Botulinum Toxin to Minimize Facial Scarring

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Abstract

Chemoimmobilization with botulinum toxin A is an ideal biochemical agent that allows near-total elimination of muscle pull on the healing facial wound. The goal of chemoimmobilization of facial cutaneous wounds is to eliminate dynamic tension on the healing tissues to improve wound healing and minimize scarring for optimal aesthetic results.

Keywords

- botulinum toxin
- chemoimmobilization
- scar
- wound healing
- facial scar

Injections of botulinum toxin A are the most commonly performed cosmetic procedure in the United States. In 2003, more botulinum type A injections were performed more than rhytidectomy, blepharoplasty, rhinoplasty, and liposuction combined.[1]

An ophthalmologist by the name of Dr. Alan Scott pioneered the use of botulinum toxin type A in humans. In 1973, his first publication detailed the effects of the biochemical agent on rhesus monkeys.[2] Soon afterward, he published an article in 1980 concerning the injection of the toxin into humans.[3] For many years, the toxin was an effective, although infrequently used, medication for blepharospasm and strabismus. Rare circumstantial reports of its use for wrinkle reduction are in existence.[4] In 1992, a team of ophthalmologists and dermatologists known as the Carruthers published the first comprehensive report detailing the cosmetic applicability of botulinum toxin type A.[5] This study reported the effects of the toxin on glabellar rhytides in 18 patients. Although the muscles affecting the glabella are still the most commonly injected muscles for cosmetic reasons, every mimetic muscle of the face has been treated with the toxin. In 2000, Dr. Holger Gassner and colleagues at the Mayo Clinic set out to pioneer an alternative use of botulinum toxin in the treatment of facial wounds to improve cosmetic outcomes in macaque monkeys.[6] Following this study at the Mayo Clinic, the body of anecdotal evidence in humans that eventually accumulated initiated a prospective, randomized control trial led by Gassner and colleagues to objectively quantify the potential beneficial effects of chemoimmobilization on human facial wound healing.[7] Numerous academic centers in the United States, Europe, and Africa have now reported in the literature on their favorable experiences with botulinum toxin A for chemoimmobilization for the treatment of cutaneous scars.[8–10]

The *Clostridium botulinum* bacteria secrete seven distinguishable exotoxins (toxins A to G; ►**Figs. 1A, 1B**). Each serotype is composed of three domains: the binding domain, the translocation domain, and the enzymatic domain. The most potent of these serotypes is A (Botox, Allergan, Irvine, CA). The toxin is a fully sequenced, 1295-amino-acid chain. It consists of a heavy chain of 97 kDa connected by a disulfide bond to a light chain of 52 kDa. The binding domain, located on the heavy chain of the Botox molecule, is responsible for attaching to the receptor on the presynaptic nerve terminal. Binding of botulinum toxin to its proper receptor initiates endocytosis and internalization of the toxin heavy chain and light chain. Although the mechanisms of action of the translocation domain are not completely understood, it is responsible for getting the toxin into the endosome of the nerve terminal that contains acetylcholine. Once inside the endosome, the acidic environment is believed to cause a change in the conformation of the toxin that allows the molecule to cross into the cytosol.

The enzymatic domain of the light chain becomes functional in the cytosol and cleaves a protein in the SNARE complex rendering it inactive, preventing the fusion of the

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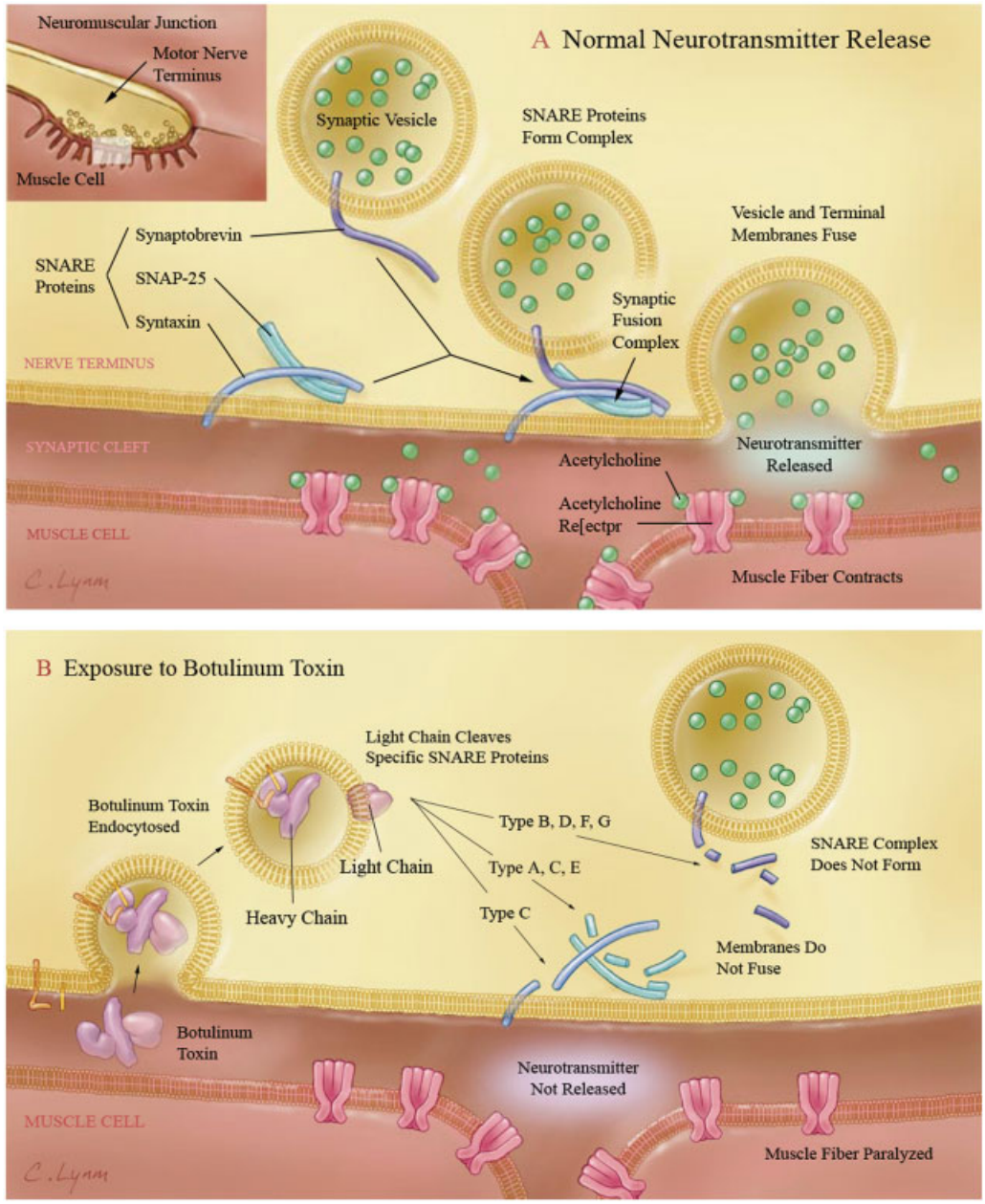

