

Use of Botulinum Toxin Type A in patients with Trigeminal Neuralgia

Julya Prüsse ¹, Fernando André Campos Viana ¹, Bruno Frota Amora Silva ¹, José Rômulo de Medeiros ^{1,*}

¹ School of Dentistry, University of Fortaleza - UNIFOR, Fortaleza, CE, Brazil.

* Correspondência: joseromulo@yahoo.com.br.

Citation: Prüsse J, Viana FAC, Silva BFA, Medeiros JR. Use of Botulinum Toxin Type A in patients with Trigeminal Neuralgia. Brazilian Journal of Dentistry and Oral Radiology. 2024 Jan-Dec;3:bjd41.

doi: <https://doi.org/10.52600/2965-8837.bjdor.2024.3.bjd41>

Received: 24 March 2024

Accepted: 28 April 2024

Published: 11 May 2024

Abstract: This article provides a systematic review of the efficacy of Botulinum Toxin Type A (TBA) in treating trigeminal neuralgia (TN), a painful disorder affecting the trigeminal nerve. TN is described in the literature as a facial pain of acute nature, often unilateral, characterized by episodes of intense and transient pain, comparable to electric shocks. The diagnosis is made through a detailed evaluation that includes anamnesis, characterization of symptoms, and imaging tests to exclude similar pathologies. Conventional therapy for TN involves the use of carbamazepine; however, in cases of pharmacological resistance or ineffectiveness of standard treatments, TBA emerges as a viable therapeutic alternative. The efficacy of TBA, as demonstrated in retrospective and prospective studies, is due to its ability to inhibit the release of neurotransmitters responsible for pain transmission and inflammatory processes. Various studies corroborate the efficacy of TBA, especially in patients over 50 years old, observing substantial improvement in symptoms with minimal adverse effects. The administration of TBA is carried out directly in the trigger zones, where it has proven to be well-tolerated, providing significant improvement in the quality of life of the affected patients. Despite promising results, the literature suggests the need for additional studies to optimize the dosage protocols and application of TBA, aiming to ensure its efficacy and safety in the long term. In conclusion, this article reiterates that TBA represents an effective and minimally invasive therapeutic alternative for the treatment of TN. However, it is essential to develop individualized therapeutic protocols and conduct more comprehensive studies to consolidate its use as the treatment of choice.

Keywords: Trigeminal Neuralgia; Botulinum Toxin; Orofacial Harmonization.



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1. Introduction

The International Headache Society (IHS) reports trigeminal neuralgia (TN) as a unilateral disorder characterized by intense, electric shock-like pain that tends to be short-lived, with sudden onset and cessation. It is considered a chronic facial pain and described as the most intense type of pain a human can experience, predominantly affecting females, often on the right side of the face, with a peak incidence around 60-70 years. It affects 4 to 29 people per 100,000 inhabitants worldwide [1]. TN is described as extremely strong spontaneous facial pain involving the fifth cranial nerve (trigeminal nerve) and its branches V1, V2, V3. The pain is felt around the maxilla (V2) and mandible (V3), with the least common in the frontal area of the head and orbit (V1). It is triggered by harmless stimuli, such as speaking, touching the so-called trigger zone, brushing teeth, ingesting liquids, wind on the face, among others [2].

According to the International Classification of Headache Disorders, there are two types of Trigeminal Neuralgias: the painful type, which can be caused by trauma, injury, or viral infection, and the classical type, which usually has no specific cause but the pain must manifest only in the innervated area and exhibit at least three of

these characteristics: recurrent and paroxysmal pain, lasting from a fraction of a second to 2 minutes, severe intensity, pain described as electric shock-like, stabbing, or jerking, triggered by harmless stimuli [3]. Another classification used is one that associates trigeminal neuralgia with other pathologies, post-trauma, post-herpetic, in addition to type I, which is the electric shock-like pain, and type II, which refers to continuous and longer-lasting pains [2].

Its diagnosis is considered complex, but to establish it, it relies on the criteria set by the IHS and the International Association for the Study of Pain (IASP), in addition to the patient's history and symptom reports. Imaging tests are indispensable for diagnosis determination, as they demonstrate possible vascular anatomical changes, neoplasms, and neurodegenerative diseases [1]. Moreover, trigeminal neuralgia presents characteristics similar to tooth pain, therefore, it is up to the dentist to analyze and structure hypotheses to ensure a correct diagnosis. The so-called "trigger zones" must be observed to understand the location and trigger of the pain [4].

