

Are There Differences Between Intradermal and Intramuscular Injections of Botulinum Toxin on the Forehead?

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BACKGROUND The intradermal technique to inject botulinum toxin is a popular procedure in upper facial rejuvenation to minimize side effects, such as brow ptosis, and can sometimes result in a lifting effect.

OBJECTIVE The present study investigated differences in effects according to injection modality.

METHODS AND MATERIALS Fifteen women received intradermal injections of botulinum toxin (total dose, 8U) into the forehead, and 14 women received intramuscular injections.

RESULTS The maximal antiwrinkle effect was recorded at Week 2, and the duration of the effect was the same in both groups. The brow position was lowered at Weeks 2 and 4 in the intramuscular injection group and was preserved in the intradermal injection group throughout the follow-up period. The amount of maximal voluntary eyebrow movement was decreased at Weeks 2 and 4 and recovered at Week 16 in both groups. The change in the electromyographic amplitude of the frontalis muscle was prolonged until Week 16 in both groups. Subjective satisfaction with wrinkles was similar in both groups. However, the intradermal injection was more painful.

CONCLUSION Intradermal injection of botulinum toxin is a safe and effective method to improve forehead rhytides.

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The use of botulinum toxin Type A (BTXA) in cosmetic procedures has increased dramatically in recent years, particularly for the treatment of facial wrinkles. BTXA has been used in many off-label applications in the field of cosmetics, sweating-related disorders, and pain-related disorders.^{1–3} These procedures are effective because acetylcholine receptors are not only present in neurons but can also be found on the surface of melanocytes, keratinocytes, and other dermal tissues.⁴ The human skin is known as not only a target but also an active source of various neurotransmitters, such as

acetylcholine. The intradermal injection of BTXA has the benefits of improving skin texture and lift while also reducing sebum production, facial flushing, and pore size.^{5,6}

Because BTXA is a potent neurotoxic protein that exerts its effect at the neuromuscular junction by inhibiting the release of acetylcholine, intramuscular injection has become the accepted standard method. In practice, physicians often use intradermal injections to obtain the benefit of natural facial expression and a wrinkle-soothing effect. Some

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physicians have noted a lifting effect after intradermal injection of BTXA to the face. The intradermal injection technique works best for flat, sheet-like facial muscles because these muscles insert into the skin rather than the bone, and BTXA blocks the superficial fibers of the facial muscles.⁷

There are many studies about aesthetically attractive eyebrow shape and position related with aging. Son and colleagues reported that the position and movement of the lateral brow of the elderly group is lower than those of the younger group.⁸ Yun and colleagues⁹ reported that motor recruitment to the frontalis and corrugator supercilii muscles decreases with aging, however age-related muscular weakness. Regarding forehead wrinkles, intradermal injection of BTXA is recommended to prevent brow ptosis.¹⁰ The incidence of brow ptosis has been reported in many studies to be approximately 1% to 5%. A previous study demonstrated that intradermal BTXA injection improves forehead wrinkles but is not effective for wrinkles in other parts of the face because the forehead skin is thin enough to allow intradermal BTXA to readily diffuse into the superficial muscle fibers to reduce wrinkles but spare the deeper muscles that maintain the resting tone required to lift the eyebrow. By contrast, the dermis and subcutis of other parts of the face is too thick, so the intradermal injection of BTXA cannot reach the superficial muscle fibers.^{11,12} Some physicians insist that there is no significant effect of intradermal injections on facial rejuvenation.¹³

Currently, many off-label cosmetic applications of BTXA are under evaluation. However, to the authors' knowledge, no confirmative studies have objectively evaluated the effect of intradermal injection of BTXA into the forehead on brow height and frontalis muscle action.

The purpose of this study, therefore, was to evaluate the efficacy of intradermal BTXA injection compared with intramuscular injection on forehead wrinkles according to electromyographic (EMG) measurements and eyebrow height and movement. In addition, subject satisfaction was measured using self-administered questionnaires.

