Neurotoxins: Evidence for Prevention

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ABSTRACT

Onabotulinum Toxin A is the gold standard treatment for temporary dynamic rhytid reduction. Clinicians have observed a long-term and preventive benefit for patients beyond muscle relaxation particularly in patients who receive repeated treatments over time. These changes include progressive reduction of rhytides, prevention of dynamic rhytides, and improvements in skin quality. In this brief paper, we review basic science, clinical, and anecdotal evidence that explores a long-term and potential preventive effect of Onabotulinum Toxin A injections.

J Drugs Dermatol. 2017;16(6 Suppl):s87-90.

INTRODUCTION

Since its introduction for the treatment of glabellar rhytides over two decades ago, botulinum toxin type A (BoNTA) has since become the most frequently performed cosmetic procedure in the United States[1] and is considered the gold standard treatment for dynamic facial wrinkles. BoNTA injections block the release of acetylcholine required for muscle contraction, causing temporary paralysis of the treated muscle.[2] However, there is evidence that regular, repeated treatments provide aesthetic benefit independent of muscular chemodenervation.[3-6] Although the exact mechanism of action is unknown, limited clinical studies, case studies, and personal experience cumulatively suggest that long-term use of BoNTA not only prevents the formation of new wrinkles but also leads to progressive improvements in skin quality and the appearance of established rhytides.

Long-term Effects: Review of the Evidence

Studies evaluating the long-term efficacy and safety of BoNTA injections beyond a year are scarce, and there are few reports evaluating the clinical benefits of repeated treatments over the course of many years. In the early nineties, Binder began documenting the facial changes over time in two identical twins living in different countries in what would become a 19-year case-report demonstrating that prophylactic use of BoNTA over a long period of time can prevent the formation of static.[4,6] One twin (based in Los Angeles) received BoNTA in the forehead and glabella regularly every 4 to 6 months for 19 years. For the last 8 years, she received additional treatment in the periorbital region. The other twin (based in Munich, Germany) received a total of four treatment sessions in the forehead, glabella, and crow's feet over the entire study. Photographs reveal a striking contrast between the two women. The treated twin displays no evidence of forehead or glabellar lines at rest, while the sporadically treated twin has visible static forehead rhytides. Similarly, the treated twin exhibits mild dynamic crow's feet; deeper lines are evident in the sporadically treated twin. Interestingly, skin texture also improved in the treated twin, while the skin of the sporadically treated twin shows signs of aging, with greater number of wrinkles and visible pores. Of note, neither twin used any topical retinoid preparation or received any other cosmetic treatments.

The long-term effects may go beyond the prevention of new wrinkles. Bowler published a case series of two individuals (one male, one female) who received 21 to 24 treatment sessions over a 7-year period every 3 to 6 months for glabellar, forehead, and periorbital rhytides.[3] Post-treatment skin quality significantly improved compared to pre-treatment in terms of wrinkles reduction and skin smoothness, with eventual effacement of non-reducible forehead lines. Similarly, Dailey demonstrated a cumulative reduction in wrinkle severity in 50 women who received 20 U BoNTA for glabellar rhytides in repeated treatment cycles (every 4 months) over a 20-month period.[5] Progressive improvement from baseline in facial wrinkles continued up to 6 months after treatment ended. Given the downward trend in wrinkle severity, the author suggests that further wrinkle effacement could be achieved with continued treatment beyond 2 years. Moreover, it may be possible to widen the treatment interval between sessions without losing aesthetic benefit, an important consideration for patient satisfaction.