However, there are well-disseminated treatments for this chronic pain, which act both in pain control and recurrence. The initial, first-choice treatment is pharmacological, considering carbamazepine, an anticonvulsant, as the first-line treatment. When this treatment is not successful, or when the patient presents pharmacoresistance, new strategies are drawn, such as neurosurgery, a more invasive method, and recently with the new discovery of the use of botulinum toxin for therapeutic purposes as a great alternative, considering that it is a non-invasive treatment, comfortable for the patient, with high efficacy and low indices of side effects [2].

In the 1990s, studies with Botulinum Toxin (BT) began after noticing improvements in patients who had the application in the area to treat involuntary muscle movements of the eyelid. The natural neurotoxin is derived from the anaerobic gram-positive bacterium *Clostridium botulinum*, which acts by inhibiting the release of acetylcholine at muscle junctions, causing the muscle to relax through the paralysis of its movement, along with neurotransmitters responsible for pain, as it also blocks substances that participate in inflammatory processes and sensitize nerves, causing the painful sensation [3]. The historical context in which Botulinum Toxin emerged in 1817, where the first article about botulism was published, which would be the poisoning by *Clostridium botulinum*. It was identified in a smoked sausage, which some people ingested and caused their deaths, acting on the autonomic and motor nervous system. It can be found in soil, animals, human feces, among others. Thus, BT is still considered one of the most lethal substances to this day [5].

In 1960, Alan B. Scott was looking for a substance that would help in treating strabismus in children, thus discovering that when BT was injected into hyperactive muscles, the expected reaction occurred. After many studies in the 1990s, it was noticed that, in addition to treating eyelid spasms, BT minimized the expression lines of patients who used it. Thus, the use of type A botulinum toxin for aesthetic purposes began, being considered an effective and safe method [6]. With the popularization of the BOTOX® brand in 1997, ANVISA together with the Ministry of Health decreed the release of the application throughout the Brazilian territory for aesthetic purposes and treatment of sweating in hands and feet [7]. It is known that the treatment of trigeminal neuralgia can be done medicinally and non-medicinally. When the use of anticonvulsants (first-line treatment) does not show the same improvement over time, surgical treatment or new therapy using BT is indicated. In the surgical procedure such as microvascular decompression, sensory rhizotomy, among others, there are high chances of post-surgical complications.

Over time, a new therapy using the natural neurotoxin from the bacterium *Clostridium botulinum* has been identified. BT is responsible for muscle relaxation and neurotransmitters responsible for pain; besides it also acts as an analgesic and has an anti-inflammatory action. Currently, studies have been published that show pos-

sible antinociceptive effects, which can be explained considering primary afferent fibers and cells releasing chemical mediators. Such a mechanism can be explained by the fact that injured cells and primary afferent fibers release a series of chemical mediators, including substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), which have direct effects on the excitability of sympathetic sensory fibers. These mediators contribute to the formation of a complex environment responsible for neurogenic inflammation [8].

There are some techniques for a correct and safe injection of BT in patients with trigeminal neuralgia, which vary according to the affected area, which can be applied in checkerboard lines or fan-like arrangement. It is mentioned that its administration must be done subcutaneously or intradermally, with fractional doses between 2.5 to 7.5 U/cm² in the painful area, which is delimited by touch, marking three equidistant points for the injection. For the safety of the procedure, it is not recommended to use more than 200 U in total [9].

Regarding side effects, it is said that they are mild to moderate, transient, and short-lived, the most common are pain at the injection site, rash, and edema. In addition, weakness, muscle paralysis, and facial asymmetry may occur due to its spread to adjacent tissues. Special attention is required for patients with pre-existing concomitant diseases, as they may present other effects such as nausea, urinary incontinence, fever, xerostomia, however, they are not frequent [10]. According to Moreau et al. [10], the anatomy, volume, and dosage of toxin to be applied, and the use of a vasoconstrictor to limit the diffusion of the toxin should be taken into consideration. TBA has great advantages, both for its duration and for the ease of administration, as it is done directly and localized exactly at the painful point. Its tolerability is considered excellent, in addition to its safety profile and absence of systemic effects.