Subjects and Methods

Subjects

This study was approved by the Institutional Review Board of Gachon University Gil Medical Center, Republic of Korea (institutional review board GCIRB 2014-360). All subjects signed a consent form, and the study was conducted according to the principles of the Declaration of Helsinki.

The study group included women between 35 and 55 years of age. Only women were selected to participate because the treatment goals and volumes of BTXA vary between men and women.

Potential subjects who received any BTXA injection(s), filler injection, or laser resurfacing within 24 months; those who exhibited marked asymmetry or scars in the forehead region, received treatment with hyaluronic acid or other fillers within 12 months; those with bleeding disorders, medical conditions that could interfere with neuromuscular functions (e.g., myasthenia gravis and aminoglycoside antibiotic intake), and infection in the injection area; and those currently breast-feeding, pregnant, or planning to become pregnant were excluded (See **Supplemental Digital Content 1**, Table S1, <http://links.lww.com/DSS/A276>).

Procedure

Sterile normal saline (2.5 mL) was slowly instilled into a vial of BTXA (prabotulinumtoxin A; Daewoong Pharmaceutical, Seoul, Republic of Korea). The toxin was injected at 1 unit per spot, for a total of 8 units (Figure 1).

Each subject was randomly assigned to the intradermal injection group or the intramuscular injection group. The end point of the injection was wheal-like swelling of the intradermal group. To ensure intramuscular injection, BTXA was injected after the tip of the needle contacted the bone. The forehead skin was prepared with 0.5% chlorhexidine before injection; no agent was applied for pain control before or after injection (i.e., analgesic cream or ice pack). The injection site was gently compressed immediately after injection to

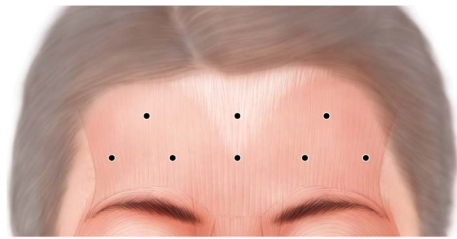


Figure 1. The injection sites of botulinum toxin: Botulinum toxin was injected at 1 unit per spot, for a total of 8 units, after dilution with 2.5 mL sterile saline.

prevent hematoma. Subjects were evaluated at the baseline visit and at 2, 4, and 16 weeks after treatment.

Measurement

Objective Wrinkle Rate

Physicians independently assessed wrinkles according to a scale graded 0 to 10, with 0 indicating no wrinkle and 10 indicating very severe wrinkle (more than 5 deep furrows that were not resolved by any method).¹⁴

Eyebrow Height

Eyebrow height was measured as the distance from the upper eyelid lash line to the inferior eyebrow margin in primary gaze.

Eyebrow Movement

Eyebrow movements were measured directly from the upper margin of the eyebrow at the mid-pupillary line when the subjects performed maximum voluntary contraction of the frontalis (eyes opened maximally) for 5 seconds.

Electromyography

Electromyographic evaluation of the frontalis muscles was performed using a commercially available system (BioPAK; BioResearch, Inc., Milwaukee, WI) before and at 2, 4, and 16 weeks after treatment. Surface EMG signals were collected using adhesive arrays of 2 electrodes: one on the midpoint of the forehead along the lateral limbus of the eye and the other on the chin as a reference. Data points were the mean value of the maximal amplitude of surface EMG activity while the subjects performed maximum voluntary contraction of the frontalis 3 times.¹⁵

Pain

Subjects self-reported pain levels immediately after treatment using a visual analog scale graded from 0 to 10, with 0 indicating no pain and 10 indicating extremely severe pain.

Satisfaction After Treatment

Subject satisfaction was measured using a self-administered questionnaire completed at 2, 4, and 16 weeks after injection using a visual analog scale graded from 0 to 10, with 10 indicating extremely disappointed. Subjects self-reported pain immediately after treatment using a visual analog scale graded from 0 to 10.

