

Intramuscular *versus* intradermal botulinum toxin for forehead wrinkles: a review of side effects and efficacy

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Abstract

Botulinum toxin type A (BTA) is a neurotoxin used for both cosmetic and non-cosmetic purposes. BTA is commonly administered as an intramuscular injection to treat wrinkles. However, when it comes to treating forehead wrinkles, intramuscular injection is associated with a greater rate of ptosis. Intradermal injection is currently thought to be a better alternative. We searched PubMed and Google Scholar for research articles published between 1989 and 2023 using the following keywords: “intradermal,” “intramuscular,” “botulinum toxin,” and “forehead wrinkle.” The search yielded three randomized controlled trials and a double-blind, split-face case report on 58 patients. We found that although intradermal and intramuscular injections have symmetrical anti-wrinkle effects, the former results in a lower rate of ptosis and a greater degree of pain.

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Introduction

Botulinum toxin type A (BTA) is a potent neurotoxin. Although its use has surged in recent years for both cosmetic and non-cosmetic purposes, its use as a treatment for facial wrinkles remains insufficiently studied.¹⁻³ BTA works by targeting the neuromuscular junction and inhibiting acetylcholine release, which leads to muscle paralysis.⁴ Therefore, it is thought to be most effective when used intramuscularly. However, many researchers have proposed that when BTA is used in superficial facial muscles, such as the frontalis, there is no difference between intramuscular injection (IM) and intradermal injection (ID).⁵ Whereas intramuscular BTA use in the frontalis muscle is associated with a higher rate of brow ptosis and a lower degree of pain,⁶ intradermal injection can reduce sebum production, improve skin texture, and reduce erythema in rosacea patients.⁷⁻⁸ In this article, we compare intramuscular and intradermal BTA injection use for treating forehead wrinkles in terms of muscle paralysis, brow ptosis, and pain and identify knowledge gaps that requires further investigation.

Materials and Methods

We searched PubMed and Google Scholar for all published research articles using the following keywords: “intradermal,” “intramuscular,” “botulinum toxin,” and “forehead wrinkle.” We included studies in which both intradermal and intramuscular botulinum toxin injections were used to treat forehead wrinkles.

Results and Discussion

Our search yielded three randomized controlled trials and a double-blind, split-face case report on 58 patients, of which only five were male. All the studies used BTA but in different commercial forms. A summary of the articles' characteristics is provided in Table 1.

Paralyzing effects

De Quadros *et al.*¹⁰ and Jun *et al.*¹¹ conducted a split-face study to compare the paralyzing effects of intradermal and intramuscular botulinum toxin injections in the forehead. The former found that only 50% of the patients had a symmetrical anti-wrinkle effect; however, the difference between the two injection technique was not significant. Jun *et al.* and Kim *et al.*⁹ found no difference between the two injection techniques in terms of the paralyzing effect. Moreover, Jun *et al.* found that the time required to achieve a maximum effect was similar in the two groups (*i.e.*, two weeks). Sapra *et al.*'s results are consistent with previous findings on forehead wrinkles.¹² However, they found that periorbital and glabellar wrinkle improvements were more significant after IM. De Quadros *et al.* found that BTA injection durability is influ-

enced by patient and injection factors: since more superficial injections had shorter effects, IM injections had longer-lasting effects. Sapra *et al.* compared onabotulinumtoxinA and abobotulinumtoxinA and found no significant differences between them in any of the measured variables. In all the studies, anti-wrinkle effects were graded by independent physicians by comparing the results to baseline photographs. Jun *et al.* used a scale from 0 to 5 developed by Tsukahara *et al.*¹³ Kim *et al.* used a scale from 0 to 10. De Quadros *et al.* developed their own questionnaire. Sapra *et al.* used questionnaires filled out by patients and a blinded evaluator assessment.

Ptosis

Kim *et al.* and Jun *et al.* discussed ptosis following ID and IM. They compared the baseline measurement of the distance from the eyebrows and upper eyelid eyelashes line in the primary gaze with post-injection readings. In both studies, the IM and ID groups showed drooping of the eyelid; however, according to Kim *et al.*, ptosis was statistically more significant in the IM group at two weeks (p=0.0117) and four weeks (p=0.0215). At 16 weeks, the ptosis in both groups recovered.

Pain, satisfaction, and adverse effects

The findings of De Quadros *et al.* and Kim *et al.* were consistent. In both articles, pain was significantly more pronounced in the ID group (P=0 .009) as measured by Kim *et al.* To rate pain, the former used a questionnaire filled out by participants, whereas the latter used the Visual Analogue Scale. Kim *et al.*, Jun *et al.*, and Sapra *et al.* reported similar levels of patient satisfaction in the two groups despite facial expression difficulties in the IM group as reported by Jun *et al.* In addition, Kim *et al.* and Sapra *et al.* found that the rates of minor discomfort were similar in the two injection groups.

Skin texture, facelift, and sebum production

Sapra *et al.* reported some advantages of ID over IM. Although skin texture improvements were significant after both ID and IM, significant midface lift was only observed after ID. Neither ID nor IM significantly reduced sebum production or pore size.

Conclusions

In conclusion, in comparison to IM, intradermal BTA injection is a promising technique due to its lower rates of ptosis and similar anti-wrinkle effects, as well as additional improvements in skin texture. However, the shorter duration of its effects and the greater degree of pain are its greatest drawbacks. Our findings need to be confirmed by similar larger-scale studies that include a wider age range and both male and female patients.

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Table 1. Summary of the included studies.

Study	Design	Demo-graphics	Injection	Wrinkles	Ptosis	Pain	Adverse effects
Kim <i>et al.</i> ⁹	Single-blind, randomized controlled clinical trial	29 patients (15 ID, 14 IM), all female, mean age 42 years (ID), 43 year (IM)	BTA reconstituted in 2.5 mL NS (pra-botulinum toxin A; Daewoong Pharmaceutical, Seoul, Republic of Korea). Injection: 1 U in each spot	No differences between two groups	IM group showed more brow ptosis	ID injection was More painful	ID: narrow eye fissure (n=2), inability to move the forehead (n=3), eyelid swelling (n=3), headache (n=2), injection-side itchiness (n=1)
Mauricio de Quadros <i>et al.</i> ¹⁰	Single-blind, randomized clinical trial	16 patients, 11 F, 5 M, mean age 33 years	BTA reconstituted in 1mL NS. Injection: 1 U in each spot	No differences between two groups	N/A	ID injection Was more painful	N/A
Ji-Young Jun <i>et al.</i> ¹¹	Double-blind, e split-fac	3 patients, all F, mean age 59 years	Botulax (C. botulinum toxin type A, purified neurotoxin complex; Hugel, Seoul, Korea) reconstituted in 0.05 mL NS. Injection: 2 U in each spot	No differences between two groups	IM side showed more brow ptosis	N/A	No serious side effect reported
Sapra <i>et al.</i> ¹²	Single-blind, split-face randomized clinical trial	10 patients, all F, mean age 51 years	OnabotulinumtoxinA and abobotulinumtoxinA were used for ID and IM. Injection: U was subjective to patients' needs	No differences between two groups	N/A	N/A	Mild self-limiting injection site reactions and drooping in both groups

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