

Botulinum Toxin In Aesthetic Medicine: Current Overview And Safety Challenges

Francine Fernanda Ribeiro Viana ¹, Patrícia Aparecida Frezarin ²,
Ana Vitória De Oliveira Neves ³, Renato Felipe Pereira ⁴,
Gestter Willian Lattari Tessarin^{5,6}

University Center North Of São Paulo (UNORTE), São José Do Rio Preto, SP, Brazil.

University Center North Of São Paulo (UNORTE), São José Do Rio Preto, SP, Brazil.

University Center North Of São Paulo (UNORTE), São José Do Rio Preto, SP, Brazil.

Department Of Basic Sciences, São Paulo State University (UNESP), School Of Dentistry, Araçatuba, SP, Brazil.

University Center North Of São Paulo (UNORTE), São José Do Rio Preto, SP, Brazil

Department Of Basic Sciences, São Paulo State University (UNESP), School Of Dentistry, Araçatuba, SP, Brazil.

Abstract:

Over the past decade, there has been a marked rise in the popularity of non-surgical and minimally invasive techniques aimed at facial rejuvenation and delaying visible signs of aging. Among these techniques, the use of botulinum toxin injections and dermal fillers has become especially prevalent worldwide. Botulinum toxin type A, derived from one of the most potent biological toxins, achieves its effects by blocking acetylcholine release at neuromuscular junctions, causing temporary muscular paralysis. While it offers notable benefits in cosmetic applications—particularly in reducing facial wrinkles—its widespread use also brings safety considerations. This article aims to explore the potential complications associated with botulinum toxin in aesthetic procedures, highlighting key adverse effects and providing strategies to reduce associated risks.

Key Word: *Aesthetic; Botulinum toxin type A; Challenges; Medicine; Safety.*

Date of Submission: 16-04-2025

Date of Acceptance: 26-04-2025

I. Introduction

Originally developed from one of the most potent biological toxins known produced by *Clostridium botulinum*—botulinum toxin type A has become a cornerstone in both therapeutic and aesthetic medicine. Its mechanism of action involves the inhibition of acetylcholine release at neuromuscular junctions, resulting in temporary paralysis of targeted muscles [1]. Despite its toxicity, with a lethal dose as low as one nanogram per kilogram of body weight [2], its controlled application has proven highly effective in various medical and cosmetic contexts.

The first clinical reports of its effectiveness in reducing facial wrinkles emerged in 1994, paving the way for a broad range of applications beyond aesthetics [3]. Botulinum toxin is now used to address facial lines around the mouth, forehead wrinkles, and marionette lines, as well as for medical conditions such as strabismus, blepharospasm, cervical dystonia, hyperhidrosis, and facial synkinesis following surgery [4-6]. Some of these uses remain off-label in certain countries. More recently, new indications have emerged, including the treatment of hypertrophic scars, keloids, rosacea, masseter hypertrophy, and parotid gland enlargement [3].

This widespread adoption is part of a broader trend: the rising demand for non-surgical and minimally invasive procedures aimed at rejuvenation and delaying the visible effects of aging. Alongside injectable agents, this movement includes advanced technologies, pharmaceutical innovations, nutraceuticals, hormonal therapies, and stem cell-based treatments [7,8]. Botulinum toxin injections and dermal fillers currently lead as the most commonly performed non-surgical procedures worldwide [9].

Although widely regarded as safe when used appropriately, the expanding use of botulinum toxin has prompted ongoing discussion regarding its safety profile. This article aims to review the potential complications linked to its use in facial aesthetic procedures, highlighting key adverse effects and suggesting strategies to reduce the risk of such outcomes.

II. Materials And Methods

This study is a bibliographic literature review based on the selection and analysis of scientific articles sourced from multiple databases, including Google Scholar, PubMed, Scielo, LILACS, and Embase. The search strategy employed specific descriptors such as *Botulinum toxin type A*, *Face*, *Aesthetics*, and *Rejuvenation*. Articles included in the review were full-text publications available in open access and written in either Portuguese or English. During the selection process, each article underwent a thorough critical evaluation, focusing on its objectives, methodology, results, and discussion. This systematic approach formed the basis for the present literature review.