Figure 1 Mechanism of action of botulinum toxin; (A) normal neurotransmitter release, (B) exposure to botulinum toxin. (Reprinted with permission from Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. JAMA. 2001;285:1059–1070[11]).

acetylcholine vesicle and thus effectively blocking the extrusion of the vesicle contents. The SNARE complex is composed of synaptobrevin, SNAP-25 (synaptosomal-associated protein 25), and syntaxin. Each of the seven serotypes has specific enzymatic action against the SNARE complex. Botulinum toxin A is known to specifically cleave component SNAP-25.

SNAP-25 is necessary for fusion of the transmitter vesicle containing acetylcholine with the cell membrane of the presynaptic nerve terminal. Without fusion of the vesicle with the cell membrane, the neurotransmitter cannot be released into the synapse and a presynaptic neural blockade results. Thus, the toxin does not directly affect the skin. Rather, it indirectly affects the underlying striated muscle by removing the innervating stimulus. More precisely, botulinum toxin A only directly affects the nerve at the level of the presynaptic nerve terminal.[1,11–14]

Botox is currently approved for the treatment of glabellar furrows in patients 65 years and younger but often it is used off-label on crow's-feet, forehead creases, and bands on the neck. Botox has also been used for blepharospasm, cervical dystonia, and hyperhidrosis. Only recently has botulinum toxin A been used as a chemoimmobilization agent to immobilize the underlying facial musculature for enhanced facial wound healing and scar minimization.

Static versus Dynamic Tension

In clinical practice, measures routinely employed to allow for favorable healing include addressing contamination of the wound, minimizing reactive suture material, performing quality closure, applying occlusive or semiocclusive dressings, avoiding sun exposure, and correcting nutritional deficiencies and systemic metabolic pathologies.[15,16] More notably, a key factor that determines the final cosmetic appearance of a cutaneous scar is the tension that acts on the wound edges during the healing phase. Tension exacerbates inflammation and leads to increased collagen synthesis and deposition of glycosaminoglycans while prolonging erythema.[17] The tension on healing wounds can be described as static tension, dynamic tension, or more often a combination of both. Static tension is determined by the location, shape, and size of the wound, the closure technique, and the inherent biomechanical properties of the healing skin. Studies by Larrabee et al[18,19] have provided us with important insights into the biomechanical properties of skin and their surgical implications. Based on these studies, numerous operative techniques have been modified and refined with the goal of minimizing the effects of static tension on healing wounds. These techniques include wide undermining, multilayered closure techniques, local flaps, external dressings, and stenting devices.

Dynamic tension, on the other hand, is exerted on the healing wound by the activity of the underlying musculature. The importance of dynamic tension first became evident in 1816 when Jules Cloquet reported that contraction of the underlying musculature creates ridges in the skin.[20] Nearly two decades later, Gullaume Dupuytren observed that circular cutaneous wounds inflicted with a round awl eventuated in linear clefts.[21] Using a similar technique, Karl Langer, a Viennese professor of anatomy, created a map of natural cutaneous lines in cadavers that reflect the tension created by underlying muscular contraction.[22] The modern concept of relaxed skin tension lines (RSTL) was derived from Borges' work based on that of Langer. Simply, RSTL lie perpendicular to the tension vector of the underlying muscular contraction. Scars aligned parallel with RSTL are subject to reduced tension and generally heal well, whereas scars oriented against RSTL are subject to repetitive bouts of tensional forces and often result in poor scar formation.[23,24] The repeated microtrauma to the overlying wound induces a prolonged inflammatory response and increased metabolic activity during the healing process. Consequently extracellular deposition of collagen and glycosaminoglycans can intensify and lead to hypertrophic and hyperpigmented scars. Furthermore, excessive tension on tissues compromises blood flow and increases the fibroblastic response. Therefore, it is common practice to plan incisions parallel to RSTL to minimize dynamic tension, thereby improving wound immobilization during the healing phase with the intention of achieving a more esthetic scar.[25]

Botulinum Toxin and Wound Healing

One way to address the deleterious effects of dynamic tension caused by local muscle pull is to temporarily denervate the muscles pulling on a wound through chemoimmobilization. Botulinum toxin A allows near-complete elimination of dynamic muscle tension on the healing wound. Lee et al designed a prospective randomized experimental study to investigate the impact of Botox on the stages of wound healing in a rat surgical model on both a macroscopic and microscopic level.[26] They hypothesized that Botox-induced paralysis of the musculature subjacent to the surgical wound with a skin defect would minimize the repetitive tensile forces on the wound edges, and this would result in a decreased fibroblastic response and fibrosis of the wound.