The pain of patients is assessed on a visual analog scale (VAS) that measures up to 11 points. Complemented by the global impression scale of patients (PGIC), which portrays the overall response to treatment, through a self-assessment of the general change of the patient since the beginning of treatment [2]. The most recent studies prove that the association of therapy with TBA and pharmacology is a safe and promising way, with positive results in the analyzed patients, considering that there was great pain control, in addition to the decrease in the frequency of episodes, thus improving the quality of life of the patients [1]. It must be kept in mind that everyone has their own characteristics, responding in different ways to the treatments available on the market, therefore, in addition to using the correct protocols for injection safely, it is necessary to individualize each procedure, assessing the diagnosis, the real needs, and conditions of the patient, thus ensuring a more effective and assertive treatment.

Thus, the use of type A botulinum toxin has been shown to be a promising treatment in patients with trigeminal neuralgia, but there is still a need for further studies to consolidate the therapy and the analysis of the evolution of patients who use TBA, thus ensuring safe and satisfactory results [3]. Here, we present trigeminal neuralgia, characterizing and showing physiological and anatomical aspects, emphasizing the study of the use of Type A Botulinum Toxin as a treatment, analyzing its efficacy, side effects, and the possibility of becoming a therapeutic option in patients with TN, both for being a good option and for use in patients who do not adapt to other treatments.

2. Methodology

For the execution of this integrative review, scientific articles from databases such as Google Scholar, Scielo, PubMed, and BVS were selected with the aim of enhancing and augmenting research, as well as verifying the efficacy of using Botulinum Toxin Type A (TBA) as a treatment for trigeminal neuralgia. Articles filtered included those published since 2017, clinical research and case reports with at least four patients in the sample, in both Portuguese and English. Exclusion criteria were duplicate articles, articles in languages other than those mentioned, articles dated before

2017, and articles whose abstracts did not meet the research objectives. The keywords used were Botulinum Toxin, trigeminal neuralgia, treatment, and orofacial rehabilitation.

3. Results

Wu et al. [11] compared the application of Botulinum Toxin Type A in older and younger patients, performing intradermal injections at the site of pain and in the so-called trigger zones, maintaining a 15 mm space between applications of 5U per point. For patients experiencing pain in the oral mucosa, injections were extended to the submucosa with 2.5U. The results were considered positive as 87 out of 104 patients reported positive outcomes, with 41 experiencing complete pain control and 46 significant pain relief. Seventeen patients reported treatment failure, with seven showing no improvement, nine with mild improvement, and one with worsening pain. The study confirmed a correlation between patient age and positive treatment response, noting that patients over the age of 50 showed considerable improvement compared to younger patients, particularly in terms of treatment onset and peak times, as well as the emergence of side effects.

Zhang et al. [12] analyzed 100 patients divided into two distinct groups. One group received a single dose of TBA ranging from 70 to 100U, while the other underwent a double application protocol of 50 and 70U. The injections were administered intradermally, submucosally, and locally. The study found no significant difference in outcomes, confirming the efficiency of a single TBA application. Some patients reported mild and transient side effects. The study in 2019 also showed that men had better treatment outcomes compared to women. The results were also positive, with more than 89% efficacy, and the most common adverse effect observed was facial asymmetry, particularly in women.

A clinical trial by Boru et al. [13] demonstrated that Botulinum Toxin was effective in patients with neuralgia who had not responded well to pharmacological treatments, showing a 50% reduction in pain levels over six months and over 44% achieving total remission of effects. Reported side effects included facial and masseter muscle weakness in three patients. According to Liu et al. [14], the treatment is considered effective and safe for both older and younger patients, and the dosage does not affect the improvement in treatment response. The application was directed by the patient's pain, injected directly into the trigger point, either submucosally or intradermally. One group received between 45 to 150U and the other 30 to 200U of TBA. Thus, both Wu et al. [11] and Liu et al. [14], who compared the use of TBA in older vs. younger patients, agreed that the treatment is effective and safe for all ages, and that dosage does not impact the outcome, noting that patients over 50 years of age achieved better results.

Unlike the study by Crespi et al. [15], which selected 10 patients but only 9 remained in the study, injections were performed using assisted navigation, involving a 1 to 2 mm incision and application of 25U of toxin combined with 0.5ml of saline solution. Follow-ups were conducted 5 to 8 weeks post-treatment, showing a 50% improvement, though the author did not consider the use of Botulinum Toxin safe as many patients experienced side effects such as facial asymmetry. Caldera et al. [16] used a protocol of 15 to 50U applied intradermally directly to the trigger zones, agreeing with most articles that also found no difference in treatment results based on dosage and/or site of application. Patients showed significant improvement in the frequency of episodes and in pain intensity.

