Medicine®

CLINICAL CASE REPORT

OPEN

Nonallergic Eyelid Edema After Botulinum Toxin Type A Injection

Case Report and Review of Literature

Yin-Shuo Chang, MD, Chang-Cheng Chang, MD, Jen-Hsiang Shen, MD, Yu-Tsung Chen, MD, and Karen Kar-Wun Chan, MD

Abstract: Periocular botulinum toxin type A (BoNTA) injections are generally safe. Ptosis is the most common adverse effect, whereas eyelid edema is rarely reported. There is no consensus on the latter's incidence, clinical course, or treatment strategy.

Here we managed a 59-year-old woman who received BoNTA injections to her forehead, glabella, and eye corner. At 3-day follow-up, she presented with painless, nonpruritic, bilateral periorbital edema, and erythema. Preliminary diagnosis was a local allergic reaction, and topical corticosteroid was administered, but upon lack of improvement, edema secondary to venous and lymphatic congestion was hypothesized, and she was advised to apply hot pads over her eyes, blink frequently, and massage the area. Her eyelid edema resolved 2 weeks later. At 4-month follow-up, the patient requested and received another course of BoNTA at half the dose. Frequent blinking was instructed, and the patient reported a satisfactory outcome with no adverse effects.

In our literature review, incidence of BoNTA-induced eyelid edema was 1.4% and showed Asian tendency. Although rare, BoNTA-induced periorbital edema is self-limiting, and normally resolves in 2 to 4 weeks without medical treatment. Patients at risk for edema, including Asian ethnicity, dermatochalasis, and poor periocular muscle tone, are advised to receive injections at half the dosage. Examination of the function and tone of the orbicularis oculi and levator palpebrae superioris muscles before treatment is recommended, and application of hot pads over the eyes, frequent blinking in the morning, and self-massage of the affected area to increase venous return have demonstrated to improve outcome.

Editor: Ismael Maatouk.
Received: June 29, 2015; revised: August 9, 2015; accepted: August 26, 2015.
From the Department of Dermatology (Y-SC), Taipei Medical University Hospital, Taipei City, Taiwan; Aesthetic Medicine Center (Y-SC, C-CC, J-HS), Department of Plastic Surgery, Chang Gung Memorial Hospital, Puzi City, Chiayi County, Taiwan; Department of Cosmetic Science (C-CC), Chang Gung University of Science and Technology, Kwei-Shan, Taoyuan, Taiwan; Department of Ophthalmology (J-HS), Chang-Gung Memorial Hospital, Taoyuan County, Taiwan; Department of Dermatology (Y-TC), Shung Ho Hospital, New Taipei City, Taiwan; and Hospital Authority (KK-WC), Hong Kong SAR.
Correspondence: Chang-Cheng Chang, Aesthetic Medicine Center, Department of Plastic Surgery, Chang Gung Memorial Hospital, No. 6 Chia-Pu Rd., West Sec., Puzi City, Chiayi County 613, Taiwan (e-mail: changcc@adm.cgmh.org.tw).
Informed Consent Patient has provided informed consent for the publication of the case report. The study was also approved by the institutional review board of the Chang Gung Memorial Hospital (CGMH 103-1942B).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001610

(*Medicine* 94(38):e1610)

Abbreviation: BoNTA = botulinum toxin type A.

INTRODUCTION

Botulinum neurotoxin type A (BoNTA) is widely used in aesthetic medicine as treatment for glabellar lines. BoNTA blocks the release of the neurotransmitter acetylcholine, resulting in blockage of neuromuscular transmission and paralyzing the target muscle. Therefore, injection of BoNTA can reduce muscle activities, decrease muscle tension, and smooth facial wrinkles.[1,2] BoNTA therapy is associated with a low rate of adverse effects. In the largest multidepartment retrospective study conducted to date, Kim et al[3] reported that the incidence of adverse events after BoNTA injection was only 3.73%.

Most adverse events related to BoNTA injection are minor and transient, and composed of eye disfiguration and vision blockage. Symptoms normally present approximately 2 weeks after injection and persist for about 15 days (range, 7–85 days).[4,5] To date, however, there is no consensus on the incidence of and treatment for all types of adverse effects after injection of BoNTA.

