

Effect of Botulinum Toxin Pretreatment on Laser Resurfacing Results

A Prospective, Randomized, Blinded Trial

Marc S. Zimpler, MD; John B. Holds, MD; Mimi S. Kokosha, MD; Dee Anna Glaser, MD; Stephen Prendiville, MD; Christopher S. Hollenbeah, PhD; J. Regan Thomas, MD

Background: Facial laser resurfacing and chemodenervation with botulinum toxin type A are used independently as means of nonsurgical facial rejuvenation. Recent reports in the literature have described combining these 2 therapies, claiming improved and longer-lasting laser resurfacing results. To date, no scientific investigation has been undertaken to prove or disprove this theory.

Design: Institutional review board—approved, prospective, randomized, blinded study at university-affiliated outpatient cosmetic surgery offices.

Intervention: Patients had one side of their face injected, at specific anatomic subsites (crow's feet, horizontal forehead furrows, and glabellar frown lines), with botulinum toxin 1 week before laser resurfacing. After receiving an injection, patients underwent cutaneous laser exfoliation on both sides of the face with either a carbon dioxide or an erbium dual-mode laser.

Main Outcome Measures: Patients' injected (experimental) and noninjected (control) sides were compared after laser resurfacing. Follow-up was documented at 6 weeks, 3 months, and 6 months after laser resurfacing. Subjective evaluation,

based on a visual analog scale, was performed in person by a blinded observer. Furthermore, a blinded panel of 3 expert judges (1 facial plastic surgeon, 1 oculoplastic surgeon, and 1 cosmetic dermatologist) graded 35-mm photographs taken during postoperative follow-up visits.

Results: Ten female patients were enrolled in the study. A 2-tailed t test showed that all sites that were pretreated with botulinum toxin showed statistically significant improvement (P.05) over the nontreated side, with the crow's feet region showing the greatest improvement. Comparing results between the carbon dioxide and erbium lasers did not result in any statistically significant differences.

Conclusions: Hyperdynamic facial lines, pretreated with botulinum toxin before laser resurfacing, heal in a smoother rhytid-diminished fashion. These results were clinically most significant in the crow's feet region. We recommend pretreatment of movement-associated rhytides with botulinum toxin before laser resurfacing. For optimum results, we further recommend continued maintenance therapy with botulinum toxin postoperatively.

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CURRENT nonsurgical rejuvenative therapy for the aging face includes injectable soft-tissue augmentation, chemical exfoliation, dermabrasion, laser resurfacing, and chemodenervation. The last 2 treatment modalities have been the focus of the cosmetic surgical community during the past decade. Advances in technology, as well as our detailed understanding of facial anatomy, have led to their popularity and predictable aesthetic results.

In 1983, Anderson and Parrish¹ described the theory of selective photothermolysis that revolutionized cutaneous laser therapy by producing localized thermal damage. Carbon dioxide lasers were now able to deliver char-free ablation with site-specific target injury within tissue. The CO₂ laser,

with a wavelength of 10600 nm, is strongly absorbed by skin's water, which allows tissue ablation with minimal diffusion of thermal damage. During the past few years, the erbium:YAG laser has gained popularity as a method of facial skin resurfacing. The erbium laser's shorter wavelength, at 2940 nm, is 10 times more selectively absorbed by water. Consequently, the residual thermal damage is much less than with CO₂ lasers, resulting in decreased postoperative erythema. However, erbium laser resurfacing does not provide the same degree of clinical improvement as do CO₂ lasers, especially in terms of collagen shrinkage and tissue tightening effects.² Erbium lasers require 3 to 4 times more passes to reach appropriate ablation depth, resulting in substantially

PATIENTS AND METHODS

A Saint Louis University (St Louis, Mo) Human Research Protocol was approved by the institutional review board, and 10 patients (all female) were entered in the study. The null hypothesis was that the experimental (botulinum toxin-pretreated) side of the face would not be smoother after healing than the control side after laser skin resurfacing. The study was conducted as a randomized, prospective, blinded study in patients undergoing facial laser resurfacing for aesthetic indications. All procedures were performed at a university-affiliated cosmetic plastic surgery clinic after informed consent was obtained.