Most studies used the Visual Analog Scale (VAS) for pain assessment. Furthermore, they reported positive results from the combination of TBA therapy and pharmacology, considered safe and effective, greatly controlling pain, and significantly reducing the frequency of episodes. Comparing the analyzed articles, TBA treatment stands out as it is considered non-invasive, with rapid and reversible effects. The average period of efficacy proven by studies for Botulinum Toxin Type A is 8 to 12 weeks after the first injection, with a decrease in pain levels, spacing between crises,

and consequently, a considerable increase in patients' quality of life. The research does not agree on the ideal dosages but emphasizes that the injection sites are at the so-called trigger points and/or painful areas, varying according to the adopted protocol. The application should be subcutaneous and/or submucosal, maintaining a safe distance of 15 mm between injection points. Some authors assert that the best method of administration is intradermal, as it directly contacts the non-myelinated sensitive nerve endings.

Overall, side effects were considered mild to moderate and transient, resolving spontaneously in a short period. Reported effects include facial asymmetry, edema, pain at the injection site, and decreased muscle contraction strength in the masseter and orbicularis oculi. Some patients exhibit resistance to TBA; however, a second application has shown to be effective without increasing risks.

All analyzed studies agree and emphasize that, although TBA is a safe and effective treatment option, there is a need to expand research to better prove its efficacy, duration, and especially to define a more precise protocol for its application.

Table 1: Description of the articles included in this study, highlighting the sample size evaluated, the methodology, the main findings, and the conclusions.

Reference	Sample Size	Methodology	Main Findings	Conclusions
[11]	104 patients	Retrospective cohort study analyzing daily attack frequency post-TBA injection on the VAS scale.	83.7% of patients showed satisfactory responses. Best results were observed in patients over 50 years old.	TBA is a safe and effective treatment, especially in middle-aged and elderly patients with possible medication intolerances.
[16]	22 patients	Observational study over 6 months. Pain assessed using a visual analog scale from 0 to 10 at 10, 20, 30, 60, 90 days post-application. Injections administered to the maxillary and mandibular nerves.	Maximum response occurred 60 days after application. No difference in outcome with higher dosages or injection strategies.	Significant pain reduction, confirming TBA as a viable treatment for TN.
[13]	27 patients	Visual analog scale and pain frequency assessed before treatment, in the first week, and in the second- and sixth-months post-application.	TBA reduced the frequency and intensity of pain episodes and was well tolerated with few adverse events.	Application of TBA to the maxillary and mandibular roots is effective.
[12]	100 patients	Division of patients into two groups: one received a single TBA dose, the other repeated doses. Followed for 6 months.	Both groups showed similar frequency and intensity of pain. However, the single-dose group had a longer duration of effect.	Repeated dosing showed no advantages over single dosing. Individual adjustments for each patient are necessary.
[14]	43 patients	Patients categorized by age, n=14 for >80 years and n=29 for <60 years.	Significant pain reduction after 1 month of application in both groups. Adverse reactions were mild and resolved spontaneously within 3 weeks.	Safe and effective treatment in elderly patients with dosages similar to those applied in younger patients.
[17]	152 patients	Follow-up period of 6 to 28 months post-application.	Women showed a higher incidence of side effects; therefore, men	Treatment effectiveness rate was 89.4%, with facial asymmetry being

[15]	10 patients	25U injected in 9 patients (1 violated the protocol), followed for 5 to 8 weeks.	responded better to the treatment. 50% improvement in TN effects and side effects such as dysphagia, nasolabial asymmetry, jaw discomfort, and diplopia were noted.	the most common adverse effect. The treatment was not considered safe due to the occurrence of side effects.
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4. Conclusion

We can conclude that Botulinum Toxin Type A, beyond its use for aesthetic purposes, is also a treatment option for patients with trigeminal neuralgia. Its application is simple, quick, and associated with mild and transient side effects, making it a viable alternative for patients who may have allergies to conventional pharmacological therapies and wish to avoid surgical intervention. It is emphasized that treatments should be individualized, and diagnosis should be conducted carefully and accurately, ensuring that the chosen treatment is indeed the most suitable for each patient. Despite evidence of effectiveness and safety in using TBA for treating TN, all reviewed articles stress the need for further long-term studies and analyses on its efficacy, suggesting the need to expand the sample size and define a protocol for its use, concerning both dosage and injection sites.

Funding: None.

Research Ethics Committee Approval: None.

Acknowledgments: None.

Conflicts of Interest: None.

Supplementary Materials: None.

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