

COSMETIC APPLICATIONS OF BOTULINUM TOXIN IN OCULOFACIAL REGION

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SUMMARY – The objective of this review was to analyze and compare the efficacy and safety of botulinum toxin for cosmetic oculo-facial use, published in articles during the last two decades. Article searches for relevant data were conducted in 2009 for the last two decades. Controlled studies showed statistically significant improvement in glabellar, frontal, and lateral canthal wrinkles after botulinum toxin therapy. Standardized documentation using clinical examinations and grading by the patient and physician supports the efficacy of botulinum toxin in the treatment of dynamic wrinkles in the glabellar region, frontal region, and lateral canthal area. Complications and unwanted effects associated with the treatment were rare and temporary. Botulinum toxin is safe and efficacious in the treatment of glabellar, frontal and lateral canthal wrinkles. Additional studies are required to assess the efficacy of botulinum toxin for other cosmetic indications. All available data suggest that the possible side effects are infrequent and completely resolved in short term after botulinum therapy. Future research is needed to determine the ideal efficacious dose and concentration for each anatomic area. The use of botulinum toxin in conjunction with laser resurfacing treatment, facial surgical procedures, facial fillers, and other treatment modalities requires further study.

Key words: *botulinum toxin*

Introduction

Botulinum toxin is one of the most potent toxins that blocks the release of acetylcholine at the neuromuscular junction. The use of botulinum toxin has spread through different subspecialties¹⁻⁶ and is probably one of the most investigated usages wherever there is the need to block muscular activity.

Scott *et al.* first used botulinum toxin in 1973⁷, and it was approved by the Food and Drug Administration for use in the treatment of strabismus in 1979. It was used in the management of blepharospasm in 1982. In 1989, the Food and Drug Administration approved botulinum toxin for the treatment of hemifacial spasm and blepharospasm. Demonstrated efficacy

and safety of botulinum toxin for the treatment of blepharospasm, hemifacial spasm and strabismus, and the coincidental finding that facial wrinkles improved in the injected areas of patients treated for noncosmetic indications, led to consideration of botulinum toxin for cosmetic indications. Cosmetic use of botulinum toxin was first reported in 1989⁸, and Carruthers and Carruthers undertook systematic evaluation of botulinum toxin for cosmetic indications⁹⁻¹¹.

The Food and Drug Administration approved the use of botulinum toxin for glabellar wrinkles in 2002. Treatment of other areas like forehead, crow's feet, nasal wrinkles, chin, and platysmal bands are off-label uses. Applications in the treatment of facial asymmetry involving the upper, middle and lower face and neck have been suggested⁸⁻¹¹.

Botulinum toxin is used to treat conditions such as hyperhidrosis, tension headaches, migraine headaches, cervical dystonia, torticollis, adductor and

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abductor laryngeal dystonia, lingual dystonia, limb dystonia, poststroke spasticity, back pain, and other conditions characterized by undesirable muscle contraction such as spastic conditions.

Botulinum toxin has been approved for blepharospasm, axillary hyperhidrosis, strabismus, and cervical dystonia. The Food and Drug Administration approved the cosmetic use of botulinum toxin type A for glabellar wrinkles in 2002¹².

Table 1 summarizes the potential cosmetic uses of botulinum toxin that are suggested in current literature¹³.

Upper face

Glabellar wrinkles
 Upper nasalis wrinkles (bunny lines)
 Lateral canthal wrinkles (crow's feet)
 Horizontal forehead wrinkles
 Asymmetric brows
 Thyroid ophthalmopathy patients with pronounced glabellar wrinkles
 Lower eyelid wrinkles

Midface

Lower nasalis wrinkles, nasal flare
 Short upper lip, gum show
 Perioral wrinkles (smokers' lines)
 Facial asymmetry

Lower face

Mouth frown, melomental folds, drooping labial commissure
 Peau d'orange chin
 Mental crease
 Lower facial asymmetry

Neck

Horizontal necklace lines
 Vertical platysmal folds

Glabellar Wrinkles

A multicenter double-blind study in 264 patients with moderate to severe glabellar wrinkles who received injections of 20 U of botulinum toxin or placebo into 5 sites in the glabella showed a statistically significant reduction in the severity of wrinkles. The decrease in glabellar-line severity at rest persisted longer than the decrease in severity in the lines noted

with maximal frown. The incidence of complications was low, and the most common complication was mild ptosis (5.4%)¹⁴.

A placebo-controlled study in 273 patients assessed efficacy for glabellar lines using a physician rating and found a statistically significant improvement in the botulinum toxin group *versus* placebo group ($P < 0.001$), with a peak effect at 30 days. Side effects included headache in 11% of patients who received botulinum toxin and 20% of patients who received placebo, and blepharoptosis in 1% of patients who received botulinum toxin; 268 of 273 patients completed the study. Follow-up in this study occurred at 7, 30, 60, 90, and 120 days¹². Both placebo-controlled studies found botulinum toxin to be safe and efficacious in reducing glabellar lines^{12,14}.

