review

Botulinum toxin type A: implications in wound healing, facial cutaneous scarring, and cleft lip repair

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Botulinum toxin is a neurotoxin that has been utilized to induce chemo-denervation of muscles. Cutaneous wounds represent a special situation in which the tensile forces applied by these muscles on wound edges might have deleterious effects on the healing process. The aim of this review was to investigate such an effect and to review other mechanisms this toxin might have on the healing process. We also reviewed the role of botulinum toxin in the management of hypertrophic scars and cleft lip repair.

One of the important factors affecting wound healing and the final cosmetic outcome of cutaneous scars is tension applied on the wound edges during the healing process.[1] The superficial attachments of facial muscles lead to a continuous tension over the healing skin wound, resulting in healing complications.[2] Several reports in the published reports document the benefits of the use of botulinum toxin type A in the management of various facial wounds including cleft lip surgery. The aim of this article was to review the value of such an intervention on facial cutaneous wound scarring and on cleft lip repair.

Botulinum toxin

Since the early days of its discovery, botulinum toxin continues to have new fields of applications. Botulinum toxin is a potent neurotoxin produced by the bacteria-Clostridium botulinum, a gram-negative, rod-shaped anaerobe that induces its action by inhibiting the release of acetylcholine at the neuromuscular junction. The purified form of botulinum toxin type A was first isolated as a pure acidic precipitate by Hermann Sommer in 1920.[3] In the late 1970s, Scott was the first to propose the use of the toxin as a medical therapy in treating strabismus.[4,5]

Although its effect was first evaluated in the treatment of several muscular conditions of excessive or abnormal tension, the use of the toxin has now expanded to include several cosmetic, dermatologic, urologic, gastrointestinal, ophthalmologic, orthopedic, and painful conditions. The paralytic effect of botulinum toxin on striated muscles is first mediated by the toxin-entering nerve terminals by a process known as "endocytosis." The toxin then interacts with the nerve's intracellular proteins (SNARE proteins) resulting in the inhibition of acetylcholine release.[6] Botulinum toxin also acts on the autonomic nervous system, where it inhibits glandular and smooth muscle acetylcholine release.[7]

The toxin has a reversible paralytic effect that usually peaks around 1 to 2 weeks after injection. Neuronal activity starts to return around 3 months after injection. Factors affecting recovery include neuronal sprouting and molecular turnover within the neuromuscular junction.[8] Permanent effects may occur in the injected muscle after repetitive treatment, but such effects are minor and do not significantly affect the overall muscle function.[9]

Botulinum toxin type A is available commercially in two different products: Botox and Dysport. The 2 formulas are different in their strengths and dosages (1 U of Botox is equivalent to 3 U of Dysport).[10]

One of the most common side effects of botulinum toxin is diffusion of the toxin from the treated muscle to other neighboring muscle groups with unwanted para-

lytic effects.[11] Other minor complications include pain, edema, erythema, ecchymosis, and hyperaesthesia.[12] The use of botulinum toxin is contraindicated in patient populations with known neuromuscular disorders such as myasthenia gravis, Lambert–Eaton syndrome, and multiple sclerosis. In these conditions, the toxin may aggravate muscle weakness.[13] The concurrent use of aminoglycosides, calcium channel blockers, cyclosporine, and cholinesterase inhibitors should be avoided because these drugs may potentiate the paralytic effect of the toxin.[14]

Botulinum toxin in wound healing and facial scarring

Wound healing is a complex biological process that involves a series of overlapping steps starting with homeostasis, followed by the inflammatory and proliferative phases, and finally remodeling.[15] The interruption of any of these phases will result in pathological wound healing complications. Mechanical tension applied on the wound during the early period of the healing process represents one of these factors. Such tension has been shown to prolong the inflammatory phase of wound healing resulting in scar hypertrophy. At the cellular level, there is the disruption of dermal fibroblast cytoplasmic extensions and increased local tissue water contents.[16]

Repeated cycles of micro-trauma from the underlying muscles on the healing skin wound are believed to play a role in the prolongation of the inflammatory phase and the increased deposition of collagen and glycosaminoglycans within the wound, resulting in scar hypertrophy and hyperpigmentation.[17,18] To reduce scarring, several surgical concepts have been utilized such as the use of deep sutures, undermining skin edges, flap reconstruction, and orienting the incision along the relaxed skin tension lines. Although such techniques reduce tension, they do not completely eliminate it.[19,20] Utilizing the temporary paralytic effect of botulinum toxin represents an interesting modality to reduce the cycles of micro-trauma in the early phases of wound healing to improve the overall scar quality.[21-27]

Gassner et al[21] investigated the use of the toxin's chemo-denervation to improve forehead scar quality in primates. One half side of the incision was treated with an injection of 7 units of botulinum toxin diluted in 0.9% normal saline and the other side of the incision was injected with 0.9% normal saline. The authors reported a significantly superior cosmetic scar outcome in the toxin group. Histological examination also showed less inflammation in the toxin group.