Patients were examined preoperatively to determine Fitzpatrick skin type and to grade the degree of facial skin actinic damage and rhytidosis by means of the Glogau scale. Exclusion criteria included active acne, psoriasis, eczema, allergic dermatitis, isotretinoin use within the previous 12 months, and facial skin resurfacing or botulinum toxin therapy within the past 6 months. To remove confounding variables, such as severity of preoperative facial rhytides and differences in skin types and wound-healing abilities, each patient served as her own control.

Lyophilized botulinum toxin type A (Botox) was obtained in vials containing 100 U and stored at -5°C until reconstitution. The toxin was reconstituted with 2.0 mL of sterile nonpreserved isotonic sodium chloride solution, resulting in a concentration of 5.0 U/0.1 mL. All patients received injections 1 week before laser resurfacing and within 48 hours after toxin reconstitution. The patients' skin was prepared with an alcohol wipe, and injections were performed with a 1-mL syringe equipped with a 30-gauge needle. The side chosen for injection was randomized by coin toss, and the physician (M.S.K.) who performed the injections was not involved in postoperative evaluation, to maintain the blinded nature of the study. Patients were examined at the time of laser resurfacing to determine that appropriate chemodeneration was obtained. Injected subsite doses were as follows: for crow's feet, 2 injections of 5.0 U (0.2 mL); for the corrugator region, 1 injection of 7.5 U (0.15 mL); and for the frontalis region, 2 paramedian injections of 5.0 U (0.2 mL).

The 2 lasers used in the study were the Sharplan CO2 Silk Laser (ECS Sharplan Corp, Norwood, Mass) and the dual-mode Sciton Erbium Contour Laser (Sciton, Palo Alto, Calif). Laser selection was based on patient's request and Fitzpatrick skin type. All laser resurfacing was performed with the patient under local anesthesia. For the CO2 laser, 2 standardized settings were used

(both with a 200-mm hand-piece and a 6- to 8-mm² computer pattern generator; one used 18W and the other, 36 W). For treatment of the periocular region, all patients underwent 1 pass with 18W followed by a second pass with 36 W. The corrugator and frontalis regions were treated with 2 passes of 18 W. For the erbium laser, the periocular region was treated with a first pass of ablation only at 60 pm (15 J/cm²) with 20% overlap, a second pass of ablative and coagulative modes at 60 and 50 pm, respectively, and a final ablative pass at 60 pm. The corrugator and frontalis regions were treated in a similar fashion; however, the settings were increased to 80 pm; followed by a second pass of ablative and coagulative modes at 80 and 100 pm, respectively; and ending with an 80-pm ablation only.

Postoperative care included an occlusive hydrogel dressing (Vigilon; CR Bard Inc, Covington, Ga) for the first 24 hours followed by application of a thick layer of ointment (Aquaphor; Beiersdorf Inc, Norwalk, Conn) until epithelialization was complete (5-10 days). Routine postoperative medications included cefadroxil, 500 mg twice daily, and valacyclovir hydrochloride, 250 mg twice daily (starting 48 hours before surgery) for 7 days. After reepithelialization, a UV-A and UV-B sunscreen with sun protective factor greater than 15 was applied. Beginning at 4 weeks postoperatively, 3% hydroquinone was prescribed as needed for early signs of hyperpigmentation.

Results were evaluated in person by a blinded observer (M.S.Z.) at 6 weeks, 3 months, and 6 months postoperatively. Standardized photography was performed at each of the postoperative visits (Nikon N2000 SLR camera; Nikon Corp, Tokyo, Japan; Tamron SP 90-mm macro lens; Tamron USA, Inc, Commack, NY; and Sunpak automatic DX-12R ring flash; Sunpak, Osaka, Japan) with 2 slave-triggered strobe studio lights; 35-mm slide film was used (Ektachrome ISO 100; Eastman Kodak Co, Rochester, NY). The photographs were shown to a panel of 3 blinded observers (a facial plastic surgeon [J.R.T.1, an oculoplastic surgeon [J.B.H.1, and a cosmetic dermatologist [D.A.G.1). A visual analog scale graded 0 to 3 was used to compare sides treated with and without botulinum toxin, where 0 indicated no difference; 1, subtle improvement; 2, moderate improvement; and 3, marked improvement.

