MAR Dental Sciences and Oral Rehabilitation (2024) 5:4
Research Article

Botulinum Toxin in Facial Treatments: Exploring Potential Reduction in Injection Intervals through Literature Review

Kamila de Campos Godoy CRISTINO [1]*, Polyne Graboschii Whittaker FRANCO [2]

1.DDS, Orthodontics and Orofacial Aesthetics Specialist, São Paulo, Brazil.

ORCID ID: 0000-0001-5691-8644.

2. Dental Student São Paulo, Brazil. ORCID ID: 0009-0003-0705-6103.

***Correspondence to**: Kamila de Campos Godoy CRISTINO. DDS, Orthodontics and Orofacial Aesthetics Specialist, São Paulo, Brazil ORCID ID: 0000-0001-5691-8644.

Received: 15 July 2024

Published: 01 August 2024

Abstract

Objective: This literature review aims to determine whether the scientific literature justifies a 3- to 6-month interval between applications of botulinum toxin type A in neuromuscular blocking procedures for orofacial harmonization. It examines the feasibility of shorter reapplication intervals.

Methods: The literature review was conducted using the PubMed electronic database. Included studies established a connection between botulinum toxin and the physiological responses it induces, focusing on the duration of muscle paralysis effects and its relationship with immunogenicity development.

Results: IncobotulinumtoxinA stands out for not containing accessory proteins, which may account for its lower propensity for immunogenicity.

Conclusion: The results indicate not only the treatment's efficacy but also suggest the potential to establish consistent guidelines applicable to other uses of botulinum toxin in aesthetic contexts, providing a solid foundation for future research and clinical practices with shorter application intervals.

Index Terms: Botulinum toxins; Botulinum toxins type A; Aesthetics.

Introduction

The increasing number of interventions in the field of orofacial harmonization over the years supports the World Health Organization's (WHO) definition of health as encompassing physical, mental, and social well-being, not merely the absence of disease. [1,2] Therefore, feeling good about one's body and smile seems to be a significant social concern, integral to overall health and self-esteem.[3]

Within the aesthetic and functional parameters addressed by orofacial harmonization procedures, aimed at improving skin appearance resulting from facial muscle contractions, botulinum toxin is a primary tool used in facial rejuvenation methods.[3]

The scientific literature review covering different approaches to botulinum toxin reveals a compilation of information that converges towards establishing application standards to enhance neuromotor block results in the most predictable manner, with an expected efficacy of 3 to 5 months. However, manufacturers' guidelines provide little clarification on the justification for recommending a minimum 3-month interval for new applications of the toxin.

Concomitant with the intervals between reapplications is the loss of treatment efficacy associated with the recovery of muscle contracture potential. Consequently, patients tend to be dissatisfied with the reduced efficacy of botulinum toxin type A (BoNT-A) action shortly before the next injection. In this cyclical scenario, the demand for BoNT-A formulations with lower immunogenicity potential and greater safety in shorter intervals is increasing.[4, 6, 7, 8, 10]

Therefore, this article seeks to review the literature, presenting data that justify the quarterly periodicity between applications of botulinum toxin type A in neuromuscular blocking procedures within orofacial harmonization. Additionally, it aims to explore the possibility of shorter intervals between applications without posing risks to patients.

Focus Question

Is it possible to reduce the interval between applications of botulinum toxin type A to less than 3 months in neuromuscular blocking procedures for orofacial harmonization without presenting significant risks to patients?

Methods

The bibliographic research was conducted through a review of articles in the PubMed database published until April 2024 which establish a connection between botulinum toxin and the physiological responses it induces, as well as provide evidence of its efficacy and correlation with immunogenicity development in the human body. Only articles in English and Portuguese were considered.

The search in PubMed used the following terms and synonyms, in Brazilian Portuguese and/or in English: ("toxina botulínica" OR "botulinum toxin") AND ("durabilidade" OR "durability") AND ("imunogenicidade" OR "immunogenicity").

Non-clinical and clinical studies with insufficient information, "grey literature," unrelated studies, and letters to editors were excluded from this study. Initially, articles were selected based on title and abstract. In a subsequent phase, full articles were sought and chosen based on inclusion and exclusion criteria.

Discussion

Based on general guidelines from articles and courses, professionals working with botulinum toxin type A for aesthetic purposes typically adhere to a standard reapplication interval of approximately 3 to 6 months. However, considering that the paralyzing effect of botulinum toxin diminishes between 3 and 5 months, in accordance with the manufacturers' prescribed instructions, patients may potentially experience 1 to 3 months without the neurotoxic effect. Consequently, this period allows for the restoration of muscle contraction potential, leading to the reappearance of facial wrinkles. These recurring periods of patient dissatisfaction can result in personal perceptions of aesthetic self-judgment, diminished perceived value of the treatment, and an erroneous association of the professional with possible technical ineptitude.