Statistical Analysis

Continuous variables are expressed as mean values with SDs. The Mann–Whitney *U* test was used to determine whether groups differed in terms of the injection method. The sign test was used to evaluate the significant difference of variables at baseline and after treatment. All statistical analyses were conducted with SAS software. A *p*-value of 0.05 was used for statistical significance.

Results

Patient Characteristics and Demographics

Twenty-nine women, ranging in age from 35 to 55 years, were enrolled in the present study. The mean age was 42.20 ± 5.35 and 43.43 ± 4.73 years in the intradermal and intramuscular injection groups, respectively ($p = .4894$).

Objective Wrinkle Rate

There were no differences in wrinkle scale scores between the 2 groups at baseline and at 2, 4, and 16 weeks after treatment. The wrinkle-soothing effect lasted until Week 16 in both groups (See **Supplemental Digital Content 2**, Table S2, <http://links.lww.com/DSS/A277>).

Eyebrow Height

Both groups exhibited lowering of brow position at 2 and 4 weeks after injection compared with baseline and recovered at 16 weeks after treatment. There was no statistically significant change in eyebrow height in

the intradermal injection group during all periods. Lowering of eyebrow position was statistically significant at 2 and 4 weeks in the intramuscular injection group (See **Supplemental Digital Content 3**, Table S3, <http://links.lww.com/DSS/A278>).

Eyebrow Movement: Force of the Frontalis Muscle

The amount of eyebrow movement when the subjects frowned their forehead forcefully was decreased at 2 and 4 weeks and recovered at Week 16 in both groups. The maximal effect of BTXA on eyebrow movement was exhibited at 2 weeks after injection in both groups (See **Supplemental Digital Content 4**, Table S4, <http://links.lww.com/DSS/A279>).

Electromyography of the Frontalis

The EMG results revealed a statistically significant decrease at 4 and 16 weeks after injection in both groups (intradermal injection group, $p < .0001$ and $p = .0002$, respectively; and intramuscular injection group, $p = .0001$ and $p = .0002$, respectively). There were no statistically significant differences between the 2 groups during all periods (See **Supplemental Digital Content 5**, Table S5, <http://links.lww.com/DSS/A280>).

Pain

Intradermal injection was more painful than intramuscular injection. The mean visual analog pain scale scores for the intradermal and intramuscular injection groups were 4.27 and 2.86, respectively ($p = .0091$) (See **Supplemental Digital Content 6**, Table S6, <http://links.lww.com/DSS/A281>).

Satisfaction After Treatment

Subjects in both groups reported good levels of satisfaction. There were no statistical differences in satisfaction scores between the 2 groups at 2, 4, and 16 weeks after treatment (See **Supplemental Digital Content 7**, Table S7, <http://links.lww.com/DSS/A282>).

Adverse Effects

There were no major local or systemic complications associated with BTXA injection. However, mild side

effects were recorded, all of which were temporary and spontaneously resolved (without any treatment) within 4 weeks. Of the 15 subjects administered intradermal injection of the toxin, 2 reported narrow eye fissures, 3 reported an inability to move the forehead, 3 reported swelling of the eyelids, 2 reported a headache, and 1 reported itching sensations at the injection sites. These minor discomfort rates were similar to those in the intramuscular group. There was no bruise at the injection sites in both groups.

Discussion

The label-indicated method of administration of BTXA is intramuscular injection. Intradermal injection of BTXA is becoming an increasingly popular technique used for facial rejuvenation because intradermal BTXA injections are reported to significantly improve wrinkles and lower sebum production; a good level of patient satisfaction and patient-reported improvement of skin oiliness and facial pores are reported for intradermal BTXA injection.¹¹

Intramuscular BTXA injection has been performed for aesthetic indications after reconstitution with 1 to 4 mL of normal saline. When BTXA was injected intradermally, physicians usually mixed-in more saline (4–10 mL) and injected at multiple sites.¹⁶

The frontalis muscle is the only elevator muscle in the upper face. The frontalis muscle fibers merge with the corrugator supercilii and the inner part of the orbicularis oculi, which work antagonistically as depressors of the eyebrow.¹⁷

