during injection and treatment cost. Functionally, frontalis deactivation is unlikely to impact quality of life; elective chemodenervation is routinely performed to efface wrinkles. Botulinum toxin type A is widely available and carries a favorable safety profile with frontalis injection. The BTX-A administration is simple and can be performed in little time.

Research participants were exclusively of Asian ethnicity. Despite variations in flap design and size, the same operation was performed in every case with uniform wound closure technique by one surgeon. Split-scar studies allow for direct comparison of treatment outcomes in a single individual. All these characteristics are expected to reduce bias and facilitate reliable data. Preoperative BTX-A injection resulted in perioperative frontalis paralysis, providing immediate therapeutic effect and eliminating any potential influence of early movement on experimentally treated areas. Preoperative BTX-A injection also eliminated the influence of surgery (inflammation, irrigation, local anesthetic, and vasoconstrictor) on therapeutic uptake.

Scars were evaluated on the basis of digital photographs using a VAS scoring system. The Vancouver Scar Scale is more comprehensive and incorporates characteristics, such as pliability, vascularity, and scar height. In our previous study of the BTX-A effect on cheiloplasty, VAS improved significantly, whereas there was no difference in Vancouver Scar Scale[25]; the implications of that disparity are unclear. We feel a subjective scoring system like the VAS reflects the way the face is evaluated in real life. Humans neither subconsciously nor consciously measure parameters or palpate tissue when we confront a patient; there is inherent subjectivity in the way we perceive a scar. For example, 1 person may be more influenced by width than color, and other contour and color than width. Qualified surgeons are no exception, and this is evidenced by our results. Four independent raters identified a significant difference between experimentally pretreated and control tissue. Intrarater agreement was reassuring; an ICC of 78.1% suggests that the focus group and the scores assigned were reliable and consistent. There was a VAS score improvement of 1.2 points. Although the difference was statistically significant, we cannot say whether that improvement is clinically relevant.

There are other limitations of this study. Because we studied a predominantly Taiwanese cohort, our results may not be relevant to other races or nationalities. We did not control for important characteristics, such as skin type, age, and flap size. We could not control for neurotoxin diffusion. Though we avoided scar evaluation within 1 cm of the treatment threshold, the influence of upper forehead paralysis on the lower wound, and vice versa, was unpredictable. Despite random assignment, there was an unequal distribution of experimental and control groups, as the upper forehead was treated 62% of the time.

TABLE 2. Results

	Overall	Experimental	Control	*P**
VAS	7.9 ± 1.2	8.5 ± 1.0	7.3 ± 1.1	<0.0001
	Overall	**BTX-A: Upper**	**BTX-A: Lower**	***P***
n =	26	16 (61.5%)	10 (38.5%)	
Composite VAS_E	8.5 ± 1.0	8.4 ± 1.0	8.6 ± 1.0	0.473
Composite VAS_C	7.3 ± 1.1	7.3 ± 1.1	7.3 ± 1.2	0.935
Benefit (VAS_E-VAS_C)		1.1 ± 1.3	1.2 ± 1.4	0.55
		Radiation Therapy	**No Radiation Therapy**	***P***
n =		4	22	
Average VAS		7.4 ± 0.4	8.0 ± 0.5	0.402
Benefit (VAS_E-VAS_C)		1.0 ± 1.8	1.1 ± 1.2	0.687
		Primary Healing	**Secondary Healing**	***P***
n =		13	13	
Average VAS		7.9 ± 0.6	7.9 ± 0.5	0.383
Benefit (VAS_E-VAS_C)		1.3 ± 1.1	0.9 ± 1.5	0.093
Comparisons, 4 Evaluators × 26 Patients (n = 104)				
$VAS_E > VAS_C$		73 (70.2%)		
$VAS_E = VAS_C$		21 (20.2%)		
$VAS_E < VAS_C$		10 (9.6%)		

*P value < 0.05 was considered significant.

VAS_E indicates experimental VAS; VASc, control VAS.

Although increased glabellar musculature and vector forces in the lower forehead might respond to BTX-A differently than the upper forehead, the data suggest that treatment of the upper or lower forehead did not influence the VAS or effect of BTX-A.

We investigated botulinum toxin injection as an adjunctive preoperative intervention that might further improve donor site scarring after forehead flap nasal reconstruction. Despite study limitations, the treated half of the donor site scar was scored higher for cosmetic appearance than the control half in the majority of cases by four independent, blinded reviewers.

CONCLUSIONS

Preoperative BTX-A injection in the frontalis is safe, feasible, well tolerated, and enhances donor site scar appearance after forehead flap nasal reconstruction in an Asian population.