More precisely, Lee et al focused on the affects of Botox as it relates to the four stages of wound healing: coagulation, inflammation, proliferation, and maturation. The coagulation phase is brief, lasting only several minutes. The end product is a blood clot on injured tissue. The inflammatory phase lasts on the order of days and is an attempt to limit the tissue damage by stopping the bleeding, sealing the surface of the wound, and removing any necrotic tissue, foreign bodies, or bacteria that are present. Inflammatory cells at this time regulate the repair of the connective tissue matrix by the actions of various secreted cytokines. The proliferative phase involves the repair processes of angiogenesis, fibroplasia, and epithelialization. The phase typically lasts for weeks and is characterized by the formation of granulation tissue, and this consists of a capillary bed, fibroblasts, macrophages, and a loose arrangement of collagen, fibronectin, and hyaluronic acid. Epithelial regeneration is greatly enhanced in wound closing by primary intention, whereas wound healing by secondary intention takes substantially longer for this process. It has been conclusively shown that epithelial regeneration is also enhanced in a moist environment, and the use of occlusive and semiocclusive dressings has become well-established clinical practice until epithelialization is complete. The final maturation phase lasts up to the ensuing year and is the period of scar contracture with collagen cross-linking, shrinking, and loss of edema. At this phase the acute and chronic inflammatory cells gradually diminish in number, angiogenesis ceases, and fibroplasia ends. At about 3 to 5 weeks, equilibrium between collagen synthesis and collagen degradation is gradually restored. Although the phases of wound healing are described as a sequence of events, these phases may occur simultaneously with overlap of the respective processes. Avoidance of both sun exposure and mechanical irritation should be continued through all phases of wound healing to minimize the potential for scar hypertrophy and hyperpigmentation changes.[26–32]

To evaluate the effects of Botox as it relates to the phases of wound healing, Lee et al assessed the degree of inflammation, fibrosis, blood vessel proliferation and the thickness of the healing wounds, collagen density, and maturation in the rat surgical wound model.[26] Two identical circular areas were prepared on the dorsum of each of 15 rats, and the distance between the areas was ~4 cm. The skin and subcutaneous tissue were then excised, but the deep muscle was preserved at the base of the defect. The diameters of the wounds were 1.2 cm (►**Fig. 2A**). One of the two wounds was selected at random and treated with Botox. Botox (10 U, 0.5 mL) was

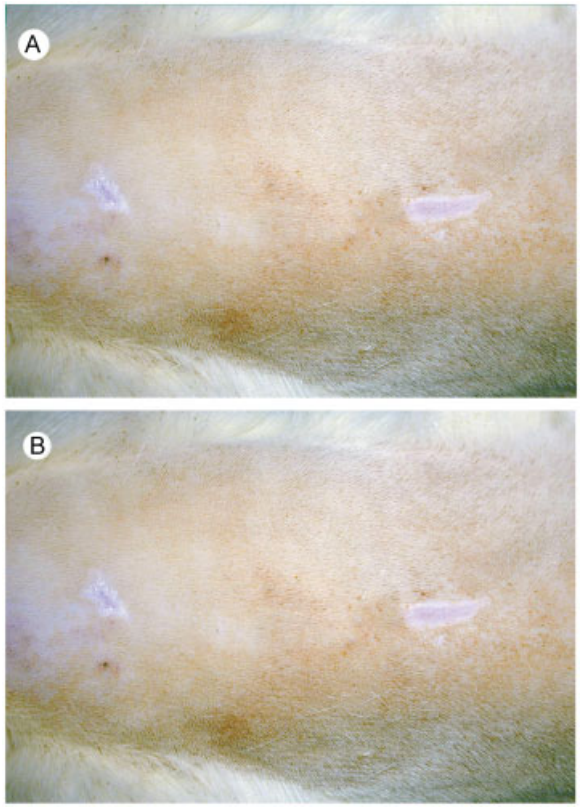

Figure 2 Dorsum of a rat showing the distinct surgical wounds (A). The surgical wound (right) is injected with Botox. (B) Assessment of the surgical wounds at the 8th week. (Reprinted with permission from Lee BJ, Jeong JH, Want SG, et al. Effect of botulinum toxin A on a rat surgical wound model. Clin Exp Otorhinolaryngol 2009;2:20–27[26]).

injected into the deep musculature subjacent to the wound immediately after the surgery. As a control, normal saline (0.5 mL) was injected into the other wound. Histological assessment of wound healing was performed at weeks 2, 4, and 8 by harvesting the skin wounds, which included the epidermis, dermis, and subcutaneous loose tissue with surrounding normal tissue. An assessment of wound size was also performed weekly by measuring the major and minor axes and calculating the area using the formula for an ellipse (►**Fig. 2B**).

There was a significant difference between the Botox and control groups for the wound size at weeks 3 and 4 ($p < 0.05$), showing a larger wound size for the Botox group. Interestingly, there was no significant difference between the wound sizes during the final week of the study (week 8). The reason for the difference of wound size is presumed to be the decreased wound contracture power of the underlying muscle tension by Botox. On hematoxylin and eosin stain, the surgical wounds of the Botox group showed a significantly smaller number of fibroblasts and less fibrosis than the control wounds at week 4 after surgery ($p < 0.05$, ►**Figs. 3C** and **3D**). The reason for the difference of the number of fibroblasts and the degree of fibrosis is presumed to be the decreased release of several cytokines, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), epithelial growth factor (EGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF), by the decreased inflammatory response and the short period of inflammation. The collagen maturation in the Botox group was increased and the maturation was faster than that of the control group at week 8 (►**Figs. 3E** and **3F**). The reason for the difference of the degree of collagen maturation is thought to be associated with the increased collagen maturation by the decreased inflammation response and the shortened period of the inflammatory phase for the surgical wound of the Botox group. On immunohistochemistry (IHC), the wound of the Botox group showed a lower expression of TGF-β1 than that of the control group at week 4 after surgery. TGF-β1 is one of the major important cytokines in the wound-healing process. This cytokine is produced by a host of cells, including platelets, fibroblasts, smooth muscle cells, endothelial cells, keratinocytes, lymphocytes, and macrophages. It increases collagen synthesis and stimulates keratinocyte migration, angiogenesis, and fibroplasias. The reason for the difference of the expression of TGF-β1 is the decreased inflammatory response at the surgical wounds of the Botox group. The final results (►**Table 1**) suggest that Botox may be used to decrease the fibrosis during the healing process of surgical wounds by eliminating the underlying muscle tension. Although it is possible that Botox has a direct biochemical effect on the inflammatory cells or may inhibit the mediators by a direct mechanism, there are no studies that report on these mechanisms of action.