III. Results

Aesthetic Applications and Mechanism of Action of Botulinum Toxin

Initially approved by the U.S. Food and Drug Administration (FDA) for the treatment of neurological conditions, botulinum toxin has since seen a substantial increase in its applications, particularly in aesthetic medicine. Its cosmetic effectiveness lies in its ability to inhibit the release of acetylcholine (ACh), a critical neurotransmitter responsible for skeletal muscle contraction and certain autonomic nervous system functions. By blocking ACh release at the neuromuscular junction, the toxin induces localized muscle relaxation, which is essential in reducing wrinkles and sculpting facial contours [10,11].

The mechanism by which botulinum toxin type A (BoNT-A) operates involves the suppression of the SNAP-25 protein within the SNARE complex, a key element for synaptic vesicle fusion. This inhibition halts ACh exocytosis, thereby decreasing muscle activity—an effect used in aesthetic procedures to smooth dynamic wrinkles and enhance facial definition [12]. Although the muscle paralysis caused by BoNT-A is temporary, with axonal regeneration and functional recovery occurring over time, its reversible nature allows for controlled clinical use [13].

Since its initial aesthetic application in 1992, BoNT-A has diversified beyond wrinkle treatment to include procedures targeting jawline definition, calf and neck contouring [14], and even correction of muscular hypertrophy. The injection of the toxin into facial muscles enables non-invasive modifications, such as mandibular reshaping. Additionally, the toxin's ability to block parasympathetic nerve signals makes it effective in treating conditions like focal hyperhidrosis and excessive salivary gland activity [15].

Innovative techniques like mesobotox, which employs microinjections for facial rejuvenation, are also being explored, although further evidence is needed to substantiate their efficacy [11]. As the toxin's interaction with post-synaptic ACh receptors has become better understood, treatments have become safer and more effective, with fewer adverse effects. Despite these promising outcomes, further research is necessary to support the full range of its aesthetic indications.

Common Complications of Botulinum Toxin Use

Eyelid Ptosis

A frequent complication when treating forehead wrinkles with botulinum toxin is eyelid ptosis, often caused by injections placed too close to the supraorbital rim. To avoid this, clinicians are advised to inject the toxin at least 2–3 cm above the orbital rim or 1.5–2 cm above the upper eyelid margin, preserving the lower fibers of the frontalis muscle [16,17]. If forehead lines are treated without addressing glabellar muscles, the resulting imbalance may increase the risk of ptosis [18,19]. Migration of the toxin toward the levator palpebrae superioris muscle, especially with medial injections near the pupillary line, can also contribute. Elderly patients with dermatochalasis are at greater risk of secondary blepharoptosis, as they often rely on frontalis compensation [20,21].

Lip Ptosis and Asymmetry

Although less common, lip ptosis and asymmetry can occur if injections are administered too close to the lateral nose or below the zygomatic arch, affecting the lip elevators. This may lead to articulation issues, difficulty eating or drinking, and excessive drooling, particularly if high doses are used [22,23].

Dysphagia, Hoarseness, and Neck Weakness

When botulinum toxin is used to treat platysmal bands or neck wrinkles, improper technique such as high doses or deep injections—can affect muscles involved in swallowing, speech, or head movement. This may lead to dry mouth, dysphagia, dysarthria, or difficulty holding the head up [17,24].

Facial Asymmetry

Asymmetry, including the characteristic “Spock eyebrow,” often results from imbalanced muscle inactivation due to injection errors or patient anatomical variation. It may be corrected with additional toxin injected into the overactive area [17,19].

Injection Site Reactions

Common local side effects include erythema, swelling, bruising, and pain. Using fine-gauge needles and avoiding superficial vessels can help minimize bruising, particularly near the eye corners. Applying cold compresses aids in reducing both pain and hematoma formation. Mild headaches and general discomfort may occur but are typically transient. Serious reactions, such as anaphylaxis, urticaria, or soft tissue edema, are rare [25].

Primary and Secondary Treatment Failures

Botulinum toxin complications can be classified as primary—where effectiveness is below 25% even after dose adjustments—or secondary, where efficacy wanes after repeated treatments. Primary failures may stem from poor injection technique or misdiagnosis, while secondary failures often involve neutralizing antibody formation. Immunogenicity is influenced by toxin formulation, dose, and injection frequency [3,26].