Although ptosis is a frequent side effect of BoNTA injection,[3] eyelid edema is a less common adverse effect of BoNTA treatment, and few studies have investigated its etiology, clinical course, and treatment outcomes. Herein we present a case with bilateral periorbital swelling and erythema after BoNTA injection. Total duration of follow-up was 16 weeks.

CASE REPORT

A 59-year-old woman with a history of well-controlled asthma received BoNTA therapy to smooth wrinkles on her forehead, glabella, and corners of her eyes (crow's feet). Physical examination revealed thick, triangular-shaped eyelids with infolding of the upper eyelid (Figure 1A).

Therapy compriss BoNTA (BOTOX®, Allergan, Inc, Irvine, CA, 100 U in 4 mL normal saline) injections to the forehead (12.5 U), glabella (12.5 U), and eye corners (crow's feet) (12.5/12.5 U). A 5-point injection was performed to glabella and eye corners.

At 3-day follow-up, the patient presented with painless, nonpruritic, bilateral periorbital swelling and erythema. Physical examination revealed no evidence of skin rash, tenderness, or conjunctival congestion. The preliminary diagnosis was a local allergic reaction to BoNTA. A topical corticosteroid (Rinderon® oph ointment, Shionogi, Taiwan) was administered to the swollen periorbital region 2 times per day for 3 days. However, the medication did not result in symptom relief (Figure 1B).

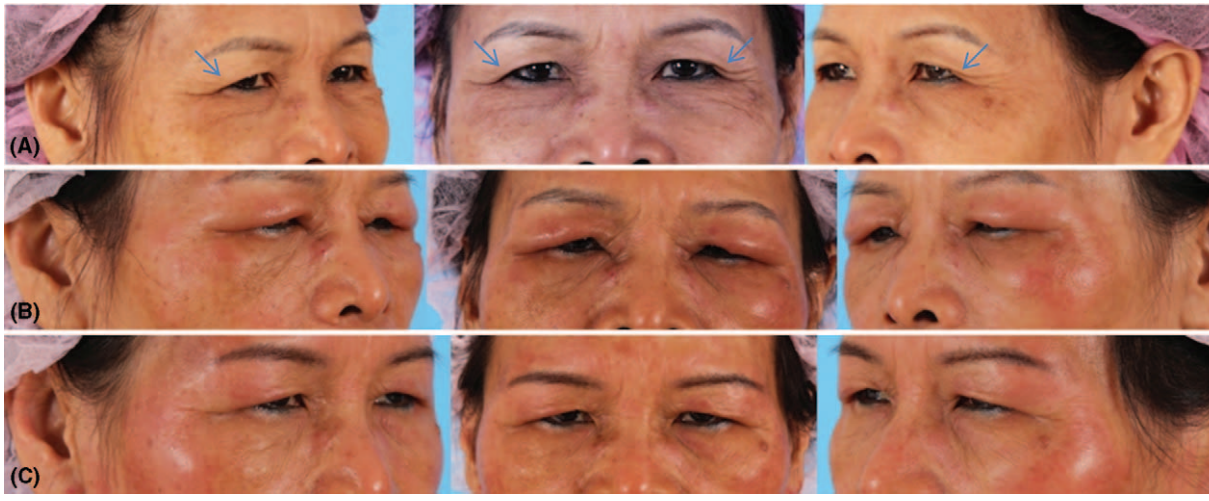

FIGURE 1. (A) Patient before botulinum neurotoxin type A injections. The patient presents with eye puffiness, eyelid hooding, and dermatochalasis (arrow), which are risk factors for secondary lymphostasis and eyelid edema. (B) One week after botulinum neurotoxin type A injections. Bilateral periorbital swelling and mild erythema are noted 3 days after injection. The patient was advised to apply hot pads over her eyes, blink frequently, and self-massage the affected area in order to increase venous return. No antibiotics or antihistamines were used. (C) Two weeks after the patient first presented with bilateral periorbital swelling and erythema. The swelling and erythema have resolved.

Based on the clinical course, we hypothesized that eyelid edema was most likely due to impaired venous and lymphatic return caused by reduced muscle tone rather than allergic reaction or infection. We advised the patient to apply hot pads over her eyes, blink frequently, and massage the affected area in order to increase venous return. No antibiotics or antihistamines were prescribed. The patient's eyelid edema eventually resolved 2 weeks later (Figure 1C).