Based on the findings of Lee et al, a mechanism for effect of Botox on wound healing was proposed (►**Fig. 4**).[26] Although Botox was shown to decrease the fibrosis in the healing process of surgical wounds in the rat model, the surgical wounds treated with Botox became larger than the control wounds at weeks 3 and 4 as a result of decreased wound contracture and the reduced number of fibroblasts during the wound-healing phase. At week 8 after surgery, all the surgical wounds had the same appearance, and there was no statistically significant difference between the sizes of the scars. Although the underlying physiology of wound healing in rats may not fully reflect that of humans, the results of the rat surgical wound model suggest that Botox can be used to decrease inflammation and fibrosis and inhibit fibroblast proliferation without damaging the epithelial growth during the healing process of surgical wounds.

Facial Wound Healing: Animal Studies

Gassner et al demonstrated statistically significant and clinically relevant improvement of the cosmetic appearance of facial scars after treatment with botulinum toxin A in a primate model.[6] Standardized excisions were performed in symmetric locations on the forehead of macaque monkeys, and subsequently the hemiforehead was randomized to botulinum toxin A or placebo injection (►**Fig. 5**). The frontalis muscle underlying each of the cutaneous wounds was injected with 7 U of botulinum toxin A in 0.9% saline or with 0.9% saline alone. Twenty-one total units of botulinum toxin A was injected into the experimental side of the forehead and resulted in complete paralysis of the side. After the healing

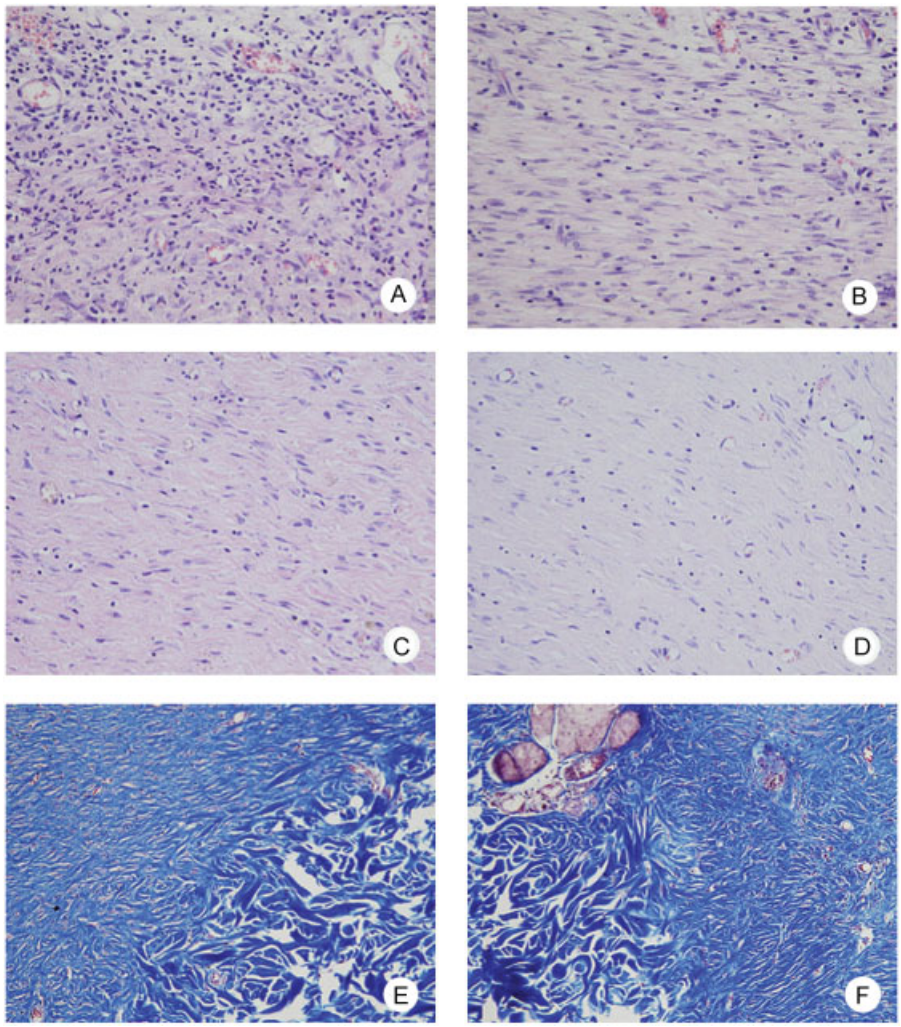

Figure 3 Histological findings of inflammatory cell infiltration, fibroblasts, and collagen density. The Botox group (B) shows less inflammatory cells than that of the control group (A) at 2 weeks after surgery. The Botox group (D) shows less fibrosis than that of the control group (C) at 4 weeks after surgery. The Botox group (F) shows a much greater amount of collagen than that of the control group (E) at 8 weeks after surgery (hematoxylin and eosin, ×400). (Reprinted with permission from Lee BJ, Jeong JH, Want SG, et al. Effect of botulinum toxin A on a rat surgical wound model. Clin Exp Otorhinolaryngol 2009;2:20–27[26]).

phase of 3 months, the scars were evaluated by three blinded facial surgeons who used a 10-cm visual analog scale. The botulinum toxin A-treated scars had a significantly superior cosmetic result compared with the respective symmetric control scars ($p < 0.01$, ►**Fig. 6**). Consensus scores of rating the scars on either side of the forehead as equal to or better than the scars on the opposite side also resulted in the experimental side having better scars than the control side ($p < 0.031$). Histological examination revealed that the scars were mature with no ongoing remodeling or inflammatory response present. The animals were not sacrificed for this study, and the resulting data formed the basis for human use and clinical trials.