A randomized study in 30 patients using 10 U of botulinum toxin injected in the glabellar area used a physician and a patient scale for outcome assessment. Injections significantly reduced wrinkles in the botulinum toxin group at 2 and 12 weeks, with a duration of 17.8 weeks¹⁵.

A case series of 30 patients reports improvement in glabellar wrinkles with botulinum toxin injection. This study showed 62% elevation of the brow with 20 U of botulinum toxin. No adverse effects were reported¹⁶.

Glabellar and Forehead Wrinkles

Two case series offered data on injection of the glabellar area and forehead. Outcome of one study was assessed using digital overlay photography to standardize the patient position and lighting. The frontal area had more prolonged onset and duration of effect than the glabellar area. Frontal muscle action was 35% at 2 weeks, and glabellar frowning was 7%. Interbrow distance increased by 13% with the treatment¹⁷.

Another case series used botulinum toxin type A injections in 12 patients in 26 paired regions: 12 glabellar, 10 orbicular, and 4 forehead. Patient estimate of efficacy was excellent in 3, very good in 4, good in 2, and fair in 1, with 10 of 11 patients completing the survey. Ecchymosis and brow ptosis were reported as adverse effects¹⁸.

Forehead Wrinkles

A dose-related response was noted in a randomized, double-masked, controlled trial showing greater

efficacy and longer duration of effect in reducing horizontal wrinkles with higher doses of botulinum toxin. The procerus and orbicular muscles were also included in the injection pattern. Fifty-nine female patients were randomized to receive a total of 16, 32, or 48 U of botulinum toxin injected into 8 injection sites. The cosmetic benefits lasted longer than the direct action on contraction. Adverse reactions included headaches, local pain and swelling, and brow ptosis¹⁹.

Lateral Canthal and Lower Eyelid Wrinkles

A double-masked randomized study (n=60) compared 6, 12, and 18 U of botulinum toxin in the orbicular muscle of eye on one side and placebo on the other side. Grading was documented at 4-week intervals for 16 weeks. Results showed that botulinum toxin was efficacious in decreasing wrinkles (botulinum toxin *vs.* placebo, $P \leq 0.045$), with no dose-response relationship²⁰. No severe adverse reactions were noted. Eleven percent to 25% in various treatment groups had mild bruising.

A randomized double-masked study in 10 women volunteers compared the use of botulinum types A and B for the treatment of lateral canthal wrinkles. All patients noted reduction of lateral canthal wrinkles. Botulinum type B produced slightly more discomfort on injection and more rapid onset but briefer duration of action. Return of wrinkles occurred in 60 days²¹.

Randomized subjects with moderate to severe crow's feet at maximum smile (mild to severe at rest) received a single bilateral botulinum-A treatment (15, 30, or 45 U) or placebo. Patient satisfaction was significantly greater for all doses than for placebo for 16 weeks ($P < 0.05$ all). All doses were well tolerated²².

Conclusions

Numerous studies support the short-term efficacy and safety of botulinum toxin for several facial cosmetic indications. Patient satisfaction, physician evaluations, and photographic analysis in randomized double-masked controlled studies support the efficacy of botulinum toxin treatment of wrinkles in the glabellar area, forehead and lateral canthus. More studies are required to assess the efficacy of botulinum toxin for other facial and neck cosmetic indications.

All available data suggest that short-term side effects are infrequent and completely resolved in no

more than several months. The frequency of adverse periocular effects may be limited to some degree by certain precautions with dosage and injection technique. Future research is needed to determine the ideal efficacious dose and concentration for each anatomic area. The use of botulinum toxin in conjunction with laser resurfacing treatment, facial surgical procedures, facial fillers, and other treatment modalities requires further study.

References

- SCHERER JR, KWIAK MA, SOPER NJ, PANDOLFINO JE, KAHRILAS PJ. Functional esophagogastric junction obstruction with intact peristalsis: a heterogeneous syndrome sometimes akin to achalasia. *J Gastrointest Surg* 2009;13:2219-25.
- SHAW L, RODGERS H. Botulinum toxin type A for upper limb spasticity after stroke. *Expert Rev Neurother* 2009;9:1713-25.
- PANIELLO RC, EDGAR JD, PERLMUTTER JS. Vocal exercise *versus* voice rest following botulinum toxin injections: a randomized crossover trial. *Ann Otol Rhinol Laryngol* 2009;118:759-63.
- PLACZEK R. Botulinum toxin A in children with infantile cerebral palsy: indications and treatment concepts. *Orthopade* 2010;39:23-30.
- OECONOMOU A, MADERSBACHER H. Botulinum neurotoxin A for benign prostatic hyperplasia. *Curr Opin Urol* 2010;20:28-36.
- PARK AJ, PARAISO MF. Successful use of botulinum toxin type A in the treatment of refractory postoperative dyspareunia. *Obstet Gynecol* 2009;114(2 Pt 2):484-7.
- SCOTT AB, ROSENBAUM A, COLLINS CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol* 1973;12:924-7.
- CLARK RP, BERRIS CE. Botulinum toxin (a treatment for facial asymmetry caused by facial nerve paralysis). *Plast Reconstr Surg* 1989;84:353-5.
- CARRUTHERS J, CARRUTHERS A. Botulinum toxin (botox) chemodenervation for facial rejuvenation. *Facial Plast Surg Clin North Am* 2001;9:197-204.
- CARRUTHERS J, CARRUTHERS A. Botox use in the mid and lower face and neck. *Semin Cutan Med Surg* 2001;20:85-92.
- CARRUTHERS A, CARRUTHERS J. Botulinum toxin type A (history and current cosmetic use in the upper face). *Semin Cutan Med Surg* 2001;20:71-84.
- CARRUTHERS JD, LOWE NJ, MENTER MA, GIBSON J, EADIE N. Botox Glabellar Lines II Study Group. Double-blind, placebo-controlled study of the safety and ef-