Lee et al[22] utilized a rat surgical wound model to study several variables such as wound size, degree of inflammation and fibrosis, blood vessel proliferation, thickness of the scar, and the expression of transforming growth factor beta 1 (TGFβ1). Ten units of Botox in 0.5 ml normal saline were injected in the treatment group compared to 0.5 normal saline injected in the control group. The authors showed significant differences in wound size reduction between the two groups at the 3rd and 4th weeks. At the second week, inflammatory cell infiltrates were less in the Botox group compared to controls. The Botox group also showed a smaller number of fibroblasts and less fibrosis than the control group. TGFβ1 expression was lower in the Botox group. There was no significant difference between the two groups in the degree of blood vessel proliferation at all investigative periods.

Several human studies were conducted to investigate the effects of Botox on facial wounds. These studies have proven the safety and efficacy of Botox to improve the eventual appearance of the scar.[1,17,23-27] A controlled prospective randomized clinical trial was conducted by Gassner et al[17] Facial wounds were allocated to receive treatment with either botulinum toxin type A in the study group or normal saline in the control group after wound closure. Photographs and a 10-cm visual analogue scale (zero-worst; ten-ideal) were used to rate the final outcome. The overall median score of the Botox group was 8.9 compared to 7.2 in the control group with a statistically significant difference between the two scores (*P* value of .003).

Gassner et al[1,24] also proposed the use of a mixture of Botox, lidocaine, and epinephrine. Lidocaine injection will result in immediate paralysis of muscle by blocking the efferent neuronal impulses; Botox will mediate delayed muscle paralysis, and epinephrine will help minimize the local diffusion of the injected toxin to adjacent areas. In elective procedures (such as lesion excision and scar revision), chemo-denervation should be done few days prior to surgery to obtain the desired effect at the time of surgery.[25]

Mahboub et al[26] conducted a study utilizing steps to determine the exact location of the muscles underlying the incision and the degree of the muscle tone present. A facial muscular diagram was used to document tension along the wound edges. Electromyography was also done before and after the injection of Botox in facial wounds. This was used as a guide to calculate the dose of the toxin to be injected and to confirm the paralytic effect prior to surgical intervention.

Other authors have shown that the injection of Botox prior to surgery on the skin will inhibit the se-

cretion of nor-epinephrine from the sympathetics, and thus increasing the circulatory perfusion with subsequent improvement of the wound healing process.[27]

Wound healing in patients undergoing reconstructive facial surgery was compared in patients receiving intra-operative injections with either Type A or Type B botulinum toxins. Both types were found to have equal effects.[28]

The uses of Botox as a treatment modality for scars have been extended to include the treatment of hypertrophic scars.[29-35] Botox inhibits the release of various neurotransmitters such as glutamate and substance P; and this inhibits the release of inflammatory mediators such as bradykinin, prostaglandins, and serotonin.[6] This will help reduce scar hypertrophy.

Xiao et al[29] investigated the injection of botulinum toxin type A into hypertrophic scars and showed an improvement in the erythema, itching sensation, and pliability scores in treated patients (patients received up to 35 units of botulinum toxin type A once a month over three months). Limitations of this study include the lack of a control group and the relatively short period of follow up.

Other studies have shown the cellular effects of botulinum toxin type A when incubated with fibroblasts derived from hypertrophic scars. The studies showed shifts in cell cycle distribution of fibroblasts,[30] inhibition of fibroblast growth, and reduction of TGFβ1 expression.[31] Markers such as calcitonin gene-related peptide, and alpha smooth muscle actin were also shown to have a decreased expression.[32] Other studies have shown an inhibitory effect of botulinum toxin type A on "connective tissue growth factor" which is a known mediator of scaring and fibrosis.[33]

Most authors have utilized fibroblasts that are derived from hypertrophic scars. Haubner et al,[34] investigated the effects of Botox on normal human skin fibroblasts and dermal micro-vascular endothelial cells. After incubating the cells with different concentrations of Botox, the toxin did not show any effect on the expression of cytokines or other growth factors (such as monocyte chemoattractant protein 2, fibroblast growth factors, macrophage colony-stimulating factor, and vascular endothelial growth factor). They also showed that the toxin did not affect the cellular proliferation of these two normal cell lines. These findings are interesting because they indicate the selective effect of Botox on abnormal fibroblasts derived from hypertrophic scars.