Facial Wound Healing: Human Studies

Human case reports with long-term follow-up also suggest safety and efficacy of this treatment, with no adverse effects observed. One particular case report described by Gassner and Sherris involved a healthy 17-year-old girl who was involved in a motor vehicle accident.[33] She presented with extensive complex traumatic lacerations across her forehead and nose with exposure of the frontal bone (►**Fig. 7A**). A total of 40 U of Botox reconstituted in 2 mL of 1% lidocaine with 1:100,000 epinephrine was injected into the frontalis, procerus, and corrugator muscles. The right upper lid was spared to prevent lagophthalmos. Healing was uncomplicated, and 1 year postoperatively, the patient demonstrated better-healed scars over immobilized areas (forehead) than over nonimmobilized areas (right upper lid; ►**Fig. 7C**).

In 2006, Wilson extrapolated these results to multiple human subjects. In 40 patients with ugly scars of the face, botulinum toxin was used to induce temporary paralysis of the muscles during revision surgery, thus minimizing tension on healing wound edges until the collagen could mature. Wilson found that through using both objective and

Table 1 The Differences of the Surgical Wounds Between the Botulinum Toxin A and Control Groups

	Wk	Group		*p* Value
		Control	Botox	
Inflammatory cells (*n*/HPF)	2	25.0 ± 8.8	11.3 ± 3.8	0.048
	4	3.3 ± 1.9	4.3 ± 2.9	0.796
	8	0	0	
Fibroblast (*n*/HPF)	2	103.0 ± 19.7	106.0 ± 14.4	0.561
	4	68.6 ± 7.0	49.8 ± 6.6	0.016
	8	37.3 ± 5.1	32.5 ± 6.2	0.248
Vessel proliferation (*n*/HPF)	2	6.0 ± 0.8	6.5 ± 1.2	0.536
	4	3.2 ± 1.3	3.0 ± 1.5	0.832
	8	2.5 ± 0.6	2.3 ± 1.3	0.730
Thickness of the wound (mm)	2	0.8 ± 0.3	0.8 ± 0.4	0.943
	4	0.7 ± 0.1	1.0 ± 0.3	0.101
	8	1.1 ± 0.1	1.2 ± 0.1	0.534
Expression of TGF-β1 (n/HPF)	2	113.2 ± 23.2	109.1 ± 18.2	0.624
	4	70.2 ± 8.3	45.2 ± 4.2	0.012
	8	54.3 ± 8.5	49.3 ± 8.9	0.312

(Data from Lee BJ, Jeong JH, Want SG, et al. Effect of botulinum toxin A on a rat surgical wound model. Clin Exp Otorhinolaryngol 2009;2:20–27.[26]) HPF, high-power field; TGF, transforming growth factor.

subjective assessment scales, 90% of patients ended up with an improved outcome. This study was shown to be as effective in humans as it was previously demonstrated in primates, yielding results superior to those of any other treatment modality.[34]

The same year, Gassner et al went on to describe the first randomized, placebo-controlled, prospective trial to investigate the effect of chemoimmobilization on the eventual cosmetic appearance of incisional and traumatic facial wounds.[7] In this blinded, prospective, randomized clinical trial, patients were randomized to botulinum toxin verses placebo injection into the musculature adjacent to the wound within 24 hours after wound closure. Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analogue scale served as the main outcome measure. Thirty-one patients presenting with traumatic forehead lacerations or undergoing elective excisions of forehead masses were included in the study. Based on the blinded evaluation by two experienced dermatologic surgeons of standardized photographs, the overall median visual analog scale score for the botulinum toxin-treated group was 8.9 compared with 7.2 (0 indicating the worst possible

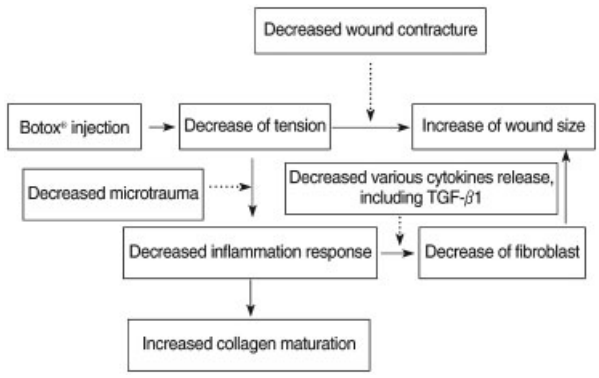

Figure 4 Proposed mechanism for the effect of botulinum toxin A on wound healing. (Reprinted with permission from Lee BJ, Jeong JH, Want SG, et al. Effect of botulinum toxin A on a rat surgical wound model. Clin Exp Otorhinolaryngol 2009;2:20–27[26]). TGF, transforming growth factor.

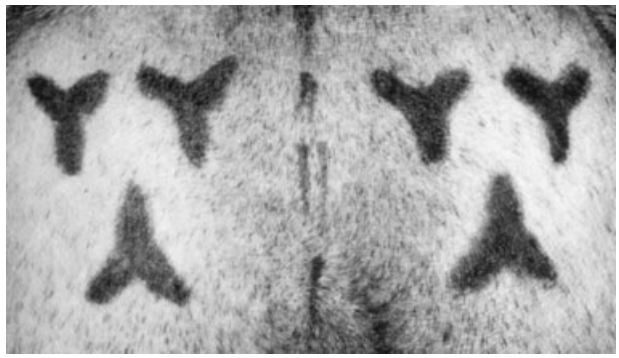

Figure 5 The shape and location of the three symmetric pairs of excisions are outlined with a template for maximal precision on the forehead of the primate. (Reprinted with permission from Gassner HG, Sherris DA, Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. Plast Reconstr Surg 2000;105:1948–1953[6]).

