Botulinum Toxin Type A Reconstituted in Lidocaine With Epinephrine for Facial Rejuvenation: Results of a Participant Satisfaction Survey

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To assess the feasibility, safety, and lack of inferiority of reconstituting botulinum toxin type A (BTX-A) in 1% lidocaine hydrochloride with epinephrine 1:100,000, 181 participants were asked to complete a satisfaction survey 3 to 6 months after treatment with the reconstituted formulation for facial rejuvenation. The addition of lidocaine was believed to achieve an immediate paralyzing effect on the injected muscles, and the addition of epinephrine was hypothesized to minimize diffusion to adjacent muscles. Participants were treated in the areas of the forehead and glabella, as well as the orbicularis oculi, orbicularis oris, and procerus muscles, in varying doses (10–60 U). Fifty-eight percent (91/157) of participants reported being more satisfied with BTX-A reconstituted in 1% lidocaine with epinephrine 1:100,000, with 85.7% (78/91) of these participants reporting that the immediate results made the formulation superior; 35.7% (56/157) were indifferent and 6.4% (10/157) reported that the modified formulation did not work better. The injection of BTX-A reconstituted in 1% lidocaine with epinephrine 1:100,000 presented no increased adverse effects (AEs), no decrease in pharmacologic potency, immediate feedback to the clinician, and higher satisfaction for the participants who previously had been treated with BTX-A reconstituted in unpreserved saline. Botulinum toxin type A reconstituted in 1% lidocaine with epinephrine 1:100,000 may increase the duration and efficacy of this widely used toxin.

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Since discovering that botulinum toxin can block neuromuscular transmission through decreased acetylcholine release,[1] its therapeutic use in medicine has increased. Use of botulinum toxin, which initially was applied as a

treatment of strabismus[2] and facial asymmetry caused by facial nerve paralysis,[3] has grown to treat cervical dystonia,[4] blepharospasm,[5] migraines,[6] and even hyperhidrosis.[7] In the field of cosmetics, botulinum toxin type A (BTX-A) has become wildly popular because it is a minimally invasive procedure with a low risk for complications.[8-10] Botulinum toxin type A for the treatment of glabellar frown lines as well as forehead and lateral periorbital rhytides is among the most popular cosmetic procedures performed today.[11]

The problems with BTX-A injections are 2-fold: (1) BTX-A can spread and inadvertently affect nondesired muscles, causing complications such as ptosis, and (2) it is difficult to accurately gauge the symmetry of the paralyzing effect at the time of injection because of delayed onset of action. The onset of its paralyzing effects usually requires hours[12] and up to 2 weeks for full effect.[13] This onset delay and inherent asymmetry of the patient's facial muscles make it difficult for some clinicians to obtain complete symmetric results.[14] Furthermore, the areas where BTX-A is most often injected[15]—the forehead, eyes, and glabella region—are highly vascularized,[16] leaving patients subject to increased risk for inadvertent toxin spread and washout. This diffusion of the toxin can cause the adverse effects (AEs) of paralysis of nearby muscles[17,18] as well as a decrease in efficacy at the targeted muscles. Limiting diffusion is desired.[19]

To address these issues, we proposed reconstituting BTX-A in a commonly available formulation of 1% lidocaine hydrochloride with epinephrine 1:100,000. Combining BTX-A with lidocaine and epinephrine has not caused AEs and has been considered a novel idea to improve the pharmacology of the paralyzing toxin.[17] We sought to assess the feasibility, safety, and lack of inferiority of reconstituting BTX-A in lidocaine with epinephrine.

METHODS

Any patients who presented for BTX-A injections over a 6-month period were included in the study. Participants were accepted and treated sequentially, except if they had a documented true allergic reaction to BTX-A, lidocaine, or epinephrine. After a thorough history and physical examination, participants provided informed consent and BTX-A was injected based on the participant's preference for various areas: forehead; glabella; and/or orbicularis oculi, orbicularis oris, and procerus muscles. Doses of BTX-A ranged from 10 to 60 U.

A vial containing 100 U of BTX-A (Botox Cosmetic, Allergan, Inc) was reconstituted with 5 mL of 1% lidocaine hydrochloride and epinephrine 1:100,000, resulting in a solution that contained 20 U of BTX-A, 10 mg of lidocaine, and 0.01 mg of epinephrine in 1 mL of solution.

Participants were seen approximately 3 months later at follow-up visits (range, 3–6 months) and were asked to complete a brief survey to indicate their satisfaction with the modified BTX-A reconstitution. Survey questions included the following:

1. Please state your sex.
2. Please provide your date and year of birth.
3. Today's date.
4. Have you ever had Botox injections before?
5. How long ago?
6. Approximately how many times have you had injections before?
7. How many units did you receive before or do you usually receive?
8. What areas did you receive them?
9. How many units did you receive this time?
10. What areas did you receive them?
11. Do you feel that our Botox formulation works better?
12. What are the positive aspects of our Botox formulation?
    a. Immediate results
    b. Lasts longer
    c. Less bruising
    d. Less pain
    e. Better cosmesis

The answers from the questionnaire were tallied, and the data were analyzed to calculate the mean, median, range, and various percentages.

