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Complications of Botulinum Toxin Type A

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Botulinum toxin type A (BTX-A), a potent neurotoxin that reversibly blocks presynaptic acetylcholine release, has been employed successfully to treat facial spastic conditions such as blepharospasm, strabismus, focal dystonias, spasmodic dysphonia, and achalasia [1,2]. In 1992 Carruthers and Carruthers [3] published the first report on cosmetic patients after noting the effect on patients injected for blepharospasm who had noted a concomitant improvement in their glabellar frown lines. BTX-A has since been used with great success to treat a variety of hyperkinetic facial lines such as crow's feet, horizontal forehead lines, melomental folds, and glabellar rhytids, among others [4–6]. Nevertheless, its mechanism of action of temporary chemodenervation of the muscle, resulting in localized reduction of muscular activity, can lead to unwanted side effects, particularly when the toxin is used by inexperienced clinicians. The risk of potential complications can often be minimized by a thorough understanding of the effects of BTX-A and careful attention to dosing and injection technique.

Side effects and injection-related complications

Most adverse effects associated with the cosmetic application of BTX-A are mild and transient. They include bruising, swelling, pain around the injection site, headache, and flulike symptoms [7]. Bruising and other side effects can be minimized by advising patients to refrain from taking medications that inhibit clotting, such as vitamin E, aspirin (or medications containing aspirin), and non-steroidal anti-inflammatory drugs, for up to 2 weeks before injection. Patients should avoid massaging the treatment site but contract the injected area for up to 2 hours following injection to expedite the uptake of the toxin.

More serious complications can occur but are usually associated with poor injection technique and lack of injector experience. Most of these complications result from diffusion of the toxin (spread of 2 to 3 cm in diameter) into adjacent musculature, leading to unexpected muscle weakening. Using more concentrated doses allows for more accurate placement of the toxin with a greater duration of effect and less diffusion.

Complications of the upper face include a cocked eyebrow, diplopia, ectropion (drooping lateral lower eyelid), asymmetric smile (from diffusion to the zygomaticus major), decreased strength of eye closure, dry eye, and ptosis of the eyelid and brow. Of these complications, brow and eyelid ptosis are the most common. Brow ptosis owing to diffusion of BTX-A into the frontalis, causing

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excessive weakening of the muscle, produces a negative appearance and can persist for up to 3 months. Avoiding the frontalis in patients with existing significant brow ptosis and preinjecting the brow depressors helps avoid this outcome. Brow ptosis is also more likely to result if the glabella and the whole forehead are injected in a single session [8].

Upper eyelid ptosis, which may become evident as early as 48 hours or as late as 14 days post treatment, can last from 2 to 12 weeks and most commonly occurs when BTX-A injections into the glabellar complex diffuse through the orbital septum, affecting the upper eyelid levator muscle. Eyelid ptosis can be avoided by using higher concentrations of BTX-A, injecting no closer than 1 cm above the bony orbital rim or 1.5 cm lateral to the lateral canthus, injecting away from the inferior margin of the zygoma, and advising patients to remain upright and to refrain from manipulating the treated area for several hours after injection.

A cocked eyebrow resulting from improper injection of the lateral fibers of the frontalis is easily treated by 1 to 3 U of BTX-A injected into the untreated fibers that are exerting the upward pull.

Complications of the lower face involve effects on muscle function and facial expression and usually occur owing to overenthusiastic use of BTX-A in large doses. These complications can include mouth incompetence, asymmetry, drooling, difficulties in speech, and an inability to whistle [8]. Initial low doses and symmetrical superficial (rather than deep) injections reduce the risk of complications. Likewise, placement of injections in the lower face is crucial. Injections placed too close to the mouth or directly into the mental fold or orbicularis oris can lead to a flaccid cheek, incompetent mouth, or asymmetric smile. Singers and musicians who use perioral muscles are poor candidates for BTX-A around the mouth. Injections of large doses (>100 U) of BTX-A in the platysma can lead to dysphagia and weakness of the neck flexors.

Clinical safety profile

The safety and efficacy of BTX-A was established in two phase III, randomized, double-blind, placebo-controlled trials (n = 405, combined studies) that led to US Food and Drug Administration (FDA) approval of the neurotoxin for the treatment of glabellar rhytids in 2002 [9]. Overall, rates of adverse events were similar in the placebo and treatment groups (41.5% versus 43.7%, respectively). Moreover, the higher frequency of headache in the placebo group compared with the group treated with BTX-A (17.7% versus 13.3%) suggests that some adverse events may be caused by the trauma of injection rather than by the toxin. In 2003, Coté and coworkers [10] reviewed 1031 reports of adverse events from the use of cosmetic BTX-A (median dose, 25 U) submitted to the FDA. Of those, 36 were classified as "serious" and included headaches, facial paralysis, muscle weakness, dysphagia, flulike symptoms, and allergic reactions. Thirteen of 36 patients had underlying disease that may have contributed to the reported adverse event. Nonserious adverse events (995 cases) included lack of the intended cosmetic effect (63%), injection site reaction (19%), ptosis (11%), muscle weakness (5%), and headache (5%).

Death and cardiovascular events with therapeutic doses

Coté and colleagues [10] concluded that serious adverse events were most common among patients receiving BTX-A for therapeutic indications and in much higher doses than those given for cosmetic purposes. Indeed, the 407 adverse events reported to the FDA for the therapeutic use of BTX-A (median dose, 100 U) included 28 deaths and other serious adverse events such as arrhythmia and myocardial infarction. The report could not determine a causal relationship between the fatalities and BTX-A injections owing to the fact that 26 patients who died had underlying cardiovascular diseases with an elevated risk of mortality. No deaths or cardiovascular complications were reported after cosmetic use.

Long-term safety studies

To date, only one review of long-term safety associated with cosmetic BTX-A has been published. That study confirms the excellent safety profile and tolerability of BTX-A when it is used in multiple treatment sessions over the long term. In a retrospective chart review, Carruthers and Carruthers [11] examined 853 treatment sessions and 50 subjects with a median of 19 sessions per subject (range, 10 to 30) for the treatment of glabellar rhytids (98% of patients), crow's feet (70%), and horizontal forehead rhytids (64%) for a period ranging from 3 to 9 years (average, 5.95 years). The median dose of BTX-A per session was 40 U. In total, adverse events occurred in 9 of 853 sessions (1.1%). Only the events occurring in five sessions (0.6%) were probably or definitely related to BTX-A treatment, and none were considered serious. All of the adverse events were transient and mild (80%) to moderate (20%) in severity and included two cases of bilateral eyebrow ptosis, one right brow ptosis (Fig. 1), one right eyelid ptosis (Fig. 2), and one case of dysphagia. Adverse events considered unrelated to BTX-A included injection pain and discomfort (three cases) and bruising (two cases). The risk of adverse events did not