Mechanism of Action: Theoretic Possibilities

There are several theories to explain the progressive reduction in wrinkle severity and improvements in skin quality observed after repeated treatments over a long period of time. First: the theory of learned response, in which patients learn to avoid using facial muscles that lead to wrinkle formation. There is also evidence of long-term physiologic change in the muscle itself (ie, atrophy) of up to 12 months after a single, low dose of BoNTA.[7] It is obvious that wrinkle formation stops after muscle

motion is inhibited, at least until the effects of the toxin begin to wane. Less clear, however, is why established rhytides appear to fade with repeated treatment sessions. Some evidence points to a direct effect on the skin at the histologic level that is not due to local inflammation.[7]

Human skin has three key biomechanical features: strength, pliability (ability to stretch), and elasticity (ability to recoil).[7] These biomechanical properties change as we age; skin elasticity, in particular, undergoes a progressive decline over time that accelerates with ultraviolet (UV) exposure.[9] Recent evidence suggests that the use of BoNTA also results in alteration in skin elasticity and pliability, producing characteristics consistent with youthful skin.[8,10] A prospective cohort study of 48 BoNTA-naïve women examined elastic recoil and pliability of the skin after only one treatment session using low doses in the glabella, forehead, and lateral orbit.[10] Elasticity and pliability was assessed at 2 weeks, 2 months, 3 months, and 4 months after treatment using a Cutometer. Mean pliability significantly increased from baseline at 2 and 3 months post-treatment across all sites. Significant improvements in elastic recoil were noted at 2 months for all sites, but only in the glabella for months 3 and 4, which correlates to the clinical observation that treatment in the glabella typically lasts longer than in the forehead or lateral orbit. The authors highlight that the biomechanical changes induced by BoNTA are the opposite of those that develop with aging and suggest the results may reflect a change in the organization of collagen network in the dermis.

The dermal extracellular matrix (ECM) is composed mainly of collagen (types I and II) in addition to glycosaminoglycans and elastic fibers.[11] Collagen is the most abundant protein in human skin and responsible for maintaining structural integrity and proper functioning within the ECM. In aged skin, disorganization of this collagen network contributes to skin laxity and wrinkle formation.[12] El-Domyati and colleagues obtained skin biopsy specimens from 16 volunteers with moderate-to-severe wrinkles before and 3 months after a single injection of BoNTA in the periorbital region.[13] Immunohistochemical changes failed to show a difference in collagen or elastin levels. However, treatment led to a significant increase in wrinkle width and granular layer thickness, and the collagen bundles became more organized and compact around the wrinkles, with the appearance of regular and smooth fibers, compared to the disorganized, enhanced breakdown of collagen seen on baseline biopsy. These findings may explain the extended improvements observed after repeated BoNTA injections: perhaps results are not solely due to ongoing denervation of facial muscles but can also be attributed to potential dermal remodeling.

Certainly, this theory has been suggested elsewhere in the literature. Some physicians have noted a face-lifting effect after intradermal injection of BoNTa, attributed, in part, to increased collagen synthesis.[14-15] However, it has also been argued that percutaneous injury with needles initiates the wound-healing cascade that eventually results in collagen production, rather than any direct influence on fibroblasts.[16,17] To weigh in on this controversy, Oh and colleagues investigated the effect of BoNTA on cultured human dermal fibroblasts in vitro.[18] Fibroblasts secrete the precursors of collagen, procollagen types I and II. Dermal remodeling requires activation of fibroblasts and is an essential aspect of facial rejuvenation. Fibroblasts treated with BoNTA showed increased production of procollagen type I carboxy-terminal peptide (PIP), which indirectly reflects overall collagen I levels, and reduced expression of two matrix metalloproteases (MMPs), the enzymes

FIGURE 1. 52-year-old male before (A) and after (B) 10 years and 18 treatments of onabotulinumtoxin A to the glabella, forehead, and lateral canthal region.

