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Botulinum Toxin as a Treatment for Trigeminal Neuralgia

Ramírez Lotty [1], Villacis Paredes Gabriela[2], Salazar Pullutacsi Karen[3]

[1]Grupo de Investigación Biomédica, Ambato, Ecuador. Email: ua.lottyramirez@uniandes.edu.ec
ORCID ID: https://orcid.org/0000-0003-4885-2520
[2]Carrera de Medicina – Ambato, Ecuador. Email: ma.gabrielaavp10@uniandes.edu.ec
ORCID ID: https://orcid.org/0000-0002-4094-8539

[3]Carrera de Medicina – Ambato, Ecuador. Email: ma.karendsp.56@uniandes.edu.ec,
ORCID ID: https://orcid.org/0000-0001-9568-502X

**Corresponding author's Email:* ua.lottyramirez@uniandes.edu.ec

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Abstract

Trigeminal neuralgia is a pathology whose main characteristic is severe facial pain of stabbing type, with a distribution in the trigeminal nerve, which transmits sensory information from the head and neck; the treatment of choice is pharmacological; however, botulinum toxin has shown a high efficacy in patients who have stopped responding to drugs or if these present intolerable adverse effects. The objective of this research work is to know the efficacy and safety of botulinum toxin as a treatment for trigeminal neuralgia in cases where pharmacological therapy is not sufficient for pain reduction; through an updated bibliographic search in search engines such as PubMed, Medline, Web of Science, Cochrane Library and Clinical Key, complementing the information with journals such as Scielo, Scopus, reviews of randomized controlled clinical studies, systematic reviews and meta-analysis approaches. With the evidence obtained, positive results were generated for the use of botulinum toxin in TN where a reduction of more than 50% in pain was demonstrated. In conclusion, botulinum toxin is an alternative treatment option in patients with TN who do not respond to pharmacological treatment, avoiding the need for surgical interventions, BTX-A has efficacy and safety in reducing pain, since it produces few transient adverse effects.

Keywords: *Trigeminal Neuralgia, Botulinum Toxin Type A (BTX-A); Neurotoxin*

1. Introduction

The International Association for the Study of Pain (IASP) defines trigeminal neuralgia (NT) as a nerve disorder characterized by sudden severe pain, usually unilateral, with recurrent, brief, stabbing crises of pain within the distribution of one or more branches of the fifth cranial nerve, defined as having a profound effect on quality of life. This type of pathology is often difficult to diagnose and treat (Buckcanan Vargas et al., 2020; Bendtsen et al., 2019).

The trigeminal nerve, is the fifth (V) and largest of the twelve pairs of cranial nerves. Transmits sensory information from the head and neck and innervates chewing muscles, eardrum tensors, mylohyoids, and digastric anterior belly (Amit M. Shelat, 2020; Santos-Velázquez, 2018).

Epidemiology
Epidemiological studies speak of an incidence of 4-29 cases per 100,000 inhabitants throughout the world**,** With a slight predilection for the female sex (3:2), it occurs most often on the right side (León-Corredor et al., 2021). The most relevant epidemiological factor is age, since three quarters of patients are over 50 years old, with a prevalence of 3 to 5 per 100,000 individuals, The most frequently affected branches of the trigeminal; They are the maxillary and/or mandibular trigeminal branches, as opposed to postherpetic neuralgia, more common in the ophthalmic branch (Buckcanan Vargas et al., 2020).

Physiopathology
The trigeminal nerve is formed by three divisions: the ophthalmic (V1), the maxillary (V2) and the mandibular (V3) (Figure 1). The V1 and V2 divisions only receive sensory stimuli, while the V3 has a motor and sensory component. NT is divided into two forms, one classic and one symptomatic or secondary. The classic form is caused by a vascular compression of the trigeminal nerve root resulting in morphological changes in the root, while the secondary is due to other neurological pathologies, such as tumors of the cerebellopontine angle, multiple sclerosis, among others. Other mechanisms that have been postulated in the etiology of NT is focal demyelination of primary trigeminal afferents near the root entrance (IHS) HCCotIHS, 2018; Maarbjerg et al., 2017).