After averaging across reviewers, scores were tested against an alternative hypothesis of no effect by means of a 2-tailed t test. All analyses were performed with SAS statistical software (version 8.0; SAS Institute Inc, Cary, NC), with statistical significance defined as $P < .05$.

more postoperative oozing. However, recent developments in erbium laser technology³ have led to the combination of ablative and coagulative pulses, a method called dual mode, which allows for deeper vaporization with hemostasis and controlled tissue coagulation.

The areas shown to be most amenable to laser resurfacing include the cheek and periorbital regions.* However, many patients who undergo laser resurfacing experience premature recurrence of rhytides at specific anatomic subsites⁵: crow's feet, horizontal forehead furrows, and glabellar frown lines. Such subsites are areas of long-term muscle animation and produce hyperdynamic facial lines. Although histologic studies have confirmed neocollagen formation associated with laser resurfacing," it appears that fibroplasia cannot

overcome the forces of long-term animation on these movement-associated rhytides.

The anaerobic bacterium *Clostridium botulinum* produces 8 serologically distinct exotoxins. However, botulinum toxin type A (Botox; Allergan Inc, Irvine, Calif) is presently the only Food and Drug Administration-approved purified neurotoxin. Botulinum toxin acts at the neuromuscular junction by inhibiting the release of acetylcholine from nerve terminals. When injected locally at therapeutic doses, botulinum toxin produces a localized chemical denervation paralysis lasting from 2 to 6 months. The presumption that specific facial lines result from forces generated by local muscle action was first observed on a microanatomic basis by Pierard and Lapiere in 1989.⁸ In 1993,

Patient No./ Age, y	Sites Injected	Fitzpatrick Skin Type	Glogau Scale	Laser
1/44	GB/CF	II	3	CO ₂
2/46	GB/CF/FH	II	3	CO ₂
3/45	GB/CF/FH	I	3	Er:YAG
4/37	GB/CF	IV	3	Er:YAG
5/47	GB/CF/FH	III	3	CO ₂
6/40	GB/CF	III	3	Er:YAG
7/40	CF	III	2	Er:YAG
8/50	GB	II	3	Er:YAG
9/40	GB/CF	II	3	CO ₂
10/40	FH	II	3	CO ₂

*GB Indicates glabellar frown lines (n=8); CF, Crow's Feet (n=8); FH, Forehead Furrows (n=4); CO₂, Carbon Dioxide; and Er, Erbium.

Blitzer et al¹⁹ were the first to describe the use of botulinum toxin treating hyperdynamic facial lines. Cosmetic denervation of hyperfunctional facial lines by means of intramuscular botulinum toxin injections has proved an excellent method of nonsurgical facial rejuvenation. Focal denervation of particular facial muscles has been shown to improve overall facial appearance by not only temporarily eliminating rhytides but also improving malposition changes.¹⁰ Today, botulinum toxin is a well-established method for treating hyperdynamic facial lines and furrows and has firmly established its role in facial plastic surgery.

Facial laser resurfacing and chemodenervation with botulinum toxin are used independently as means of facial rejuvenation. Anecdotal clinical experience¹ suggests that skin pretreated with botulinum toxin before laser resurfacing heals in a smoother wrinkle-free fashion. It is postulated that paralysis of specific facial muscles could result in reepithelialization and the remodeling of collagen in an adynamic wound healing environment. Thus, botulinum toxin pretreatment could prevent recurrence and/or severity of movement-associated rhytides after laser resurfacing.

The purpose of this investigation was to evaluate the effect of botulinum toxin on hyperdynamic facial rhytides after cutaneous laser resurfacing. A 1-time unilateral botulinum toxin injection was administered to specific anatomic subsites of the face before laser resurfacing. The injected and noninjected sides were compared at 6 weeks, 3 months, and 6 months after facial laser resurfacing.