Antibody-Mediated Resistance

Short intervals between treatments, high total doses, and antigenic protein content increase the risk of resistance due to antibody formation. Experts recommend spacing injections at least six months apart to reduce this risk. Nevertheless, product choice is often guided more by cost-benefit analyses than by immunogenic potential [27].

Allergic Reactions

Allergic responses, though rare, have been reported—especially with certain formulations like Chinese-manufactured botulinum toxin serotype A (CBTX-A), which contains bovine gelatin. This component may trigger type I hypersensitivity reactions upon re-exposure [28]. In some cases, patients experienced erythematous, edematous lesions at injection sites [29]. While severe reactions like anaphylaxis are rare, the use of purified formulations such as Xeomin, which lack complexing proteins, may reduce sensitization risks [30].

Diplopia

Double vision can occur if the toxin inadvertently affects extraocular muscles, particularly the lateral rectus, through diffusion into the orbital septum. This complication is more frequent following injections near the lateral canthus and may develop between 3 and 60 days post-treatment, typically resolving spontaneously within 1 to 12 weeks [31].

IV. Discussion

Safety And Adverse Effects

Although controlled clinical trials can provide valuable data on the safety of botulinum toxin, they often do not report severe or long-term adverse events. Most of the information on these events comes from spontaneous reporting systems and case reports. However, these systems have limitations, such as underreporting and challenges in determining causality. Studies suggest that serious adverse events, such as botulism, generalized paralysis, dysphagia, and even death, may occur due to the local diffusion of the toxin or hypersensitivity reactions to its protein structure. Diffusion to adjacent muscles, and even to contralateral muscles, has been documented, with potential for systemic dissemination after prolonged use [32].

With an increasing number of professionals from various specialties and experience levels administering botulinum toxin, it is expected that complications associated with its use will also increase, making a deep understanding of the subject essential. Sethi et al. (2021) [3] analyzed 9,398 cases to investigate the safety of the toxin in various aesthetic indications. The results revealed a low incidence of complications, most of which were mild, reversible, and self-limiting. Headaches were commonly reported, typically associated with the injection procedure, such as trauma to the periosteum, intramuscular hematomas, anxiety in new patients, or temporary muscle spasms. However, some cases of prolonged headaches were recorded after injections in the forehead and glabellar region.

A systematic review with meta-analysis published in 2022 by Zargaram et al. [33] demonstrated that the incidence of adverse events related to BoNT-A injection in the glabellar and forehead areas is approximately 16%, with few serious complications possibly linked to the treatment. The most common complications were headaches and local skin reactions, which were present in both BoNT-A-treated patients and those in the placebo group. However, facial neuromuscular symptoms and asymmetries occurred more frequently in BoNT-A injections, suggesting that these complications were due to the toxin, whereas the skin reactions and headaches were not.

V. Conclusion

Based on this literature review, it can be concluded that the use of botulinum toxin for aesthetic purposes, although widely used, is not without risks. Complications such as ptosis, facial asymmetry, and other adverse effects, although rare, highlight the importance of careful application based on a thorough understanding of anatomy. While the incidence of serious adverse events is low, concerns about antibody formation and toxin resistance are emerging issues that require attention. Therefore, it is crucial that healthcare professionals administering botulinum toxin are well-informed and up-to-date on the best practices and injection techniques to ensure both safety and effectiveness of the treatment. Further studies are needed to deepen the understanding of appropriate dosages and associated complications, contributing to the continued safe and effective practice of botulinum toxin in aesthetics.

Acknowledgments

We thank the North University Center of São Paulo, UNORTE and School of Dentistry of Araçatuba, São Paulo State University (UNESP), Araçatuba, Brazil for supporting this study.

Funding

None.