Clinical Manifestations
Its clinical manifestation is usually severe and recurrent facial pain, TN may have autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, runny nose, eyelid edema, ptosis, and facial edema, making it difficult to differentiate from other causes of facial pain (Maarbjerg et al., 2017)

Diagnosis
Diagnosis is based solely on the medical history and it is necessary to take some time to determine the key features and differentiate it from toothache or one of the trigeminal autonomic headaches. In addition, the diagnosis of TN is made if the patient's clinic meets the criteria of The International Classification of Headache Disorders 3 (ICHD-3), which are mentioned below:(1) Recurrent paroxysms of unilateral facial pain in the distribution of one or more divisions of the trigeminal nerve, without irradiation; (2) The pain should have all of the following characteristics: Severe intensity, lasting fractions of a second up to two minutes and sensation of electricity, stabbing, or gunshots; (3) It is caused by innocuous stimuli within the distribution of the trigeminal nerve (De Toledo et al., 2016; Buckcanan Vargas et al., 2020).

Treatment

The treatment of trigeminal neuralgia is initially pharmacological, but there are often cases of drug resistance, which forces doctors to seek new therapeutic strategies, among which various surgical treatments have been used; and in recent years a new therapeutic strategy has emerged consisting of the use of "botulinum toxin", which is a neurotoxin produced in cultures of the bacterium Clostridium botulinum naturally; in the process of sporulation there are 7 subtypes, subtype A being the most used in neurological problems (Castillo-Álvarez et al., 2017; Naranjo, 2018).

The application of this botulinum toxin leads to temporary muscle paralysis, in order to produce a final effect, which is a temporary chemical denervation at the neuromuscular junction without producing any physical injury to the nerve structures; the injection of botulinum toxin is used as adjuvant therapy in TN, all this in order to support patients in their process of physical relief and the intense pain they present, however clinical studies are increasingly controlled and extense, to strengthen the effectiveness and safety of it (Naranjo, 2018).

2. Methods
An exhaustive bibliographic search was carried out in various search engines such as PubMed, Medline, Web of Science, Cochrane Library and Clinical Key, as well as several medical journals such as Scielo, Scopus and international specialty journals. In addition, we used as a reference reviews of randomized

controlled trials, systematic reviews and meta-analysis approaches with an optimal sample size, excluding non-updated publications, that is, those that are not published within the last 5 years.

3. Results And Discussion

Trigeminal neuralgia is a pathology that can cause facial pain and that can often be confused or misdiagnosed, which is why it is important to find the cause of pain since treatments can be different. The therapeutic approach for TN includes medications such as anticonvulsants, antidepressants, analgesics, and complementary techniques; If medications do not relieve pain, surgical treatment may be recommended. However, with the passage of time, some patients stop responding to medications or may suffer intolerable side effects or simply refuse surgery, botulinum toxin type A (Botox) injections may be a treatment option (Santos-Velázquez, 2018).

Evidence suggests that botulinum toxin type A (BTX-A) injected subcutaneously has a clinically significant benefit in the treatment of trigeminal neuralgia with therapeutic results including: 50% reduction in pain and an average frequency of paroxysms per day, significant decrease in pain occurs after 2 weeks of treatment and after 3 months of therapy, Its effects last up to 1-6 months which is beneficial for the patient (Morra et al., 2016; Shackleton et al., 2016).

In recent years, the application of botulinum toxin has been extended in clinical care practice to different headaches and trigeminal neuralgia; It is a therapeutic option that is progressively incorporated into the management of these entities, for this several clinical trials have been carried out in order to establish an administration protocol, then we will review them (Santos-Lasaosa et al., 2020).

Table 1. Randomized, double-blind, placebo-controlled clinical trials of onabotulinumtoxinA in patients with trigeminal neuralgia

Author, Year of publication	Number of patients	OnabotA Dosage	Technique used	Evolution	Adverse effects
Wu et al.2012	42	75 U	VAS, visual analogue pain scale; ND: not available; onabotA: onabotulinumtoxinA; PGIC: Patient Global Impression of Change scale; QoL:10-point Quality of Life scale; SF-36: Short Form-36 Health Survey; U: Units	68% response rate vs. 15% placebo. Reduction in VAS score and crisis frequency. Improvement in PGIC	Facial asymmetry (5) Facial edema (3)
Shehata et al.2013	20	40-60 U	40-60 U (8-12 points) distributed in trigger zones. Additional units in masseter if V3 affected	Reduction in VAS score and seizure frequency Increase in QoL score	Facial asymmetry (4) Infiltration point hematoma (1) Infiltration point pain (2)
Zúñiga et al.2013	36	50-60 U	50 U distributed in affected branch and with 1 cm of separation. Additional 10 U in masseter if V3 affected	Reduction in VAS score and seizure frequency	Infiltration point hematoma (2) Facial asymmetry (2)
Zhang et al.2014	84	25/75 U	25 and 75 U in 20 points in painful, intradermal and submucosal area	Reduction in VAS score. Improvement in PGIC. No difference between groups (25/75 U)	Facial asymmetry (3) Facial edema (2)
Sirois et al.2011	17	ND	Trellis of the painful area. 2.5 U/cm2intradermal	11/15 > 50% VAS vs. 2/8placebo. Decrease in frequency and intensity of seizures. Improvement in the SF-36	Facial asymmetry (5) Drooping lip (1)
VAS, visual analogue pain scale; ND: not available; onabotA: onabotulinumtoxinA; PGIC: Patient Global Impression of Change scale; QoL:10-point Quality of Life scale; SF-36: Short Form-36 Health Survey; U: Units					