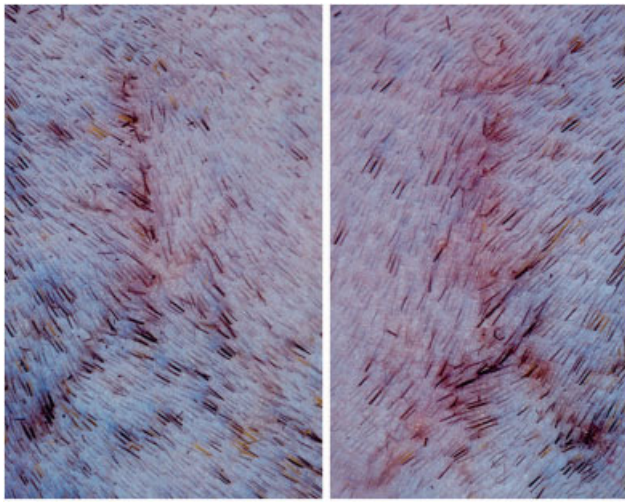

Figure 6 Representative pair of experimental (left) and control (right) scars. (Reprinted with permission from Gassner HG, Sherris DA, Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. Plast Reconstr Surg 2000;105:1948–1953[6]).

outcome and 10 indicating the ideal outcome) for the placebo group ($p = 0.003$, based on the Wilcoxon rank sum test) at 6 months' follow-up. Thus, indicating enhanced healing and improved cosmesis of the experimentally immobilized scars. ►**Figures 8** and **9** are representative examples of experimentally treated and placebo-treated wounds, respectively. ►**Figure 8** depicts a botulinum toxin-treated, well-healed scar of the lateral forehead. ►**Figure 9** shows a placebo-treated vertical midline forehead wound of the central forehead with notable scarring.

Traditionally, chemoimmobilization with botulinum toxin A has largely focused on the treatment of forehead and periorbital wounds and has since proven to be an attractive adjunct in enhancing wound healing and scar minimization of these regions. The forehead is a particularly favorable area to treat because the risk of inducing temporary functional deficits is minimal. Furthermore, the injection techniques for the forehead are imitated from the widespread experience with cosmetic injections. In recent years, the indications for treating facial lines and wrinkles have been extended beyond the forehead to include the periorbital and perioral region. Comparable to the progression of cosmetic indications in the lower face, treatment of wound healing in the lower third of the face with botulinum toxin A has been recently reported in the literature.[35]

When considering chemoimmobilization of the perioral musculature, the important functions of facial expression, oral closure, and articulation must be addressed as they may be compromised with injection of botulinum toxin A. The perceived risk of inducing such anticipated functional deficits may explain the relatively late emergence of reports on perioral and lower facial wound immobilization. In contrast to the forehead, botulinum toxin A injections to the perioral musculature necessitate only mild reduction in activity and not near-complete paralysis. Adverse effects are avoided by

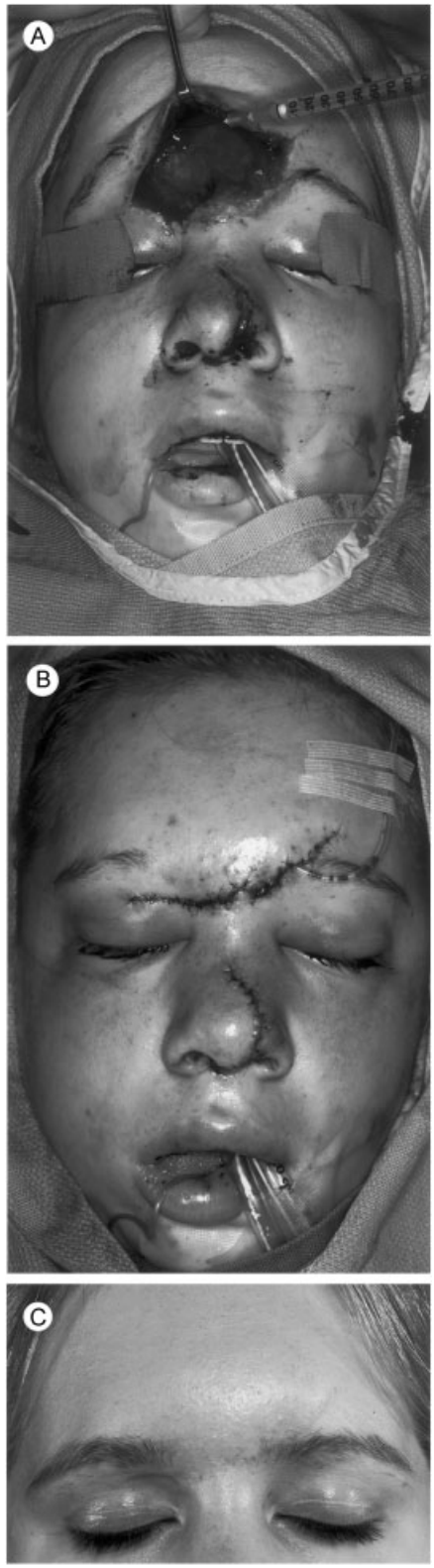

Figure 7 (A) A 17-year-old girl with traumatic forehead and upper lid wound. The underlying musculature is immobilized with botulinum toxin reconstituted in lidocaine and epinephrine. The right upper lid was not injected to prevent lagophthalmos. (B) The wound is closed in a standard fashion. (C) At 1 year postoperatively, the patient demonstrated more favorable scars over the immobilized forehead than over the nonimmobilized right upper lid. (Reprinted with permission of Gassner HG, Sherris DA. Chemoimmobilization: improving predictability in the treatment of facial scars. Plast Reconstr Surg 2003;112:1464–1466[33]).

