J Skin Stem Cell. 2017 March; 4(1):e63334. doi: 10.5812/jssc.63334.

Published online 2016 June 30. **Research Article**

Complications of Botulinum Toxin-A Injection in an Iranian Population

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Received 2016 May 04; **Revised** 2016 May 30; **Accepted** 2016 June 20.

Abstract

Background: The use of botulinum toxin-A is increasing for aesthetic treatments and new reassuring data have been reported in recent studies. The purpose of this study was to evaluate the complications of botulinum toxin-A (BoTo-A) (NEURONOX) injection to eliminate wrinkles in the upper one-third of the face.

Methods: The present study was conducted on 235 patients referring to the dermatology clinic of Rasoul Akram hospital in Iran (including 82 men and 153 women with a mean age of 50 years) for the treatment of forehead, frown, and lateral orbital rim wrinkles between 2011 and 2015. The injection level was 35 units of botulinum toxin-A (NEURONOX) for women and 45 for men in the glabella area, and 15 units for women and 20 units for men in the crow's feet area.

Results: The complications of botulinum toxin-A injection among 235 subjects were as follows: 1.3% ptosis (n = 3), 1.7% angioneurotic edema (n = 4), 2.1% vasovagal syncope (n = 5), 3.8% haematoma (n = 9), 1.7% diplopia (n = 4), and 2.1% musculoskeletal pain (n = 5). The satisfaction rate of patients with a complication measured one month after injection indicated that 63.3% (19/30) were satisfied with the injection and 36.7% (11/30) were dissatisfied. The satisfaction rate of patients without a complication showed that 91.7% (188/205) were pleased and 8.3% (17/205) were dissatisfied with the injection.

Conclusions: According to the findings of this study, the injection of BoTo-A (NEURONOX) to attenuate glabellar lines and the lateral orbital rim was safe and effective. The complications in this study were not serious and generally were transient and self-limiting.

Keywords: Botulinum Toxin-A, Complications, Glabella, Ptosis

1. Background

Currently, four formulations of botulinum toxin have been approved by FDA, including on a botulinum toxin A (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and Botulinum toxin type B (Myobloc). The first three items are employed for the temporary improvement in moderate to severe glabellar lines while Myobloc is used for the treatment of cervical dystonia (1). Ideal candidates for Botulinum-toxin A (BoTo-A) injections are men and women aged 40 to 60 who have wrinkles caused by habitual muscle contraction (2). Beauty indications include the treatment of hyperfunctional facial lines of the forehead, periorbital, perioral, neck and facial asymmetry, and muscle spasms. Neuromodulatory effects of BoTo- A are also used in strabismus, cervical dystonia, headaches, and temporomandibular diseases (3). Recent reports demonstrate the unexpected effects of BoTo-A, which is similar to botulinum toxin. The reported symptoms include dysarthria, dysphagia, urinary incontinence, and respiratory distress (4). It should be noted that these serious complications are seen in patients who receive high doses of the drug, such as severe spasticity associated with cerebral palsy and cervical dystonia (5). There are no reports of severe complications in cosmetic applications. In the event of a serious complication of BoTo-A in aesthetic cases, it should be assured that the complications are transient and temporary. Subcutaneous and intramuscular injections of BoTo-A for facial beauty cases are generally safe and well tolerated. The complications can be divided into several groups, involving transient, localized problems near the injection site or functional complications in certain anatomical sites. The effects of BoTo-A begin to disappear within 10 to 12 weeks after treatment (6). The unpleasant outcomes and complications are ultimately self-limiting. These self-limiting reactions include a headache, bruising, swelling, mild pain in the injection site and Flu-like symptoms that occur in about 3% of the patients who are exposed to repeated injections (7-9).

The most commonly reported serious complication is eyebrow ptosis. The ptosis occurs by the effect of the toxin on levator palpebrae superioris muscle that can be created

when the toxin is injected directly into the muscle. For this reason, the injection into or under the eyebrows along the middle part of the pupil is not recommended, as this site is most at risk. The ptosis manifests itself within 2 to 10 days and can last up to 1 month. In the event of this complication, apraclonidine 0.05% or phenylephrine 2.5% can be used 2 to 3 times a day. These alpha-adrenergic agonist therapies stimulate superior tarsal (Muller's) muscle, which elevates the upper eyelid by 1 to 2 mm (1). BoTo-A in the treatment of periorbital wrinkles in the elderly requires careful pre-treatment examination because excessive lower eyelid laxity can lead to ectropion or lid lag. Other symptoms are asthenia, muscle weakness, diplopia, dysphagia, dysphonia, dysarthria, and dyspnea. These symptoms are seen a few hours to several days after the injection and are accompanied by reports of death from swallowing and breathing problems. Those at risk include children treated for spastic disorders such as cerebral palsy. Low doses are safer in aesthetic applications. There are no reports of these serious complications associated with the dermatological use of BoTo-A in standard doses (10).