RESULTS

The study population included 174 women and 7 men aged 24 to 71 years (Table 1). Various areas of the face (forehead; glabella; and/or orbicularis oculi, orbicularis oris, and procerus muscles)(Table 2) were treated with 10 to 60 U of BTX-A (Table 3). Responses from the participant satisfaction survey completed at 3-month follow-up were analyzed. All of the participants did not complete the survey in its entirety. Of 157 participants who were treated, 58.0% (91/157) stated that the BTX-A reconstituted in 1% lidocaine with epinephrine 1:100,000 worked better, 35.7% (56/157) were indifferent, and 6.4% (10/157) felt that the modified formulation did not work better (Table 4). For those who reported that the modified formulation did not work better, bruising, headache, and decreased potency and duration were provided as the reasons for their dissatisfaction. Seventy-eight participants (85.7%) reported immediate results as one of the reasons why this formulation was superior, and 50.5% (46/91) reported increased duration (mean, 3.9 months)(Tables 5 and 6). The increased duration possibly was due to the vasoconstrictive effects of epinephrine

Table 1

Participant Demographics (N=181)

Demographic	Participants
Sex, n	
Female	174
Male	7
Age, y	
Mean	45.1
Median	44.0
Range	24–71
Prior BTX-A injections at other clinics, n	
Yes	173
No	8

Abbreviation: BTX-A, botulinum toxin type A.

Table 2

Areas Treated

Treatment Area	Areas Normally Treated, n (%) (N=171)	Areas Treated Today, n (%) (N=160)
Forehead	125 (73.1)	119 (74.4)
Glabella	87 (50.9)	97 (60.6)
Orbicularis oculi muscle	92 (53.8)	90 (56.3)
Orbicularis oris muscle	14 (8.2)	13 (8.1)
Procerus muscle	12 (7.0)	14 (8.8)

Table 3

History With BTX-A Treatment

	Time Since Last Injection (N=162)	No. of Prior Injections (N=161)	BTX-A Normally Received, U (N=161)	BTX-A Received Today, U (N=153)
Mean	6.2 mo	7.0	31.1	30.0
Median	4 mo	5.0	30.0	30.0
Range	1 wk–4 y	0–40	10–60	10–60

Abbreviation: BTX-A, botulinum toxin type A.

as well as the decreased hemoperfusion and spread that allowed the BTX-A to be localized in the injected area for a longer period of time.

COMMENT

Since its approval for cosmetic use in 2002,[20,21] the application of BTX-A has been pervasive.[22] In clinical trials (N=687), rates of inefficacy were reported as 19.8% by investigators and 10.6% by participants. Also, AEs of headaches and ptosis were reported in 5% and 4% of the treated participants, respectively.[20] In a study that reviewed 995 nonserious AEs from cosmetic BTX-A injections, the most commonly reported AEs were inefficacy (63.0%), reaction at the injection site (19.0%), and ptosis (11.0%).[23] The onset of the paralyzing effects of BTX-A generally occurs within 24 to 48 hours,[24] which is not ideal, as the clinician will not be able to know the eventual results. Lidocaine, a local anesthetic, has fast, dose-dependent, reversible paralyzing effects and can greatly aid the clinician in minimizing the dose required to obtain proper paralysis; the injected area quickly becomes paralyzed and is indicative of the eventual

Table 4

Participant Satisfaction With BTX-A Formulation (N=157)[a]

Answer	Participants, n (%)
Yes	91 (58.0)
Indifferent	56 (35.7)
No	10 (6.4)

Abbreviation: BTX-A, botulinum toxin type A.
[a]Survey question: Do you feel that our Botox formulation works better?

Table 5

Positive Aspects of Reconstituted BTX-A Formulation

Parameter	All Participants, n (%)(N=157)	Participants Who Felt Modified Formulation Was Better, n (%)(N=91)
Immediate results	110 (70.1)	78 (85.7)
Lasts longer	57 (36.3)	46 (50.5)
Less bruising	49 (31.2)	39 (42.9)
Less pain	40 (25.5)	28 (30.8)
Better cosmesis	30 (19.1)	25 (27.5)

Abbreviation: BTX-A, botulinum toxin type A.