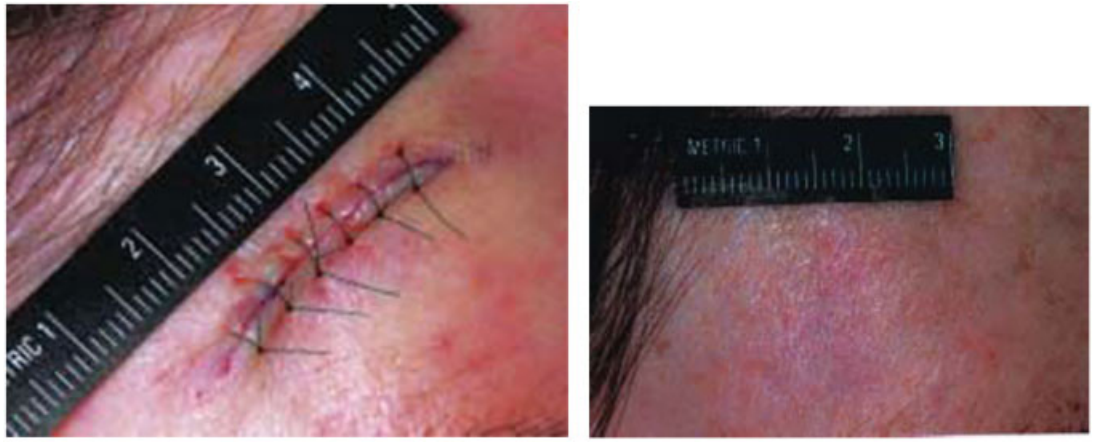

Figure 8 (Left) A 44-year-old white woman 1 week after excision of a basal cell carcinoma of the right lateral aspect of the forehead. The longest postoperative excisional size was 2.7 cm. Fifteen units of botulinum toxin was injected, and layered closure was performed with 5–0 Monocryl subcutaneous and 6–0 nylon simple running sutures. (Right) The resulting scar 6 months after botulinum toxin treatment displays good color match and no hypertrophy or inversion. (Reprinted with permission from 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[7]).

careful injection technique and application of small dosages in the range of 1 to 5 U of botulinum toxin A in the lower face.

The following case describes a 42-year-old white woman who presented with a widened, midline vertical chin scar from a laceration she sustained as a teenager (►**Fig. 10A**). She had the scar revised at the age of 14 and then again at the age of 16 without much success. Nearly 25 years later, she presented to Dr. David Sherris in July 2007 for scar revision via primary excision with intermediate closure and injection of botulinum toxin. The chin scar was excised down to bone and the scar tissue was subsequently removed. The wound was irrigated copiously with normal saline and then 30 U of Botox was injected into the surrounding musculature. The wound was closed in layers with 4–0 polydioxanone (PDS) deep sutures and 5–0 nylon skin sutures. A pressure dressing was then applied. Clinically significant paralysis ensued, and no dynamic tension or distortion of the wound was observed. Ten weeks after surgery, muscle function had returned completely. Additionally, the patient underwent three treatments of microdermabrasion to her chin between July 2007 and August 2008 with the first treatment occurring on postoperative day 50. Approximately 13 months after surgery, the wound had healed with favorable results (►**Fig. 10B**).

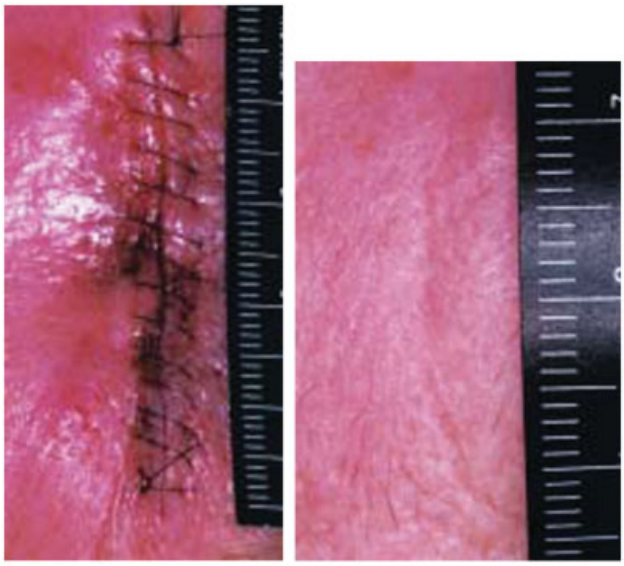

Figure 9 (Left) A 67-year-old white woman 1 week after excision of a squamous cell carcinoma of the central forehead. Postoperative excisional size was 4.0 by 6.0 cm. Six milliliters of the placebo medication (1% lidocaine with 1:100,000 epinephrine) was injected, and layered wound closure was performed with 5–0 Monocryl and 6–0 running nylon suture. (Right) The resulting scar at 6 months after placebo treatment shows notable widening of the scar. (Reprinted with permission from 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[7]).

Botulinum Toxin Injection Dosing and Reformulation

For more than 25 years, the application of botulinum toxin A has proven safe and effective in the treatment of various disorders, including blepharospasm, spastic dysphonia, hyperfunctional facial lines, and recently chemoimmobilization. The maximal dose suggested for administration to one muscle at one injection site is 25 U, and the maximal dose suggested per host is 200 U/mo. In previous primate studies, no systemic side effects were experienced at doses less than 33 U/kg body weight. Most authors inject 1.25 to 5.0 U per injection site and thereby effectively chemodenervate the muscle and surrounding area. When a forehead is treated for hyperfunctioning glabellar and forehead creases, a total dose of 25 to 50 U is effective for treating the entire forehead. Therefore, the dose necessary to theoretically