REFERENCES

1. Zitelli JA. Secondary intention healing: an alternative to surgical repair. *Clin Dermatol*. 1984;2:92–106.
2. Deutsch BD, Becker FF. Secondary healing of Mohs defects of the forehead, temple, and lower eyelid. *Arch Otolaryngol Head Neck Surg*. 1997;123:529–534.
3. Becker GD, Adams LA, Levin BC. Mohs wounds of the forehead: healing by secondary intention. *J Wound Care*. 1998;7:497–500.
4. Han DH, Mangoba DC, Lee DY, et al. Reconstruction of nasal alar defects in Asian patients. *Arch Facial Plast Surg*. 2012;14:312–317.
5. Eleopra R, Tugnoli V, Quatrale R, et al. Different types of botulinum toxin in humans. *Mov Disord*. 2004;19(suppl 8):S53–S59.
6. Galárraga IM. Use of botulinum toxin in cheiloplasty: a new method to decrease tension. *Can J Plast Surg*. 2009;17:e1–e2.
7. Tollefson TT, Senders CM, Sykes JM, et al. Botulinum toxin to improve results in cleft lip repair. *Arch Facial Plast Surg*. 2006;8:221–222.
8. Chang CS, Wallace CG, Hsiao YC, et al. Botulinum toxin to improve results in cleft lip repair. *Plast Reconstr Surg*. 2014;134:511–516.
9. Kim YS, Lee HJ, Cho SH, et al. Early postoperative treatment of thyroidectomy scars using botulinum toxin: a split-scar, double-blind randomized controlled trial. *Wound Repair Regen*. 2014;22:605–612.
10. Flynn TC. Use of intraoperative botulinum toxin in facial reconstruction. *Dermatol Surg*. 2009;35:182–188.
11. Gassner HG, Brissett AE, Otley CC, et al. Botulinum toxin to improve facial wound healing: a prospective, blinded, placebo-controlled study. *Mayo Clin Proc*. 2006;81:1023–1028.
12. Gassner HG, Sherris DA, Friedman O. Botulinum toxin-induced immobilization of lower facial wounds. *Arch Facial Plast Surg*. 2009;11:140–142.
13. Gassner HG, Sherris DA, Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. *Plast Reconstr Surg*. 2000;105:1948–1953.
14. Sherris DA, Gassner HG. Botulinum toxin to minimize facial scarring. *Facial Plast Surg*. 2002;18:35–39.
15. Wilson AM. Use of botulinum toxin type A to prevent widening of facial scars. *Plast Reconstr Surg*. 2006;117:1758–1766.
16. Ziade M, Domergue S, Batifol D, et al. Use of botulinum toxin type A to improve treatment of facial wounds: a prospective randomised study. *J Plast Reconstr Aesthet Surg*. 2013;66:209–214.
17. Choi JC, Lucarelli MJ, Shore JW. Use of botulinum A toxin in patients at risk of wound complications following eyelid reconstruction. *Ophthal Plast Reconstr Surg*. 1997;13:259–264.
18. Lee BJ, Jeong JH, Wang SG, et al. Effect of botulinum toxin type a on a rat surgical wound model. *Clin Exp Otorhinolaryngol*. 2009;2:20–27.
19. Wang L, Tai NZ, Fan ZH. Effect of botulinum toxin type A injection on hypertrophic scar in rabbit ear model. *Zhonghua Zheng Xing Wai Ke Za Zhi*. 2009;25:284–287.
20. Neumeister MW. Botulinum toxin type A in the treatment of Raynaud's phenomenon. *J Hand Surg Am*. 2010;35:2085–2092.
21. Neumeister MW, Chambers CB, Herron MS, et al. Botox therapy for ischemic digits. *Plast Reconstr Surg*. 2009;124:191–201.
22. Schweizer DF, Schweizer R, Zhang S, et al. Botulinum toxin A and B raise blood flow and increase survival of critically ischemic skin flaps. *J Surg Res*. 2013;184:1205–1213.
23. Liu RK, Li CH, Zou SJ. Reducing scar formation after lip repair by injecting botulinum toxin. *Plast Reconstr Surg*. 2010;125:1573–1574; author reply 1575.
24. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. *Plast Reconstr Surg*. 2009;124:275e–277e.
25. Chang CS, Wallace CG, Hsiao YC, et al. Botulinum toxin to improve results in cleft lip repair: a double-blinded, randomized, vehicle-controlled clinical trial. *PLoS One*. 2014;9:e115690.