RESULTS

The ages of the 10 female patients ranged from 37 to 50 years (mean \pm SD, 42.9 \pm 4.6 years). Fitzpatrick skin type and Glogau rhytidosis scores are seen in **Table 1**. Five patients underwent resurfacing with the CO₂ laser and 5 with the erbium dual-mode laser. Twenty anatomic sub-sites were treated and evaluated for the study.

Examination for the paralytic effects of botulinum toxin showed complete resolution by 3 months in all patients. Both the blinded in-person observer and the blinded panel of 3 expert judges (using 35-mm photographs) were able to identify greater improvement in the botulinum toxin-pretreated side in all subsites analyzed. Site-specific

Region	Average Score	SD	P
Crow's feet at (n = 40)			
6 wk	1.10	0.74	<.001
3 mo	0.93	0.62	<.001
6 mo	0.85	0.48	<.001
Glabella at (n = 28)			
6 wk	0.71	0.81	<.001
3 mo	0.57	0.79	<.001
6 mo	0.43	0.63	.001
Forehead at (n = 12)			
6 wk	0.75	0.75	.006
3 mo	0.50	0.67	.03
6 mo	0.50	0.67	.03

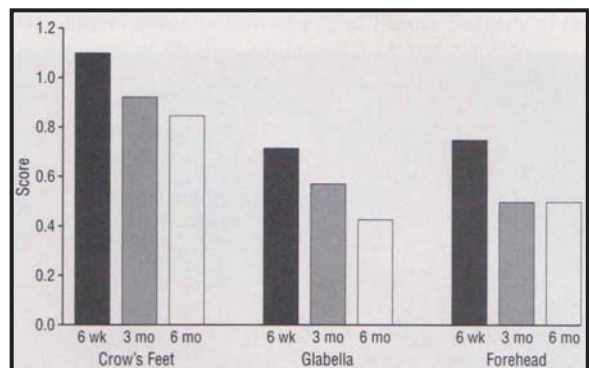


Figure 1. Average improvement score by region and follow-up time. A score of 0 indicated no improvement; 1, subtle improvement; 2, moderate improvement; and 3, marked improvement.

analysis is given in **Table 2**, with all subsites showing statistically significant improvement ($P < .05$). **Figure 1** demonstrates that the crow's feet subsite showed the highest level of improvement. Moreover, this improvement was sustained at the 6-month visit after the paralytic effects of the botulinum toxin had worn off. No perioperative complications were observed, and only 1 patient maintained mild hyperpigmentation after 3 months.

Figure 2 illustrates a patient's preoperative and 6-month follow-up photographs. The patient's right glabellar frown line was pretreated with botulinum toxin before laser resurfacing. **Figure 3** illustrates another patient's preoperative and 6-month follow-up photographs. The patient's right crow's feet were pretreated with botulinum toxin before laser resurfacing.

COMMENT

Immediately after laser resurfacing, hyperdynamic facial rhytides as well as fine rhytides associated with photoaging often resolve. Studies have shown¹⁵ clinical improvement of non-movement-associated rhytides to be as high as 94%, whereas hyperdynamic facial lines average improvement between 45% and 85% and generally recur within 6 to 12 months. Pretreatment with botulinum toxin has been anecdotally reported¹⁰⁻¹⁴ to improve results after laser resurfacing. To date, however, no published studies are available that prove or disprove this theory.

Wound immobilization is a basic concept for proper wound healing. Casts, plates, and sutures minimize the