References

- [1] Zhou, K.; Luo, W.; Liu, T.; Ni, Y.; Qin, Z. Neurotoxins Acting At Synaptic Sites: A Brief Review On Mechanisms And Clinical Applications. *Toxins*, V.15, N.18, 2023.
- [2] Willis, B.; Eubanks, L.M.; Dickerson, T.J.; Janda, K.D. The Strange Case Of The Botulinum Neurotoxin: Using Chemistry And Biology To Modulate The Most Deadly Poison. *Angew Chem Int Ed.*, V.47, N.44, P.8360–8679, 2008.
- [3] Sethi, N.; Singh, S.; Debouille, K.; Rahman, E. A Review Of Complications Due To The Use Of Botulinum Toxin A For Cosmetic Indications. *Pharmacology*, V.95, P.65–69, 2021. DOI: 10.1159/000370245.
- [4] Trindade, A.R.; Secco, L.C.; Carruthers, A. Handling Botulinum Toxins: An Updated Literature Review. *Dermatol Surg.*, V.37, N.11, P.1553–1565, 2011.
- [5] Awan, K.H. The Therapeutic Usage Of Botulinum Toxin (Botox) In Non-Cosmetic Head And Neck Conditions—An Evidence-Based Review. *Saudi Pharm J.*, V.25, N.1, P.18–24, 2017.
- [6] Rzany, B.; Zielke, H. Overview Of Botulinum Toxin. In: From May M, Rzany B (Eds) *Botulinum Toxin In Aesthetic Medicine*. Springer, Berlin, P. 1–10, 2007.
- [7] Arora, B.P. Anti-Aging Medicine. *Indian J Plast Surg.*, V.41, N.3, P.130-133, 2008.
- [8] Stipp, D. *The Youth Pill: Scientists At The Brink Of An Anti-Aging Revolution*. New York: Penguin; 2013.
- [9] American Society Of Plastic Surgeons (ASPS). *Plastic Surgery Statistics Report, 2020*. Disponível Em: <https://www.plasticsurgery.org/documents/news/statistics/2020/plastic-surgery-statistics-full-report-2020.pdf>. Acesso Em: Maio De 2024.
- [10] Aurora, S.K.; Dodick, D.W.; Turkel, C.C.; Degryse, R.E.; Silberstein, S.D.; Lipton, R.B., Et Al. Onabotulinumtoxin A For Treatment Of Chronic Migraine: Results From The Double-Blind, Randomized, Placebo-Controlled Phase Of The PREEMPT 1 Trial. *Cephalalgia*, V.30, P.793–803, 2010.
- [11] Park, M.Y.; Ahn, K.Y. Scientific Review Of The Aesthetic Uses Of Botulinum Toxin Type A. *Arch Craniofac Surg*, V.22, N.1, P.1–10, 2021.
- [12] Blasi, J.; Chapman, E.R.; Link, E.; Binz, T.; Yamasaki, S.; De Camilli, P.; Südhof, T.C.; Niemann, H.; Jahn, R. Botulinum Neurotoxin A Selectively Cleaves The Synaptic Protein SNAP-25. *Nature*, V.365, P.160-163, 1993.
- [13] Simpson, L.L. Molecular Pharmacology Of Botulinum Toxin And Tetanus Toxin. *Annu Rev Pharmacol Toxicol*, V.26, P.427–53, 1986.
- [14] Kane, M.; Donofrio, L.; Ascher, B.; Hexsel, D.; Monheit, G.; Rzany, B., Et Al. Expanding The Use Of Neurotoxins In Facial Aesthetics: A Consensus Panel’s Assessment And Recommendations. *J Drugs Dermatol*, V.9, N.1 Suppl, P.S7–22, 2010.
- [15] Jung, G.S.; Cho, I.K.; Sung, H.M. Submandibular Gland Reduction Using Botulinum Toxin Type A For A Smooth Jawline. *Plast Reconstr Surg Glob Open*, V.7, E2192, 2019.
- [16] Carruthers, A.; Carruthers, J. Clinical Indications And Injection Technique For The Cosmetic Use Of Botulinum A Exotoxin. *Dermatol Surg*, V.24, P.1189–1194, 1998.
- [17] Klein, A.W. Complications And Adverse Reactions With The Use Of Botulinum Toxin. *Dis Mon*, V.48, P.336–356, 2002.
- [18] Klein, A.W. Dilution And Storage Of Botulinum Toxin. *Dermatol Surg*, V.24, P.1179–1180, 1998.
- [19] Carruthers, A.; Carruthers, J. Botulinum Toxin Type A: History And Current Cosmetic Use In The Upper Face. *Semin Cutan Med Surg*, V.20, P.71–84, 2001.
- [20] Carruthers, A.; Carruthers, J. The Treatment Of Glabellar Furrow With Botulinum A Exotoxin. *J Dermatol Surg Oncol*, V.16, P.83, 1990.
- [21] Carruthers, J.D.; Carruthers, J.A. Treatment Of Glabellar Frown Lines With C. Botulinum-A Exotoxin. *J Dermatol Surg Oncol*, V.18, P.17–21, 1992.
- [22] Matarasso, S.L.; Matarasso, A. Treatment Guidelines For Botulinum Toxin Type A For The Periocular Region And A Report On Partial Upper Lip Ptosis Following Injections To The Lateral Canthal Rhytides. *Plast Reconstr Surg*, V.108, P.208–214, 2001.
- [23] Goldwyn, R.; Rohrich, R. Consensus Recommendations On The Use Of Botulinum Toxin Type A In Facial Aesthetics. *Plast Reconstr Surg*, V.114 Suppl, P.1S–22S, 2004.
- [24] Blitzer, A.; Binder, W.J.; Aviv, J.E. The Management Of Hyperfunctional Facial Lines With Botulinum Toxin: A Collaborative Study Of 210 Injection Sites In 162 Patients. *Arch Otolaryngol Head Neck Surg*, V.123, P.389–392, 1997.
- [25] Kassir, M.; Gupta, M.; Galadari, H.; Kroumpouzou, G.; Katsambas, A.; Lotti, T.; Vojvodic, A.; Grabbe, S.; Juchems, E.; Goldust, M. Complications Of Botulinum Toxin And Fillers: A Narrative Review. *J Cosmet Dermatol*, V.19, P.570–573, 2020. DOI: 10.1111/Jocd.13266.
- [26] Wee, S.Y.; Park, E.S. Immunogenicity Of Botulinum Toxin. *Arch Plast Surg*, V.49, N.1, P.12–18, 2022.