At 4-month follow-up, the patient requested an additional course of BoNTA therapy. This time, we adjusted the dose to half of the original. We instructed the patient to blink frequently, especially in the early morning after long-term venous stasis during sleep, and to massage the periorbital area to increase venous return. No adverse effects were noted after the second treatment and the patient reported a satisfactory outcome (Figure 2A,B).

DISCUSSION

The most common complications among patients who receive BoNTA to eye corner for treatment of crow's feet are bruising, dry eye, corneal exposure, diplopia, ectropion, lid retraction, other lid malpositions, and an asymmetrical smile (caused by the spread of toxin to the zygomaticus major).[6] Little is known about the development of periocular eyelid edema after botulinum toxin injection. In a retrospective study of 5310 botulinum toxin injection treatments among 1819 patients, only 2 (0.04%) patients developed eyelid edema.[3] In a meta-analysis of BoNTA injection for the treatment of glabellar lines or crow's feet in 1678 patients, Brin et al[4] found that the median time of eyelid edema onset was 5 days (range, 2–106 days) and that the median duration of symptoms was 15 days (range, 7–85 days). They also found that the incidence of treatment-related eyelid edema (1.4%, 21/1492) was significantly higher among patients who received 20 U botulinum toxin A injection than among those who received placebo. Furthermore, the researchers noted that Asian populations are at greater risk for BoNTA-induced eyelid edema than Caucasian populations (3.1%, 8/260 vs 0.7%, 4/614).[4]

Eyelid edema is often due to allergy, infection, or trauma, but can be caused by poor venous or lymphatic return to the eyelid or decreased muscle tone. Definitive diagnosis can be made by understanding the mechanism and tracing the clinical course if there is no response to antiallergic treatment. Procedural and possibly even local adverse effects are likely to be

FIGURE 2. (A) Four months later, the patient underwent a second procedure where BoNTA of half the previous dosage was injected in the perioccular region. (B) One week after the injection. No adverse effects were noted this time.