Interestingly, this mentioned interval between applications is not specified in the package inserts of the three toxins studied here. Even in the Inco insert, it is explicitly stated that the clinical effect of botulinum toxin A can be enhanced or attenuated by repeated injections, which may be caused by different preparation techniques, different intervals, injections into other muscles, slightly fluctuating activity of the toxin's active ingredient, or lack of response to treatment.

To optimize these intervals, it seems plausible to increase or decrease the injected doses, as various studies indicate a relationship between the volume in units, time, and potential efficiency in the application of botulinum toxin with rare manifestations of SNR.[3, 4, 6, 7, 10] The fact that higher doses lead to a longer duration of efficacy, and lower doses result in shorter periods of efficacy, supports this dose dependency.

The combination with various proteins supposedly protects and stabilizes the neurotoxin. However, this may trigger immunogenicity as an obstacle in a treatment prone to generating PNR or SNR. It is known that only the pure neurotoxin is responsible for the therapeutic effect, and the accompanying accessory proteins have shown immunomodulatory activity. These proteins are not essential for stabilizing the neurotoxin in a formula, as they quickly dissociate from the neurotoxin in a physiological environment, not affecting its dissemination. Therefore, the complexing proteins are not bound to the neurotoxin and do not influence the diffusion profile of the active toxin.[8] In this context, Inco has shown to be the only botulinum toxin currently apparently free of complexing proteins.[9]

Furthermore, there is a convergence in the conclusions of several studies, according to which Inco exhibits a very low potential for the development of immunogenicity compared to other BoNT formulations and offers safety for applications at intervals shorter than 12 months. [8, 10,17,18]

It is worth noting that, even though the minimum application interval is 12 weeks, injection intervals of up to 6 weeks with Inco were well tolerated. [7,8] In a meta-analysis of 461 studies conducted on treatments for blepharospasm using various doses of Inco, it was indicated that in nearly 45% of the cases (207 studies), applications were performed at intervals shorter than 12 weeks. Significant adverse effects included eyelid ptosis and dry mouth, depending on the treated area. At the same time, all reported adverse effects were the same when respecting an interval of 12 weeks or more. Therefore, the authors of these studies concluded that there is no increased risk if a strategy of more frequent applications is recommended to patients.[8] Thus, the feasibility of new clinical protocols for the administration of BoNT-A for aesthetic purposes, including smaller doses and shorter intervals between applications, appears plausible.

It is important to emphasize that the reapplications mentioned in the study by Wolfgang et al. were based on analyses conducted during follow-up visits scheduled every 6 weeks. During these evaluations, patient feedback was considered, along with the clinical need observed by the researchers, using a standardized wrinkle severity scale.[8] This meticulous approach, integrating both patient perspectives and healthcare professionals' expertise, not only reinforces the validity of the obtained results but also highlights the importance of collaboration between professionals and patients in optimizing botulinum toxin treatments. This paves the way for a more personalized treatment approach with BoNT-A, focusing on patient’s needs.

Final Considerations

Therapeutic approaches using botulinum toxin have proven to be safe and effective solutions in a wide range of applications in the fields of aesthetics and health. Despite the prevalent concern about the development of neutralizing antibodies to the effects of botulinum toxin, scientific studies and the pursuit of improvement and knowledge of the properties of injectable BoNT-A provide ways to mitigate the risk of immune resistance. It is also noteworthy that studies with dosages in glabellar lines, reaching up to 100 U applied in the region, or even studies where the application occurs in larger body muscles with dosages of up to 1,000 U, show that the formation of antibodies is non-existent or minimal.

The obtained results not only indicate the treatment's efficacy but also suggest the possibility of establishing consistent guidelines that can be extrapolated to other applications of botulinum toxin in aesthetic contexts, thereby providing a solid basis for future research and clinical practices aimed at shorter intervals between applications as well as reduced dosages.

Reference

1. Kichese ALS, Moraes JA de, Souza CS de. Simmetria Orofacial Harmonization in Science. 2020;1(3).

2. WHO, World Health Organization [homepage on the internet]. Resolution of July 22, 1946 – La salud es un estado de completo bienestar físico, mental y social, y no solamente la ausencia de afecciones o enfermedades. [cited 2023 June 12]. Available from: https://www.who.int/es/about/who-we-are/constitution.