2. Methods

The present cross-sectional study was conducted on 235 patients referring to dermatology clinic (including 82 men and 153 women with a mean age of 50 years) for the treatment of forehead, frown, and lateral orbital rim wrinkles. The study population was the patients referring to the dermatology clinic of Rasoul Akram hospital in Iran during 2012 - 2013 within 18 months, who underwent botulinum toxin-A(NEURONOX) injection. The sample was collected using convenience sampling method. First, a checklist was prepared for patients containing demographic information on age, gender, medications, underlying diseases, pregnancy, or lactation, as well as findings of injection-related complications (such as ptosis, haematoma and bruised injection site, visual impairment such as diplopia, musculoskeletal pain, angioneurotic edema, and vasovagal syncope). In addition, information about injections was given to the patients and informed consent was obtained from all patients. The injection level was 35 units for women and 45 for men in the glabella area, as well as 15 units intramuscular for women and 20 units for men in the crow's feet areas using insulin syringe 30 Gauge. The patient was in a state of about 65 degrees to start the injection, and certain areas for injection were determined in each injection area. Intramuscular injection was performed at 8 points and 2 - 2.5 units at each point in order to repair the forehead lines. Intramuscular injection took place in the frown line at 5 points as 5 units in procerus muscle and 2.5 - 5 units in the corrugator muscle. Finally, the subdermal injection was carried out in the crow's feet areas at three points, 2.5 units in each point. The patients were followed up at the time of injection, the second week, and the fourth week after injection to investigate the complications of botulinum toxin-A injections. The patient satisfaction with injections was also recorded in the fourth week.

3. Results

The outcomes and complications obtained in this study are as follows (Table 1).

The ptosis was observed in three cases (including one male and two females). Interestingly, all three patients were exposed to IPL laser with the 510-nm filter in the forehead at the ptosis side a week later to eliminate the ptosis, which significantly was attenuated before the third session (between the second and third weeks).

Angioneurotic edema was seen in four cases (including one male and three females).

Of these, three cases occurred during the touch-up injection two weeks after injection (the amount of injection when repairing was between 5 and 10 units at different points of the forehead and between the eyebrows) as well as one case in the first injection. Patients with hypersensitivity had mental stress during the injection including sleep disorders, anxiety, and depression, and they used drugs such as lorazepam, nortriptyline, amitriptyline, and Inderal. In such sensitivities, the problem was resolved using oral dexamethasone (three tablets daily, 1.5 mg) and resting between 4 and 7 days. The vasovagal syncope occurred when injecting in five cases (including two males and three females). The shock was resolved using water, sugar, and putting the patient in a Trendelenburg position in all of the above and using oxygen in less than 15 minutes in one case. The cardiovascular status and blood pressure levels of the patients were monitored. The appearance of bruising and haematoma at the injection site was in nine cases (including two males and seven females). This complication was usually resolved in less than a week. The diplopia was observed in four cases (including one male and three females). The musculoskeletal pain was reported in five cases (including two males and three females). The satisfaction level of patients was measured one month after injection. Of 30 patients with these complications, 11 were dissatisfied (including three males and eight females) (Table 2). Of 205 patients without a complication (including 74 males and 131 females), 188 patients (including 71 males and 117 females) were satisfied with the injection, while 17 people (3 males and 14 females) were dissatis-

Table 1. Complications of BoTo-A Injection in the Study Group[a]

Gender	Number of Patients	Ptosis	Angioneurotic Edema	Vasovagal Syncope	Haematoma	Diplopia	Musculoskeletal Pain	Total
Male	82 (34.9)	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.9)	1 (0.4)	2 (0.9)	9 (3.8)
Female	153 (65.1)	2 (0.9)	3 (1.3)	3 (1.2)	7 (2.9)	3 (1.3)	3 (1.2)	21 (8.9)
Total	235	3 (1.3)	4 (1.7)	5 (2.1)	9 (3.8)	4 (1.7)	5 (2.1)	30 (12.7)

[a]Values are expressed as No. (%).

fied, and they thought they were not in the ideal state (Table 3).