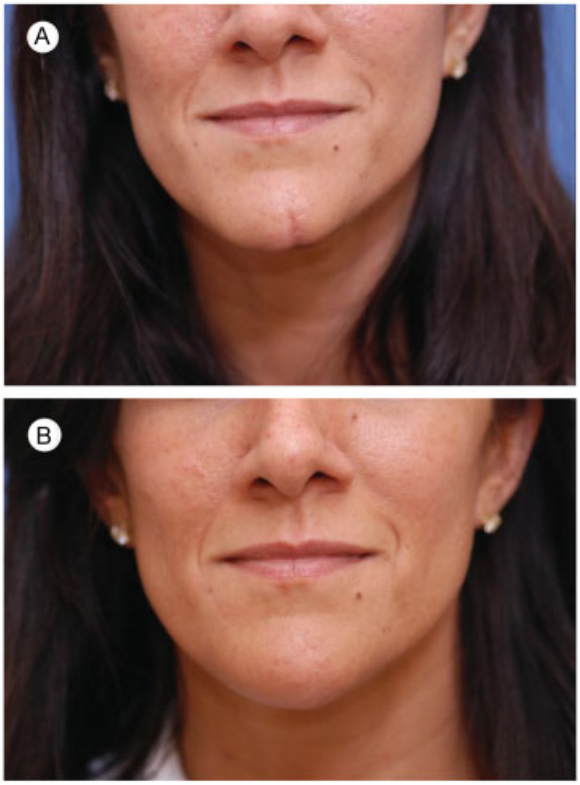

Figure 10 A 42-year-old white woman presented for scar revision and excision of a midline vertical chin scar. (A) The patient before surgery and (B) 13 months after surgery. With three treatments of microdermabrasion, the wound had healed with a favorable result. (Printed with permission from Sherris DA. The Clinic of Facial Plastic Surgery, David A. Sherris, M.D.).

immobilize a facial wound would not be expected to exceed 1 U botulinum toxin A/kg body weight. Regarding the pediatric population, Tollefson et al demonstrated safe dosages of 1 to 2 U/kg at 25 U/mL for infants (ages 3 to 6 months) receiving botulinum toxin A injections to improve results in cleft lip repair.[37] On the forehead lacerations, the dose may range from 20 U to more than 60 U for extensive wounds. As mentioned before, only mild reduction in muscle activity is necessary for wounds of the lower face as to avoid adverse effects of oral incompetence and to maintain appropriate movements in facial expression. Smaller dosages in the range of 1 to 5 U of botulinum toxin A is the effective recommended injection dose used for chemoimmobilization of the lower face.[25,36] The botulinum toxin A injections should be targeted to the superficial muscles that create unwanted pulling tension on a cutaneous wound. Wounds under high tension may require additional injections to the deeper muscles when a wound is found overlying an area of multiple muscle layers.

Because most patients do not attain full chemodenervation of the treated muscle groups for 48 to 72 hours after injection, reconstituting Botox in a solution of 1% lidocaine with 1:100,000 epinephrine is a useful method that allows the surgeon to better predict the delayed paralysis ensuing from botulinum toxin A. This method may disregard the need for titration of the amount of the toxin required for the desired treatment as it gives the injecting physician immediate feedback on the eventual treatment effect. The anesthetic agent, lidocaine, acts by stabilizing the neuronal membrane and inhibiting the ionic fluxes required for the initiation and conduction of neuronal impulses. Through this mechanism, efferent fibers are blocked and muscle paralysis immediately ensues. The temporary effect of the lidocaine on paralysis immediately creates the level of paralysis eventually seen from the botulinum toxin 3 days later. The vasoconstrictive agent epinephrine achieves its effect through its sympathomimetic properties, acting on both α- and β-receptors. It thereby reduces local diffusion of the anesthetic agent and of other simultaneously injected agents and may decrease local adverse effects caused by diffusion of the botulinum toxin A to adjacent areas. Therefore, when compared with pure botulinum toxin type A injections, this novel formulation may be a safer alternative with superior pharmacologic properties.[37]

Adverse Effects and Complications

In the experienced hands, botulinum toxin A has proved to be a safe adjunctive treatment of cutaneous lacerations. The side effect profile of botulinum toxin A injections, as observed for the treatment of various disorders over many years, is very low. Complications may occur from drift of the toxin to adjacent muscles, thereby weakening them. Other complications include headache, ecchymosis, and eyelid ptosis. Botulinum toxin A injection is contraindicated in disorders of neuromuscular transmission, such as myasthenia gravis and Lambert-Eaton syndrome. It should not be used in patients taking aminoglycoside antibiotics, which may potentiate the effects of the botulinum toxin. Although there is no current evidence to suggest teratogenicity, treatment of pregnant women, women actively attempting to become pregnant, or those who are breast-feeding is under the physician's discretion. The toxin does not cross the blood-brain barrier.[1] Patients typically comprehend well that effective immobilization of a healing wound will transiently compromise muscular activity of relevant surrounding anatomic areas. These patients are quite accepting of the expected temporary functional deficits. Gassner and Sherris noted that these patients frequently request aggressive immobilization and are agreeable to trade the transient functional deficits for a potentially better appearance of the resulting scar.

Conclusion

The reports of favorable outcome data, the remarkable safety profile, and the long-term experiences with facial injections of botulinum toxin are factors likely contributing to the increasing and widespread acceptance of chemoimmobilization for the treatment of cutaneous scars. The concept of immobilization in medicine is ancient and firmly established

for the treatment of fractures and tendon and soft tissue injuries. A variety of devices have been developed for this purpose: splints, casts, dressings, wired screws, internal and external fixators, and others. These devices share a common objective: to minimize the effect of muscular contraction on healing tissues. Therefore, the objective of botulinum toxin A injections in facial wound healing is to completely eliminate unwanted muscle contractions rather than merely minimize their effects.[38] The injection technique for facial wound healing resembles that applied to treat age-related rhytides, but it must be tailored appropriately. The method of chemoimmobilization is applicable for both elective and traumatic lacerations to the face. For elective incision, such as lesion excision, scar revisions, or flap reconstruction, injection of the chemodenervating agent can be performed in advance. Regarding traumatic lacerations, it is advised that botulinum toxin A be available in urgent and emergent care settings to allow for injection at the time of closure of lacerations for both adult and pediatric patients. In light of the favorable risk-to-benefit ratio of this therapy, the investigators of chemoimmobilization consider the use of botulinum toxin A injections for the treatment of facial wounds in selected patients who are concerned with the eventual appearance of a resulting scar.

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