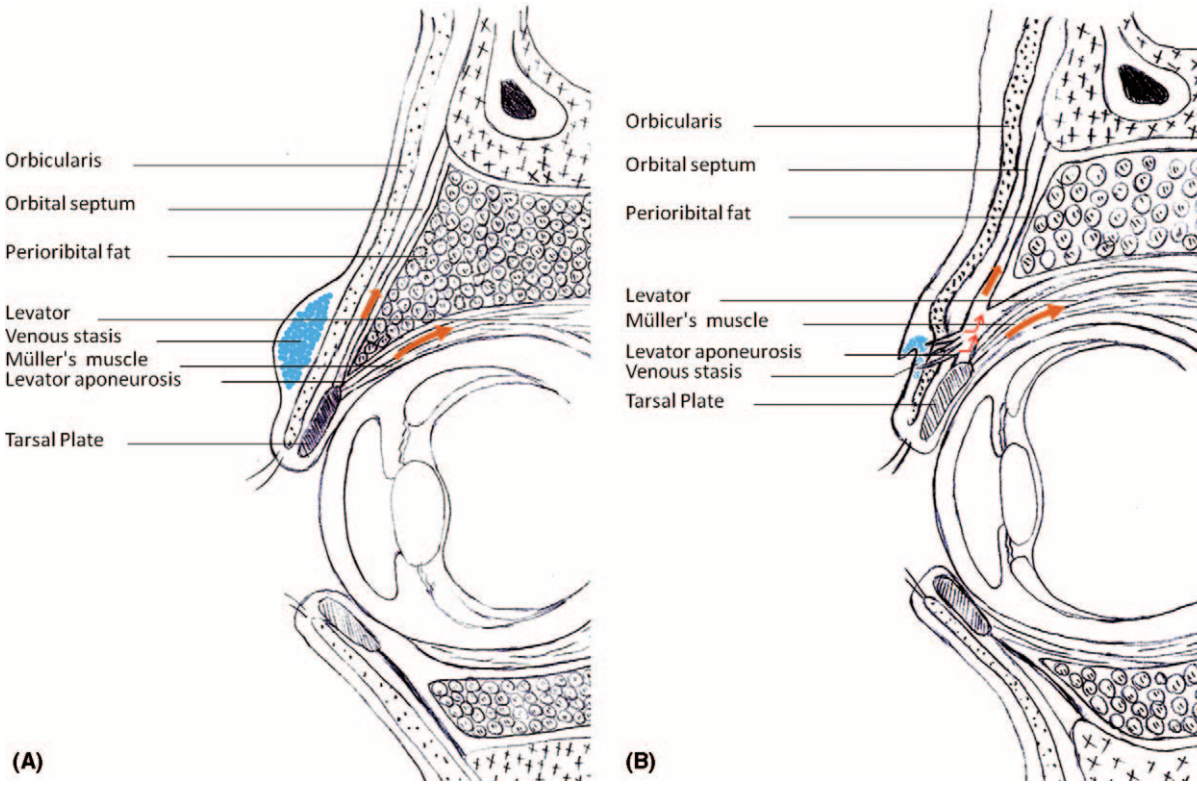

FIGURE 3. (A) Asian eyelid: the orange arrow indicates the stretch direction of eyelid retraction. There are fewer fibrous attachments between the levator aponeurosis, the orbicularis, and skin of the eyelid, which leads to less contracture and a decrease in venous drainage function. More perioribital fat is noted. These features cause the characteristic puffiness and increase the possibility of venous stasis. (B) Caucasian eyelid: less perioribital fat is noted. The end fibers of the aponeurosis implanted into the orbicularis and skin bring additional traction force in the inner and upper directions (red arrows). The stretch between aponeurosis and the insertions further improves venous drainage function and decreases the possibility of venous stasis.

related, to some extent, to injector experience, and are thus expected to decline with the number of treatment cycles. We found that repeated treatments are associated with a lower incidence of eyelid ptosis, eyelid sensory disorder, and eyelid edema. Similar findings were reported by Brin et al.[4]

Multiple muscles are involved in the blinking reflex. In the upper eyelid, the levator palpebrae superioris, which divides into an aponeurosis and a deeper portion that contains the Müller's (superior tarsal) muscle, is responsible for eyelid retraction. The orbicularis oculi is the main muscle that controls closing of the eyes. Pretarsal and posttarsal plexuses contain the venous drainage of the eyelid, which included ophthalmic vein and the veins that drain the forehead and temple. Preauricular and parotid nodes drain the lymphatics from the lateral segment of the lids. Submandibular lymph nodes drain the medial side of the lids.[7]

In our case, eyelid edema onset was 3 days after 12.5 U botulinum toxin injections each to the glabella and bilateral eye corners. The total duration of treatment was 2 weeks. Kim et al[3] suggested that the local spread of toxin into adjacent muscle and tissue might be responsible for the development of eyelid edema. Brin et al[4] suggested that the relaxation of the underlying muscle tone after periocular injection with BoNTA and its secondary effects on interstitial fluid mechanics were the main reasons for the development of eyelid edema. Based on the findings in this study, we propose that the mechanism governing the development of eyelid edema after BoNTA injection might be the combined effect of venous or lymphatic stasis related to the individual eyelid structure and decreased muscle tone caused by local diffusion of neurotoxin, which lessens the interstitial fluid return against gravity. The mechanism of eyelid edema is different from ptosis, which is caused by unintended relaxation of the levator muscle.[4]

Eyelid edema due to impaired mechanical venous return is more common in Asians than Caucasians.[4] In Asians, there are fewer fibrous attachments between the levator aponeurosis, orbicularis, and skin of the eyelid. This results in a lack of supratarsal crease and less eyelid retraction for venous drainage while blinking.[8,9] The fusion of the levator aponeurosis and orbital septum is closer to the eyelid margin, causing the characteristic puffiness in Asian eyelids.[9,10] This puffiness compresses the vein and obstructs venous return, which is already impeded by gravity (Figure 3A,B).