3. Costa AMC, Nogueira R da S, Lemos AC de A, Santos BN dos, Silva LS de A, Costa LLL da et al. Harmonização orofacial frente ao uso da toxina botulínica / Orofacial harmonization in front of the use of botulinic toxinin. Braz. J. Hea. Rev. [Internet]. 2021 Jun. 11 [cited 2024 Mar. 18];4(3):12864-72. Available from: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/31162

4. Eleopra R, Rinaldo S, Montecucco C, Rossetto O, Devigili G. Clinical duration of action of different botulinum toxin types in humans. Toxicon. 2020 May;179:84-91. doi: 10.1016/j.toxicon.2020.02.020. Epub 2020 Mar 14. PMID: 32184153

5. Dorizas A, Krueger N, Sadick NS. Aesthetic uses of the botulinum toxin. Dermatol Clin. 2014 Jan;32(1):23-36. doi:10.1016/j.det.2013.09.009. PMID: 24267419.

6. Dressler D, Saberi FA, Barbosa ER. Botulinum toxin: mechanisms of action. Arq Neuropsiquiatr. 2005 Mar;63(1):180-5. doi: 10.1590/s0004-282x2005000100035. Epub 2005 Apr 13. PMID: 15830090.

7. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology. Pharmacol Rev. 2017 Apr;69(2):200-235. doi: 10.1124/pr.116.012658. PMID: 28356439; PMCID: PMC5394922.

8. Jost WH, Benecke R, Hauschke D, Jankovic J, Kaňovský P, Roggenkämper P, Simpson DM, Comella CL. Clinical and pharmacological properties of incobotulinumtoxinA and its use in neurological disorders. Drug Des Devel Ther. 2015 Apr 1;9:1913-26. doi: 10.2147/DDDT.S79193. PMID: 25897202; PMCID: PMC4389813.

9. Frevert J. Xeomin: an innovative new botulinum toxin type A. Eur J Neurol. 2009 Dec;16 Suppl 2:11-3. doi: 10.1111/j.1468-1331.2009.02879.x.

10. Bellows S, Jankovic J. Immunogenicity Associated with Botulinum Toxin Treatment. Toxins (Basel). 2019 Aug 26;11(9):491. doi: 10.3390/toxins11090491. PMID: 31454941; PMCID: PMC6784164.

11. Wissel J, Bensmail D, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, Rekand T, McGuire J, Scheschonka A, Flatau-Baqué B, Simon O, Rochford ET, Dressler D, Simpson DM; TOWER study investigators. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: The TOWER study. Neurology.

2017 Apr 4;88(14):1321-1328. doi: 10.1212/WNL.0000000000003789. Epub 2017 Mar 10. PMID: 28283596; PMCID: PMC5379931.

12. Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs: a help or a hindrance? Biologics. 2010 Dec 9;4:325-32. doi: 10.2147/BTT.S14902. PMID: 21209727; PMCID: PMC3010823.

13. Kaufman-Janette J, Cox SE, Dayan S, Joseph J. Botulinum Toxin Type A for Glabellar Frown Lines: What Impact of Higher Doses on Outcomes? Toxins (Basel). 2021 Jul 16;13(7):494. doi: 10.3390/toxins13070494. PMID: 34357966; PMCID: PMC8310242.

14. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M; CD-017 BoNTA Study Group. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. Mov Disord. 2008 Jul 30;23(10):1353-60. doi: 10.1002/mds.22157. PMID: 18546321.

15. Naumann M, Carruthers A, Carruthers J, Aurora SK, Zafonte R, Abu-Shakra S, Boodhoo T, Miller-Messana MA, Demos G, James L, Beddingfield F, VanDenburgh A, Chapman MA, Brin MF. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BOTOX®) across multiple indications. Mov Disord. 2010 Oct 15;25(13):2211-8. doi: 10.1002/mds.23254. PMID: 20737546.

16. Haussermann P, Marczoch S, Klinger C, Landgrebe M, Conrad B, Ceballos-Baumann A. Long-term follow-up of cervical dystonia patients treated with botulinum toxin A. Mov Disord. 2004 Mar;19(3):303-8. doi: 10.1002/mds.10659. PMID: 15022184.

17. Dressler D, Saberi FA. Safety of botulinum toxin short interval therapy using incobotulinumtoxin A. J Neural Transm (Vienna). 2017 Apr;124(4):437-440. doi: 10.1007/s00702-016-1628-0. Epub 2016 Oct 17. PMID: 27747444.

18. Truong DD, Gollomp SM, Jankovic J, LeWitt PA, Marx M, Hanschmann A, Fernandez HH; Xeomin US Blepharospasm Study Group. Sustained efficacy and safety of repeated incobotulinumtoxinA (Xeomin(®)) injections in blepharospasm. J Neural Transm (Vienna). 2013 Sep;120(9):1345-53. doi: 10.1007/s00702-013-0998-9. Epub 2013 Feb 23. PMID: 23435927; PMCID: PMC3751217.