Table 2. Satisfaction Level in Patients with a Complication One Month After Injection[a]

Gender	Number of Patients	Satisfied	Dissatisfied
Male	9 (30)	6 (20)	3 (10)
Female	21 (70)	13 (43.3)	8 (26.7)
Total	30	19 (63.3)	11 (36.7)

[a]Values are expressed as No. (%).

Table 3. Satisfaction Level in Patients Without a Complication One Month After Injection[a]

Gender	Number of Patients	Satisfied	Dissatisfied
Male	74 (36.1)	71 (34.6)	3 (1.4)
Female	131 (63.9)	117 (57.1)	14 (6.9)
Total	205	188 (91.7)	17 (8.3)

[a]Values are expressed as No. (%).

4. Discussion

Botulinum toxin, one of the most known biological substances, is a neurotoxin produced by the bacterium Clostridium botulinum. It blocks neural transmission by interfering with the release of acetylcholine, the main neurotransmitter at the neuromuscular junction, causing muscle paralysis. The weakness induced by injection with botulinum toxin A usually lasts about three months. Botulinum toxins now are used in the management of a wide variety of medical conditions, especially strabismus and focal dystonias, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis, and some chronic conditions that respond only partially to medical treatment. The cosmetological use includes correction of lines, creases, and wrinkles all over the face, chin, neck, and chest. Injections of botulinum toxin are widely used and side effects are few and temporary (11). Complications may be more serious in patients who have more severe rhytids (which requires more Botox), previous facial plastic surgery (altered anatomy), and those who have a pre-existing neuromuscular disease. The physician can reduce complications by using appropriate injection techniques, Botox dosing (12).

This study was conducted to investigate the complications of botulinum toxin-A injection in an Iranian population. Several studies also examined the complications of Botox injections in patients. Murad Alam et al. (2002) examined the rate of a headache after injection in 320 patients who received botulinum exotoxin-A. Approximately 1% of the patients (4 out of 320) experienced severe headaches (13). Another study in 2002 was conducted by J. Alastair Carruthers et al. in 264 patients to evaluate the effect and safety of botulinum toxin-A injection on glabellar lines. The patients received 20 units of BTX-A in five glabellar sites. The rate of blepharoptosis was mild (5.4%) (14). A study in 2005 carried out by Timothy R. Cote et al. to investigate the complications reported to the US.FDA in medical and beauty cases showed that 995 out of 1437 cases of complications reported to the FDA were associated with non-serious complications of injection for beauty applications. The most common cases included the lack of effect (63%, 623), injection site reaction (19%, 190), and ptosis (11%, 111) (11). A study was conducted in 2009 by Alastair Carruther et al. to compare the reliability, effects, and the duration of the effects of 3 doses of botulinum toxin-A on the treatment of multiple upper facial wrinkles among 60 women (with total doses of 32, 64, and 96). The results showed that all BoToA doses were effective and reliable. There were no significant differences in complications between the groups and no serious complication occurred (15). In a recent study by the American Academy of Family Physicians, complications were related more to injection reactions than to botulinum toxin effects. These complications are technique-dependent and temporary.

Blepharoptosis (upper eyelid droop) is uncommon (1% to 5%) (12, 16). It is usually unilateral and marked at the end of the day with muscle fatigue. Blepharoptosis

may be treated using ophthalmic solutions with alpha-adrenergic effects, such as over-the-counter naphazoline 0.025%/pheniramine 0.3% or prescription of apraclonidine 0.5% (Iopidine). Apraclonidine should be used with caution because it can exacerbate or unmask underlying glaucoma. Facial asymmetry is caused by uneven dosing of botulinum toxin. It can be solved by careful attention to injection volume (17, 18).

4.1. Conclusions

According to the findings of this study, the injection of BoTo-A to attenuate glabellar lines and the lateral orbital rim is safe and effective. The complications in this study were not serious and generally were transient and self-limiting. They often occurred within a week after injection and lasted a few days to several weeks. Therefore, botulinum toxin-A (NEURONOX) injection could be a safe and effective rejuvenation without any surgical procedure.

Acknowledgments

We would like to thank the dermatology clinic at Rasoul Akram hospital for collaboration in the implementation of this project.

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