Another characteristic of Asian eyes is eyelid hooding (dermatochalasis). Patients with dermatochalasis tend to have less elastic fibers and greater breakdown of collagen networks, which lead to secondary lymphostasis and eyelid edema.[11] Incidence of dermatochalasis increases with age,[12] and was also noted in our patient, who was 59 years old. The excess of skinfolds also hinders venous return (Figure 1A). Based on the

TABLE 1. The Mechanism, Clinical Course, Risk Factors, Treatment, and Prevention Strategies for Eyelid Edema After BoNTA Injection Based on Findings in the Literature Review and Our Opinion

Study	Mechanism	Clinical Course	Risk Factors	Treatment Strategy	Prevention
Brin et al 2009 Total	Relaxation of the underlying muscle tone and secondary effects on interstitial fluid mechanics	Onset: 5 (2–106) d Duration: 15 (7–85) d	Asian ethnicity	N/A	N/A
Kim et al 2013 South Korea	Local spread of toxin into adjacent muscle and tissue	N/A	Female Higher dose	Not needed any treatment	N/A
Chang et al 2015 Taiwan	1. Mechanical venous or lymphatic stasis related to the individual eyelid structure 2. Decreased muscle tone caused by local diffusion and of neurotoxin	Onset: 3 d Duration: 2 wk	1. Asian ethnicity 2. Dermatochalasis 3. Poor periocular muscle tone 4. Higher dose	1. Applying hot pads 2. Frequent blinking 3. Self-massage of the affected area 4. No medication required	1. Performing winking test first 2. Dose and injection points adjustment

mechanical factors governing eyelid edema after periocular BoNTA injection, we suggest that patients undergo examination of the function and tone of the orbicularis oculi and levator palpebrae superioris muscles before treatment as preventive strategies. Doses of BoNTA and injection points should be adjusted in patients at risk for developing periorbital edema (Table 1).

CONCLUSION

Although rare, periorbital edema due to BoNTA injection is self-limiting and does not require medical treatment. As reflected from the case, edema can be managed by application of hot pads over the eyes, frequent blinking in the morning, and self-massage of the affected area in order to increase venous return. Preventive strategies include examination of the function and tone of the orbicularis oculi and levator palpebrae superioris muscles before treatment. Patients at risk for edema such as Asian ethnicity, dermatochalasis, and poor periocular muscle tone should receive half the usual dosage of BoNTA.

REFERENCES

1. Ascher B, Talarico S, Cassuto D, et al. International consensus recommendations on the aesthetic usage of botulinum toxin type A (Speywood Unit)—part I: upper facial wrinkles. *J Eur Acad Dermatol Venereol.* 2010;24:1278–1284.
2. Ascher B, Talarico S, Cassuto D, et al. International consensus recommendations on the aesthetic usage of botulinum toxin type A (Speywood Unit)—part II: wrinkles on the middle and lower face, neck and chest. *J Eur Acad Dermatol Venereol.* 2010;24:1285–1295.
3. Kim BW, Park GH, Yun WJ, et al. Adverse events associated with botulinum toxin injection: a multidepartment, retrospective study of 5310 treatments administered to 1819 patients. *J Dermatolog Treat.* 2014;25:331–336.
4. Brin MF, Boodhoo TI, Pogoda JM, et al. Safety and tolerability of onabotulinumtoxinA in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. *J Am Acad Dermatol.* 2009;61: 961–970.
5. Rzany B, Ascher B, Monheit G. Treatment of glabellar lines with botulinum toxin type A (Speywood Unit): a clinical overview. *J Eur Acad Dermatol Venereol.* 2010;24 (suppl 1):1–14.
6. Klein AW. Complications with the use of botulinum toxin. *Dermatol Clin.* 2004;22:197–205.
7. Paul RE, John PW. Anatomy & Embryology of the Eye. Vaughan & Asbury's General Ophthalmology. 17th ed. McGraw Hill Professional; 2007. pp. 16–19.
8. Kikkawa DO, Kim JW. Asian blepharoplasty. *Int Ophthalmol Clin.* 1997;37:193–204.
9. Nguyen MQ, Hsu PW, Dinh TA. Asian blepharoplasty. *Semin Plast Surg.* 2009;23:185–197.
10. Jeong S, Lemke BN, Dortzbach RK, et al. The Asian upper eyelid: an anatomical study with comparison to the Caucasian eyelid. *Arch Ophthalmol.* 1999;117:907–912.
11. Nagi KS, Carlson JA, Wladis EJ. Histologic assessment of dermatochalasis: elastolysis and lymphostasis are fundamental and interrelated findings. *Ophthalmology.* 2011;118:1205–1210.
12. Jacobs LC, Liu F, Bleyen I, et al. Intrinsic and extrinsic risk factors for sagging eyelids. *JAMA Dermatol.* 2014;150:836–843.