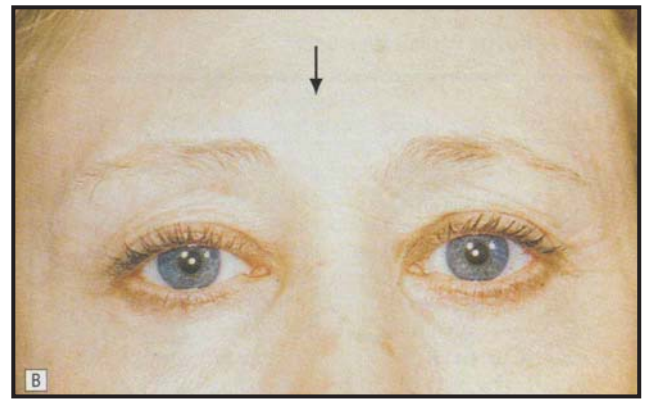
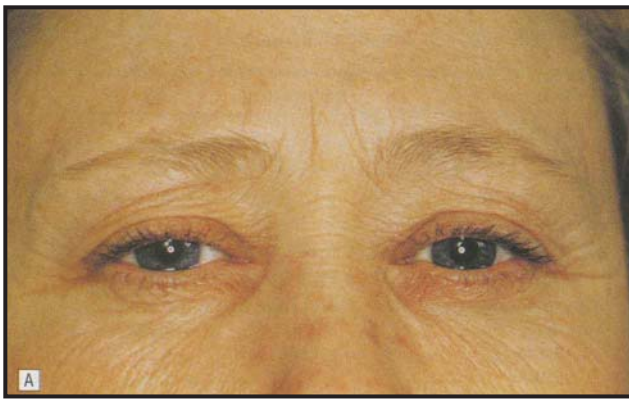


Figure 2. A, Glabellar frown lines before treatment. B, Six months after laser resurfacing. Patient's right glabellar frown lines (arrow) were pretreated with botulinum toxin.

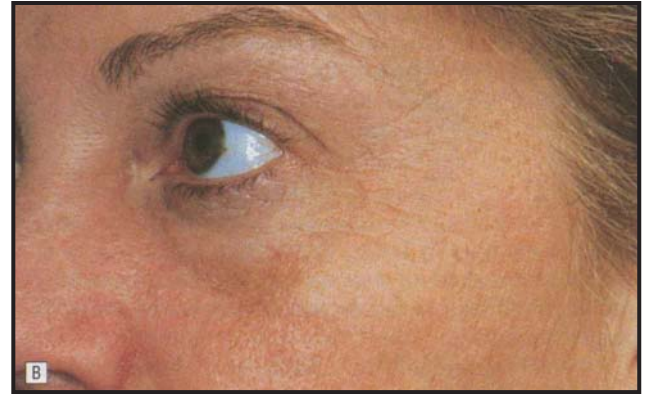


Figure 3. A and B, Crow's feet before treatment. C and D, Six months after laser resurfacing. Patient's right inferior crow's feet (C) were pretreated with botulinum toxin.

negative effect of muscle tension on healing tissue. The dynamic musculature of the face is in constant movement and can impede healing after facial surgery. It is postulated that paralysis of specific facial muscles could result in reepithelialization and the remodeling of collagen in an adynamic wound-healing environment. This, in theory, could prevent recurrence and/or severity of movement-associated rhytides after laser resurfacing. Choi et al¹⁶ described 11 patients who underwent botulinum toxin therapy to promote wound immobilization for high-risk patients undergoing complex eyelid reconstruction. They found improved wound-healing results in the botulinum toxin-treated wounds compared with simple tarsorrhaphy alone. Recently, Gassner et al¹⁷ examined the cosmetic results of facial wounds in primates treated

with botulinum toxin. They found that the cosmetic appearance of unfavorably oriented cutaneous scars were improved by pharmacologic chemodenervation of the surrounding tissue.

Fagien^{10,12} reported "enhanced" laser results, especially in the crow's feet region, in patients pretreated with botulinum toxin before resurfacing. He suggested that the pretreatment with botulinum toxin may improve the smoothing of newly resurfaced skin long enough to effect "more permanent eradication of wrinkles." Carruthers and Carruthers^{13,14} treated 4 female patients asymmetrically with botulinum toxin before CO₂ laser resurfacing. They reported that patient "satisfaction" was highest in the botulinum toxin-pretreated side. Furthermore, they stated that

the recurrent crow's feet were "coarser, thicker and more obvious" in the nonpretreated side. However, they did note deterioration of the botulinum toxin-pretreated side at approximately 10 months. West and Alster¹⁸ reported the effects of botulinum toxin on movement-associated rhytides after CO₂ laser resurfacing. They studied 20 patients who underwent botulinum toxin therapy 1 to 3 months after resurfacing was complete. They found prolonged correction of laser resurfacing if botulinum toxin treatment was instituted during the postoperative period. Without such treatment, they claimed return of most movement-associated rhytides within 6 to 12 months. Unfortunately, their control population (patients who did not receive botulinum toxin therapy after laser resurfacing) consisted of a separate random group of 20 patients who underwent laser resurfacing and did not account for differences in preoperative rhytidosis severity.