Source: *Santos-Lasaosa S,et al. 2020*

Most patients respond positively to botulinum toxin type A injections with good tolerability, however, some transient adverse effects such as facial asymmetry, ptosis, local oedema and haematoma have occasionally occurred; Operator-dependent effects and side effects were probably more related to the "learning curve." With practice, these problems would likely be eliminated (Xia et al., 2016).

To obtain conclusive results on the use of botulinum toxin in trigeminal neuralgia, more randomized clinical trials and follow-up studies with optimal sample sizes are needed, in order to determine aspects such as: exact time it takes to achieve pain reduction, duration of effect, dose to be used, indications for reinjection and adverse effects in the short and long term (Fragueiro Paz, 2018).

Trigeminal neuralgia is a disease characterized by intense pain that can last from a few seconds to several minutes, it is described as neuropathic pain at the orofacial level, producing a great limitation in the quality of life of people suffering from this condition; And it is for this reason that it is necessary an adequate knowledge of its clinical characteristics to differentiate it and above all avoid confusion with other pathologies since one could think of other causes of facial pain that are more frequent and avoid unnecessary and irreversible treatments such as dental extractions (Marín-Medina & Gámez-Cárdenas, 2019).

It is a chronic disease that has no definitive cure, has a high prevalence constituting one of the 89 facial neuralgias in people over 60 years. The annual incidence is 5.7 and 2.5 cases per 100,000 inhabitants in women and men, respectively, unfortunately there is no statistical data on the incidence of this pathology in Ecuador. The Treatment that is applied has the objective of reducing the symptoms and in this way improve the quality of life of the people who suffer from it (Grin et al., 2018; Marín-Medina, & Gámez-Cárdenas, 2019; Buckcanan Vargas et al., 2020).

NT is notorious for its complex and difficult treatment, with approximately 2% of patients failing their first trial with pharmacotherapy. It is estimated that up to 50% of patients have poor pain control with carbamazepine (the gold standard pharmacotherapeutic for TN) after 5-10 years of treatment; and approximately 27% discontinue treatment much earlier due to intolerable adverse effects (Llerena, 2019).

It is for this reason that there are different therapeutic options used to treat patients suffering from this disease, one of them being the administration of botulinum toxin at an extra and intraoral level, It is considered a viable treatment option since it works as a local neuromuscular blocker to inhibit the release of acetylcholine to the synaptic space, functioning as a neurotransmitter to produce local muscle relaxation, which promotes relaxation of the masticatory muscles, thus decreasing pain and yielding the proper function of the jaw and its application goes according to the location of pain (Naranjo, 2018).

Treatment with botulinum toxin for this pathology is used as adjuvant therapy mainly when oral medications do not give adequate control of the patient's pain, since over time it is expected to reduce the drugs as the patient reports that the pain has decreased or is controlled. In patients with uncontrolled pain of the trigeminal nerve, botulinum toxin is placed extraorally in the orofacial region, with high effectiveness, but studies on administration in the intraoral submucosa are lacking (Naranjo, 2018).

The administration of botulinum toxin has been shown to be a safe and effective therapeutic strategy in patients with idiopathic drug-resistant trigeminal neuralgia, but numerous questions remain to be answered that end up placing its role within the therapy of this disease and that is why giving an accurate diagnosis is crucial because the interpretation of neuroimaging and clinical management differ between the various forms of facial pain (Bendtsen et al., 2020; Castillo-Álvarez et al., 2017).

4. Conclusion

Trigeminal neuralgia is one of the most common diseases present in the hospital environment but is often misdiagnosed, botulinum toxin is an alternative treatment option in patients who do not respond to pharmacological treatment, avoiding the need for surgical interventions in refractory cases of trigeminal neuralgia, as BTX-A is a specific muscle relaxant with an effectiveness in reducing pain by

more than 50%, In addition, it produces few transient adverse effects, this being a safe therapeutic option that achieves lasting relief in patients suffering from this pathology, in order to provide them with a better quality of life.

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