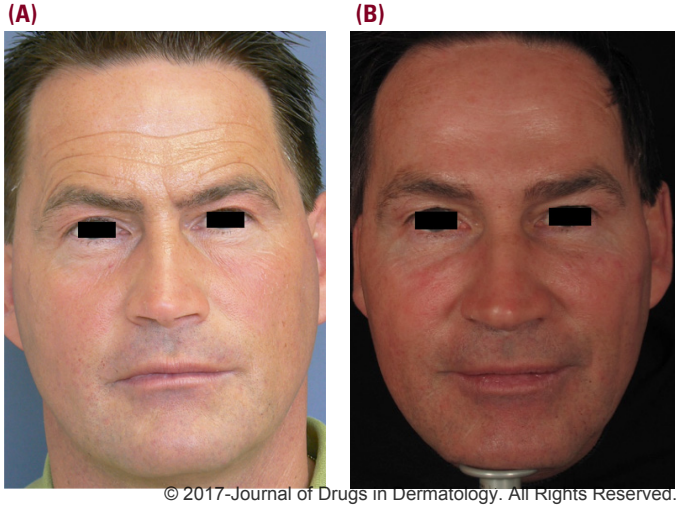

FIGURE 2. 48-year-woman before (A) and after (B) 10 years and 20 treatments with onabotulinumtoxin A to the glabella and lateral canthal region.

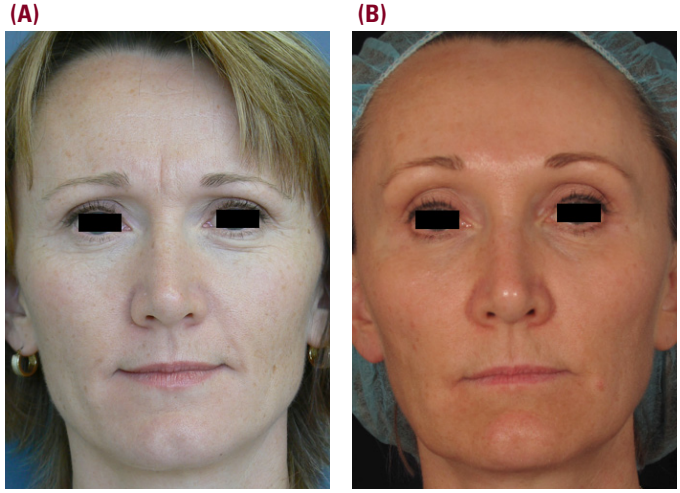

FIGURE 3. 54-year-old female over a 7-year period (A-G) during which she received 23 treatments with onabotulinumtoxin A to the glabella.

responsible for the degradation of collagen and other components of the ECM.[18] Levels of two pro-alpha collagen chains—alpha-1, the major component of type I collagen, and alpha-2—were also higher after treatment. These results provide further evidence that BoNTA promotes fibroblast activity and has the potential to stimulate dermal remodeling.

Anecdotal Evidence

Evidence-based medicine is the optimal approach for patient care. As individual clinicians, however, we are heavily influenced by clinical observation and patient feedback. Clinical practice yields certain observation: first, regular, sustained injections of BoNTA lead to consistent, ongoing improvements in wrinkles—initial treatment leads to softening of wrinkles that often fill in over time with repeated injections; second, long-term treatment leads to an intangible improvement in skin quality, with improved light reflection for skin that is more luminous and radiant (Figures 1-3). Patient satisfaction is higher for men and women who receive regular injections over several years compared to those who receive only sporadic treatment, and this makes sense: a regular treatment regimen means that muscles do not regain function, the skin is not repeatedly creased by dynamic musculature, and the collagen network is able to reorganize cohesively in a way that prevents the formation of new wrinkles for a more youthful appearance and better clinical results.

CONCLUSION

Over the past two decades, BoNTA has become an indispensible part of aesthetic medicine and the most popular non-invasive option for facial rejuvenation. However, evidence suggests that injections do more than temporarily stay wrinkle formation. Data show that BoNTA alters biomechanical properties of the skin and may enable dermal remodeling for improvements in elasticity, pliability, and radiance. Although clinical evidence for the prophylactic use of BoNTA may be limited, anecdotal evidence and case studies tell us what we have yet to prove

via controlled trials: repeated treatment cycles with BoNTA for facial rhytides over a long period of time not only prevent new wrinkle development but also improve skin texture and appearance and lead to progressive wrinkle reduction of established rhytides. Clinically, these reports and observations translate to better aesthetic outcomes and much higher levels of patient satisfaction.

DISCLOSURES

The author has not disclosed any conflicts of interest.

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