The most important finding in our study was that all of the blinded judges were able to identify the botulinum toxin-pretreated side with some level of improvement. This improvement was clinically most marked for the crow's feet subsite. Even though the improvement seen was statistically significant, clinical correlation shows that this was only "subtle" improvement. The visual analog scale that was graded 0 to 3 showed that the average (\pm SD) improvement for the crow's feet subsite was 1.10 ± 0.74 at 6 weeks postoperatively and 0.85 ± 0.48 at 6 months postoperatively. This improvement was sustained after the major effects of botulinum toxin had worn off, implying that the effects of the botulinum toxin pretreatment were more than merely simultaneous effects of the 2 treatment modalities. Six-month follow-up of the forehead and glabellar region did show statistically significant results. However, clinical examination of these data shows that most blinded observers graded these patients between "no improvement" and "subtle improvement" when compared with the control side. One could argue that the amount of toxin injected preoperatively was not sufficient to cause complete paralysis of the anatomic subsite. However, these conservative doses were chosen so as not to create severe asymmetries for the patient. Of further interest was that no statistical difference was found when results were compared between the CO₂ and erbium lasers. Perhaps this is the result of the newer dual-mode erbium technology.

Botulinum toxin pretreatment did enhance laser resurfacing results of hyperdynamic facial rhytides, resulting in the rejection of the null hypothesis. Six-month follow-up suggested that the improvement obtained was more than merely the simultaneous effects of the botulinum toxin therapy. As West and Alster¹⁸ suggested in treating movement-associated rhytides, laser improvement could be maintained if botulinum toxin therapy were begun in the postoperative period. It would seem from our study, and the results by West and Alster, that optimum results could be obtained by pre-treating patients with botulinum toxin and then continuing treatment well into the postoperative period.

CONCLUSIONS

Facial laser resurfacing and chemodenervation with botulinum toxin are used independently as means of facial rejuvenation.

Laser exfoliation is the treatment of choice for fine to medium rhytides, while chemodenervation appears to be superior for the treatment of glabellar frown lines, crow's feet, and horizontal forehead furrows. Our study showed that hyperdynamic facial rhytides, pretreated with botulinum toxin before laser resurfacing, heal in a smoother rhytid-diminished fashion. We recommend pretreatment of movement-associated rhytides with botulinum toxin before laser resurfacing. For optimum results, we also recommend continued maintenance with botulinum toxin therapy postoperatively.

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From the Division of Facial Plastic Surgery, Department of Otolaryngology-Head and Neck Surgery, Beth Israel Medical Center, New York, NY (Dr Zimble); Departments of Ophthalmology (Dr Holds), Otolaryngology-Head and Neck Surgery (Dr Holds), and Dermatology (Dr Glaser) and Division of Facial Plastic Surgery of the Department of Otolaryngology-Head and Neck Surgery (Drs Kokoska and Prendiville), Saint Louis University Hospital, St Louis, Mo; Departments of Surgery and Health Evaluation Sciences, Penn State College of Medicine, Hershey, Pa (Dr Hollenbeak); and Division of Facial Plastic Surgery, Department of Otolaryngology-Head and Neck Surgery, University of Illinois at Chicago School of Medicine (Dr Thomas). Corresponding author and reprints: Marc S. Zimble, MD, Division of Facial Plastic Surgery, Department of Otolaryngology-Head and Neck Surgery, Beth Israel Medical Center, 10 Union Square E, Suite 4J, New York, NY 10003 (e-mail: mzimble@bethisraelny.org).

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