To avoid eyebrow ptosis, it is recommended to also treat the depressors of the glabellar complex and the lateral periorbital lines in practice.¹⁸ Brow ptosis has been reported with an incidence as low as 0.6% and as high as 20% after the BTXA treatment of horizontal forehead lines. Best aesthetic outcomes can be achieved by tailoring the opposing effects of the frontalis muscle and its intricate interactions with the procerus, corrugator supercilii, depressor supercilii, and orbicularis oculi muscles.¹⁹ Some authors insist that the forehead should never be injected alone even if other depressor muscles are not indicated for the treatment

of wrinkles.²⁰ In this study, subjects may have experienced eye aperture narrowing because BTXA was injected alone into the frontalis muscle.

Although intramuscular injection of BTXA is commonly used for the treatment of forehead wrinkles, some physicians claim that intradermal injection has beneficial effects on eyebrow heaviness or brow ptosis.¹²

In this study, there was no significant change in eyebrow position in the intradermal injection group. The results of this study support the practice of using intradermal injection of BTXA for forehead wrinkles.

There are important points to consider when intradermally injecting BTXA on the face. First, intradermal injection of BTXA is suitable for flat, sheet-like muscles and is known to soften wrinkles and preserve some muscle function. The intradermal injection technique recommends reconstitution of BTXA with 2 to 4 volumes of saline and a significantly higher number of injection points compared with the conventional intramuscular technique.^{7,16} In most double-blind studies, the reconstitution volume was smaller than the traditional intradermal injection method. The authors' investigation was a single-blinded study; therefore, they injected BTXA into the same location of the forehead using the same dilution volume. In the study by Hsu, some practitioners found that results were short-lived in the large-volume injection group and, perhaps, only weakened but did not completely eliminate contraction of the target muscles.²¹ This is why many practitioners prefer a lower concentration and multiple injection sites. However, the concentration appeared to exert less influence on the field effect and other factors, including the dose of BTXA; as such, bulk and dynamic movement of the muscles should be considered.²²

Second, BTXA can spread at least 10 mm in the horizontal dimension, regardless of whether it is intradermally or subcutaneously injected.^{23,24}

Considering that the thickness of the skin on the forehead is <10 mm, BTXA could spread throughout the entire layer of the forehead, regardless of

whether it is injected intradermally or intramuscularly, although the intradermal injection technique minimizes BTXA diffusion more than subcutaneous injection. When injected deeply, BTXA diffuses more along the axis of the muscle in the forehead area. Sometimes, BTXA can spread to the contralateral facial muscles.²⁵

Third, Sneath and colleagues²⁶ reported that injecting BTXA at different depths is not effective for the correction of eyebrow asymmetry because of the diffusion of BTXA between muscle layers; moreover, the eyebrow depressor muscles cannot be accurately targeted with deep injection into the muscle belly.

Finally, do the effects of intradermal injection of BTXA have a shorter duration compared with intramuscular injection? There was no apparent difference in the duration of effects of the toxin between the 2 injection techniques, as our results and others have shown.¹² One noteworthy aspect of the present study was that eyebrow position and movement recovered, but muscle power recorded using EMG remained weak 16 weeks after injection.

When physicians study frontalis wrinkle(s), the authors recommend choosing only one sex. The skeletal and muscular structures of males are different from those of females. Men exhibit a large divergency between the 2 frontalis muscle bellies. As such, the dose of BTXA and the interval of injection sites vary.²⁷

The authors did not investigate the soothing effect of BTXA, such as reduction in sebum production or pore size. Intradermal injection of BTXA may be better when it is used to treat skin texture than muscle paralysis.

There were limitations to the present study, among which included the relatively young age of the participants (all <55 years) and the small sample size.

Conclusion

There were no appreciable differences in the anti-wrinkle effect and duration of BTXA between intradermal and intramuscular injections. Intradermal

injection is associated with more pain; however, it is beneficial to use intradermal injections for the forehead to prevent brow ptosis.

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