Other studies utilized animal models to investigate the toxin's effect on hypertrophic scars and showed reduction in the thickness of hypertrophic scars which was associated with reduced collagen expression and normalization of the ratio of collagen I to III.[35,36]A summary of selected studies on the topic is provided in **Table 1**.

Botulinum toxin in cleft lip repair and repair of lower facial wounds

Botulinum toxin chemo-denervation has been applied in cleft lip repair. Knowledge of the facial muscular anatomy and function in cleft patients is required to aid in the interpretation of the botulinum toxin effect. Lip muscles include the orbicularis oris (deep and superficial parts), zygomaticus major, zygomaticus minor, levator labii superioris, levator labii superioris alaeque nasi, and levator anguli oris.[2,37] In cleft lip, there is hypoplasia and interruption of orbicularis oris. Furthermore, there are abnormal muscle insertions to the alar bases [38]. Functional anatomy of the facial muscles varies among patients and even between both sides of the face in the same patient.[39,40] Articulation, facial expression, and oral sphincteric control are important functions the peri-oral muscles.[41] Therefore, the use of Botox in the repair of cleft lip and lower facial wounds may be associated with complications such as oral incompetence, difficulties in speech and whistling, drooling, asymmetric smile, and transient flattening or ptosis of the lip.[42-44] Despite these potential complications, several authors highly recommend the use of Botox the peri-oral region.[41,51-56]

Gassner et al[41] treated lower facial wounds with Botox. The toxin was injected into the orbicularis oris, buccinator, and zygomaticus muscles to reduce the tension over the wound edges. The resulting scars had excellent appearance and patients accepted the minor temporary functional limitations of the mouth.

The repair of the cleft lip deformity represents a special situation because the upper lip pressure is increased after the repair. In wide clefts, the high tension may lead to wound dehiscence. The use of Botox may help reduce this complication in wide clefts. Furthermore, the high pressure across the maxilla may affect the growth of the mid-face.[45,46] Once again, Botox may be of benefit although its paralytic effect is temporary. Similar beneficial effects were demonstrated experimentally using antispasmotic drugs such as Papaverine.[47-50]

The use of Botox in infants undergoing cleft lip repair was shown to be safe and effective. Tollefson et al[51] reported the use of pre-operative injection of botulinum toxin in infants with cleft lip deformity. The toxin was injected 7 days prior to the surgical procedure at a dose of 1 to 2 units/kg. Tension across

Table 1. A summary of studies on the effects of Botulinum toxin on wound healing.

	Type	Target	Parameter	Outcome	Significance	Comment
Xiao et al[31]	In vitro	Fibroblast	Botulinum toxin effect over: -Fibroblast growth rate - Expression of transforming growth factor β1	Slower growth rate than control - Decreased TGF-β1 expression than control	*P*<.01	The cells are derived from hypertrophic scar
Xiao et al[33]	In vitro	Fibroblast	Botulinum toxin effect over: - Fibroblast growth rate - Connective tissue growth factor	- Slower proliferation rate than control - Dose-dependent reduction in the expression of connective tissue growth factor	*P*<.01	The cells are derived from hypertrophic scar
Haubner et al[34]	In vitro	- Dermal fibroblast - Dermal micro-vascular endothelial cells	Botulinum toxin A effect over: - Cell proliferation - Cytokine expression	-No effect over cell proliferation, cytokine nor growth factors expression (interleukin 6, monocyte chemoattractant protein 2, fibroblast growth factor, macrophage colony-stimulating factor, and vascular endothelial growth factor)	-	Botulinum toxin A was incubated in a cell culture model of cutaneous scarring.
Gassner et al[21]	In vivo animal study	Cutaneous scar	Botulinum toxin effect over: - Cosmetic appearance of cutaneous scars	The wounds in treatment group were rated as significantly better in appearance than the control wounds - Histologic examination confirmed that all scars were mature.	*P*<.01	- A randomized, double blind, placebo-controlled primate study - Standardized excisions were made in the forehead of 6 primates
Wang et al[32]	In vivo animal study	Healing wound	Botulinum toxin A effect over: - Healing time - The expression of substance P - The expression of calcitonin gene–related peptide - The expression of transforming growth factor β1 - The expression of alpha smooth muscle actin A	- No effect over healing time. - A dose dependent reduction in the expression of studied parameters than the control group.	-	60 rats were randomly assigned into control group, low-dose group and high-dose group, in which 20 rats were in each group.
Wang et al[35]	In vivo animal study	Fibroblast	Botulinum toxin effect over: - Wound healing time. - Collagen I and III expression - Histological analysis to assess hypertrophic index	- Fibroblasts were more in G2–M phase in control group. -Expression of collagen I, III and the ratio of I to III were higher in control group - Hypertrophic index was lower than control	*P*<.01 *P*<.05	The hypertrophic scar model was established in 16 Japanese rabbits' ears in which one side was used for injection and the other as control