- DOI: 10.5999/Aps.2021.00766.
- [27] Rho, N-K.; Han, K-H.; Kim, H-S. An Update On The Cosmetic Use Of Botulinum Toxin: The Pattern Of Practice Among Korean Dermatologists. *Toxins (Basel)*, V.14, N.5, P.329, 2022. DOI: 10.3390/Toxins14050329.
- [28] Rieder, C. R.; Schestatsky, P.; Socal, M. P., Et Al. A Double-Blind, Randomized, Crossover Study Of Prosigne Versus Botox In Patients With Blepharospasm And Hemifacial Spasm. In: *Clin Neuropharmacol.* 2007; 30(1): 39-42.
- [29] Tamura, B. M.; Cucé, L. C.; Rodrigues, C. J. Allergic Reaction To Botulinum Toxin: Positive Intradermal Test. In: *Dermatol Surg.* 2008; 34: 1117-1119.
- [30] Caretta, M. F.; Delgado, L.; Patriota, R. Report Of Allergic Reaction After Application Of Botulinum Toxin. *Aesthet Surg J*, V.35, N.5, P.NP102–105, 2015.
- [31] Khan, S.; Pathak, G.; Milgraum, D.; Tamhankar, M.; Milgraum, S. Double Vision Due To Lateral Rectus Injury After Cosmetic Botulinum Toxin Injections. *Australas J Dermatol*, V.64, P.E220–E223, 2023.
- [32] Yiannakopoulou, E. Serious And Long-Term Adverse Events Associated With The Therapeutic And Cosmetic Use Of Botulinum Toxin. *Pharmacology*, V.95, N.1-2, P.65–69, 2015.
- [33] Zargaran, D.; Zoller, F.; Zargaran, A.; Rahman, E.; Woollard, A.; Weyrich, T.; Mosahebi, A. Complications Of Cosmetic Botulinum Toxin A Injections To The Upper Face: A Systematic Review And Meta-Analysis. *Aesthet Surg J*, V.42, N.5, P.NP327–NP336, 2022.