- ficacy of botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg* 2003;112:1089-98.
13. KALTREIDER SA, KENNEDY RH, WOOG JJ, BRADLEY EA, CUSTER PL, MEYER DR. Cosmetic oculofacial applications of botulinum toxin: a report by the American Academy of Ophthalmology. *Ophthalmology* 2005;112:1159-67.
 14. CARRUTHERS JA, LOWE NJ, MENTER MA, GIBSON J, NORDQUIST M, MORDAUNT J, *et al.* Botox Glabellar Lines I Study Group. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol* 2002;46:840-9.
 15. LOWE NJ, MAXWELL A, HARPER H. Botulinum A exotoxin for glabellar folds (a double-blind, placebo-controlled study with an electromyographic injection technique). *J Am Acad Dermatol* 1996;35:569-72.
 16. PRIBITKINEA, GRECOTM, GOODERL, KEANEWM. Patient selection in the treatment of glabellar wrinkles with botulinum toxin type A injection. *Arch Otolaryngol Head Neck Surg* 1997;123:321-6.
 17. HECKMANN M, SCHON-HUPKA G. Quantification of the efficacy of botulinum toxin type A by digital image analysis. *J Am Acad Dermatol* 2001;45:508-14.
 18. GOODMAN G. Botulinum toxin for the correction of hyperkinetic facial lines. *Australas J Dermatol* 1998;39:158-63.
 19. CARRUTHERS A, CARRUTHERS J, COHEN J. A prospective, double-blind, randomized, parallel-group, dose-ranging study of botulinum toxin type A in female subjects with horizontal forehead rhytides. *Dermatol Surg* 2003;29:461-7.
 20. LOWE NJ, LASK G, YAMAUCHI P, MOORE D. Bilateral, double-blind, randomized comparison of 3 doses of botulinum toxin type A and placebo in patients with crow's feet. *J Am Acad Dermatol* 2002;47:834-40.
 21. MATARASSO SL. Comparison of botulinum toxin types A and B (a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides). *Dermatol Surg* 2003;29:7-13.
 22. ASCHER B, RZANY BJ, GROVER R. Efficacy and safety of botulinum toxin type A in the treatment of lateral crow's feet: double-blind, placebo-controlled, dose-ranging study. *Dermatol Surg* 2009;35:1478-86.

Sažetak

KOZMETSKA PRIMJENA BOTULINUM TOKSINA U PODRUČJU OČIJU I LICA

D. Šarić

Cilj ovoga prikaza je analiza i usporedba učinkovitosti i neškodljivosti upotrebe botulinum toksina za kozmetičku primjenu na licu objavljenih u literaturi tijekom posljednja dva desetljeća zaključno s 2009. godinom. Kontrolirane studije pokazale su statistički značajno poboljšanje bora na području čela, među obrvama te lateralnih kantalnih bora nakon terapije botulinom toksinom. Standardizirana dokumentacija kliničkih pregleda kako ju ocjenjuju liječnici i klijenti govori u prilog djelotvornosti botulinum toksina u navedenim područjima lica. Komplikacije i neželjene pojave su rijetke i prolazne. Terapija botulinom toksinom je sigurna i učinkovita u obradi bora glabellarne, frontalne i lateralne kantalne regije lica. Potrebne su dodatne studije za procjenu uspješnosti terapije botulinom toksinom za druge indikacije. Svi dostupni radovi govore u prilog činjenici da su moguće neželjene pojave nakon ove terapije rijetke i u potpunosti nestaju kroz kratko vrijeme od nastanka. Daljnja će istraživanja pokazati koje su doze i koncentracije botulinum toksina optimalne u pojedinoj anatomske regiji. Upotreba botulinum toksina u kombinaciji s laserskom terapijom pojedinih regija lica, te kombinacije s ostalim tretmanima navedenih regija zahtijevaju daljnja istraživanja.

Ključne riječi: *botulinum toksin*