Xiao et al[36]	In vivo animal study	Fibroblast	Botulinum toxin effect over: - Collagen deposition - Scar thickness	- The thicknesses of hypertrophic scars were lower than in the control groups - Collagen fibers were thicker in the control group	*P*<.01	Eight rabbits were employed in this hypertrophic scar model in which one ear was used for injection and the other as control
Lee et al[22]	In vivo animal study	Cutaneous scar in surgical wound	Botulinum toxin effect over: - Wound size, degree of fibrosis, and inflammation, blood vessel proliferation, thickness of the wound, and the expression of transforming growth factor TGF- β1.	- Less infiltration of inflammatory cells than control group - Smaller number of fibroblasts and less fibrosis than control group - Strong collagen density than control group - Lower (GF-1 expression than control group	*P*<.05	- A prospective randomized experimental study involving 15 rats
Gassner et al[17]	Human clinical trial	Surgical and traumatic forehead wounds	Botulinum toxin A effect over: - Enhancing wound healing and scar visualization using 10-cm visual analog scale	- The median visual analog scale score was 8.9 compared with 7.2 for the control group	*P*=.003	A blinded, prospective, randomized clinical trial involving 31 patients
Xiao et al[29]	Human clinical trial	Scar tissue	Botulinum toxin effect over: - Overall therapeutic satisfaction - Scar erythema, itching sensation, and pliability	- Rate of therapeutic satisfaction was high - Erythema, itching sensation, and pliability scores were all lower than before the toxin injection	*P*<.01	- Nineteen patients with hypertrophic scar were randomly assigned - Injections were made 1 month apart for a total of 3 months receiving 2.5 U cm3 of lesion - Follow-up period was at least half a year

the lip was measured using a manometer. The authors reported satisfactory aesthetic results with no complications. They also utilized this modality in infants with wide bilateral clefts.

Galárraga[52] reported the use of Botox (a total of 10 Units) in unilateral cleft lip repair. Electromyography was obtained before the injection of the toxin as well as 10 days after cleft lip repair. The author reported a significant reduction in the electromyographic tracing with no complications.

Other modalities to evaluate the use of Botox in cleft surgery have been utilized. Salgado et al[53] reported the use of a three-dimensional (3D) videography system together with a video-based tracing system to evaluate the peri-oral motion prior to and 1 week after the injection of Botox. The toxin was injected at a dose of 2 units/kg into lip muscles. The authors reported decreased lip displacement by video analysis after the chemo-denervation took effect and the cosmetic outcome was excellent.

Gallego et al[54] utilized a rating scale survey to evaluate the effectiveness of Botox in cleft lip repair. Botox was injected at the time of cleft lip repair and photographs were obtained and compared with a control group. The authors showed that the quality of scar was better in the Botox-treated group.

Finally, botulinum toxin has been used to improve speech and grimacing in patients with cleft lip and palate. Aizenbud et al[55] reported the use of the toxin to modulate nasal and facial grimaces of patients with clefts. Prior to injections, grimacing analysis revealed the hypertonicity of levator labii, levator anguli oris, nasalis, and zygomaticus major and minor muscles. After injecting 30 units of Botox, there was reduction of nasal air emission, complete disappearance of abnormal grimaces, and improvement in speech intelligibility.

Conclusion

Botulinum toxin has proven its safety and efficacy through its chemo-denervative function. It reduces tension on the wound edges by denervating the underlying muscles, and this improves the quality of the resulting scar. The effects of botulinum toxin appear on the cellular and molecular levels as well as on the neurogenic pathways. The use of Botox in cleft lip repair has received special attention and was shown to improve the overall aesthetic outcome. However, controlled randomized clinical trials are required to evaluate the efficacy of such a treatment in patients with cleft lip deformity. Such trials should take in consideration not only ethical issues, but also the cost of the toxin.

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