Table 6

Duration of Effect (N=146)

	Duration, mo
Mean	3.9
Median	3.5
Range	1–8

effect of BTX-A. The need for reinjection is dramatically reduced, thereby greatly increasing the efficacy of the drug. The safety of administering BTX-A and lidocaine together has been evaluated.[25] Lidocaine also may serve to decrease pain during injection, as demonstrated with lidocaine mixed with hyaluronic acid injections.[8,15]

With any injectable drugs, the risk for the drug's migration outside the targeted muscles is greatly increased when higher doses are administered.[26] Although the addition of lidocaine to BTX-A injections increases accuracy and decreases the dose required to achieve the same desired effects, the issue of diffusion still persists. Diffusion that results in systemic uptake is of far greater concern than local risk, and an investigation of the AEs of BTX-A demonstrated that using the drug in low concentrations and low volumes was ideal to minimize the occurrence of side effects.[27] In several studies, the addition of epinephrine to BTX-A was recommended because no cross-reaction occurred between the 2 drugs and the vasoconstrictive effect of epinephrine minimized diffusion[14,17,27]; less diffusion means fewer nearby muscles are affected and systemic toxicity is less likely.

In our formulation, a vial of 100 U of BTX-A was reconstituted with 5 mL of 1% lidocaine hydrochloride and epinephrine 1:100,000, which resulted in a solution that contained 20 U of BTX-A, 10 mg of lidocaine, and 0.01 mg of epinephrine per 1 mL of solution. We felt that the increased diluent volume allowed easier manipulation of the injecting solution, lowered the dose required to achieve paralyzing effect, and minimized waste during reconstitution and transference into the injecting syringes. Also, this method of preparation is in line with the tumescent local anesthesia theory of Dr. Jeffrey Klein.[28] Tumescent local anesthesia is a technique that uses infiltration of a large volume of a solution with a low concentration of local anesthetic and epinephrine. Its main advantages include the following: (1) it achieves adequate local anesthesia for procedures that otherwise would require general anesthesia; (2) it notably minimizes bleeding; and (3) its prolonged duration eliminates the need for narcotics or lengthened administration of analgesic drugs postoperatively. Although tumescent local anesthesia is used more often for invasive procedures such as liposuction or phlebectomy, the hypothesis of achieving greater hemostasis with this method is a novel idea. For example, the addition of epinephrine to tumescent fluid

has been shown to decrease the rate of hematoma and hyperpigmentation to 0% in participants who underwent phlebectomy.[29] Similarly, the epinephrine present in the BTX-A reconstitution may have served to minimize bruising caused by the trauma on microvessels in the face during the injection rather than by the drug formulation.

To truly follow Klein's[28] instructions for preparing tumescent fluid, 100 U of BTX-A should be reconstituted in 0.25 to 0.5 mL of 1% lidocaine with epinephrine 1:100,000 and 2.75 to 4.5 mL of unpreserved 0.9% sodium chloride, which correlates to 2.5 to 5 mg of lidocaine and 0.0025 to 0.005 mg of epinephrine per 1 mL of solution. Perhaps changing the formulation to 100 U of BTX-A, 2.5 mL of 1% lidocaine with epinephrine 1:100,000, and 2.5 mL of unpreserved 0.9% sodium chloride could be investigated in the future. Also, the addition of sodium bicarbonate (10 mEq) will increase the pH of the solution and may decrease the pain that is related to the acidity of the lidocaine in the injection process.[28]

Because of the presence of lidocaine and epinephrine in our BTX-A preparation, participants experienced numbness and blanching in the injected areas. However, they did not report being concerned about these effects or consider them to be AEs; the numbness and blanching were temporary and actually allowed the clinician to better assess the accuracy of the injections. Participants also did not present with any immediate local reactions or concerns of heart palpitations. The largest amount of total BTX-A injected was 60 U, which correlates to 0.03 mg of epinephrine. In addition to being a small amount, both icing of the area prior to treatment and the vasoconstrictive effects of epinephrine serve to decrease hemoperfusion and localize the injection in the facial muscles. The presence of epinephrine in this treatment, therefore, presents little risk for systemic uptake or cardiac complications.

Our objective was to assess the feasibility, safety, and lack of inferiority of reconstituting 100 U of BTX-A in 5 mL of 1% lidocaine with epinephrine 1:100,000 compared to the manufacturer's recommendation to reconstitute 100 U of BTX-A in 2.5 mL of unpreserved 0.9% sodium chloride.[20] A randomized controlled study to test for superiority of our reconstitution formulation versus the manufacturer's recommended formulation would not have been possible. First, our reconstitution gives an immediate dose-dependent paralyzing effect. Second, our formulation immediately blanches the skin because of the epinephrine, making blinding impossible. Third, participants' evaluation of pain, bruising, duration, and cosmesis is subjective, and no participant presents with a perfectly symmetric face. If the formulation had been randomized, the test participants could not have been blinded, as the results would have been immediate.

Because the safety of this formulation had already been established by Gassner and Sherris,[17] questions concerning AEs were not part of the satisfaction survey. Few data regarding AEs were collected and any AEs reported were expected with BTX-A injections (eg, headaches, pain at injected areas, ptosis).

CONCLUSION

Reconstituting BTX-A in lidocaine and epinephrine is an innovative method to increase patient satisfaction of BTX-A injections for facial rejuvenation. The combination of the drugs presents a low AE profile and offers patient satisfaction with faster results, longer duration of effect, less bruising, less pain, and better cosmesis.

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