Botulinum toxin in pain management of trigeminal neuralgia: literature review

Toxina botulínica no tratamento da dor na neuralgia trigeminal: revisão de literatura

João Gabriel de Azevedo José Romero[1], Roberto Brígido de Nazareth Pedras[2], Camila Megale Almeida-Leite[3]

DOI 10.5935/2595-0118.20200185

ABSTRACT

BACKGROUND AND OBJECTIVES: Botulinum neurotoxin type A has been an interesting therapeutic complement to the conventional treatment of trigeminal neuralgia, especially in patients without satisfactory response to pharmacotherapy and/or surgical procedures. A detailed and comprehensive literature review its important for the description of the available evidence, allowing for a critical view on the topic. Therefore, this study's objective was to describe the scientific evidence on the use of botulinum toxin type A in the trigeminal neuralgia treatment.
CONTENTS: Pubmed and Scielo databases were searched using the descriptors: "trigeminal neuralgia and botulinum toxin". Inclusion criteria were human studies (open-label, double-blind, randomized, and placebo-controlled trials) and reviews of the use of botulinum toxin type A in trigeminal neuralgia treatment, published in English, Spanish or Portuguese from January 2008 to March 2020. Twenty-one articles met the inclusion criteria. Overall, studies demonstrated that botulinum toxin type A significantly reduced pain intensity and paroxysmal episodes, as well as improved quality of life.
CONCLUSION: Use of botulinum toxin type A in treatment of refractory trigeminal neuralgia shows promising results, but further studies are needed to increase the knowledge and consolidation of this therapeutic alternative.

Keywords: Botulinum toxins, Facial pain, Trigeminal neuralgia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A neurotoxina botulínica do tipo A tem se mostrado interessante como opção terapêutica complementar ao tratamento convencional da neuralgia trigeminal, sobretudo em pacientes sem resposta satisfatória à farmacoterapia e/ou procedimentos cirúrgicos. Uma revisão da literatura detalhada e abrangente se faz importante para descrever as evidências disponíveis e permitir uma visão crítica sobre o tema. Sendo assim, este estudo teve como objetivo apresentar as evidências científicas disponíveis na literatura sobre o uso da neurotoxina botulínica do tipo A no tratamento da neuralgia trigeminal.
CONTEÚDO: Foi realizada uma busca nas bases de dados Pubmed e Scielo utilizando-se os seguintes descritores "trigeminal neuralgia and botulinum toxin". Os critérios de inclusão foram estudos em humanos (estudos abertos e ensaios clínicos duplamente encobertos, randomizados e controlados por placebo) e revisões sobre o uso da neurotoxina botulínica do tipo A no tratamento da neuralgia trigeminal nos idiomas inglês, espanhol ou português durante o período de janeiro de 2008 a março de 2020. Apenas 21 artigos preencheram os critérios de inclusão. De um modo geral, os trabalhos demonstraram efeitos significativos da neurotoxina botulínica do tipo A na diminuição da intensidade da dor e no número de episódios paroxísticos, assim como na melhoria da qualidade de vida.
CONCLUSÃO: O uso da neurotoxina botulínica do tipo A no tratamento da neuralgia trigeminal refratária apresenta resultados promissores, mas são necessários novos estudos para ampliação do conhecimento e consolidação dessa alternativa terapêutica.

Descritores: Dor facial, Neuralgia do trigêmeo, Toxinas botulínicas.

INTRODUCTION

Trigeminal neuralgia (TN) is described, according to the International Headache Society (HIS), as a unilateral disorder, which features electric shock, high intensity, short duration, with abrupt onset and termination pain, in one or more division of the trigeminal nerve[1]. The pain crisis can be triggered by innocuous stimuli (allodynia), like speaking or touching a specific area on the head or mouth cavity named trigger zone[2].
TN impacts 4,7 in each 100.000 people above 50 years old, being prevalent in females[3]. The diagnostic criteria of TN are based on the parameters established by the HIS and the International Association for the Study of Pain (IASP) associated with the patients history[1,4]. Using imaging exams, like nuclear magne-

João Gabriel de Azevedo José Romero – https://orcid.org/0000-0002-3891-8648;
Roberto Brígido de Nazareth Pedras – https://orcid.org/0000-0001-9781-2774;
Camila Megale Almeida-Leite – https://orcid.org/0000-0003-2694-8521.

1. Universidade Federal de Minas Gerais, Faculdade de Medicina, Programa de Pós-Graduação em Patologia, Instituto de Ciências Biológicas, Belo Horizonte, MG, Brasil.
2. Centro Universitário Newton Paiva, Ciências da Saúde/Odontologia, Belo Horizonte, MG, Brasil.
3. Universidade Federal de Minas Gerais, Departamento de Morfologia, Instituto de Ciências Biológicas, Belo Horizonte, MG, Brasil.

Submitted on March 30, 2020.
Accepted for publication on May 10, 2020.
Conflict of interests: none – Sponsoring sources: none.

Correspondence to:
Camila Megale Almeida-Leite
Avenida Antônio Carlos, 6627, Pampulha
31270-901 Belo Horizonte, MG, Brasil
E-mail: camila@icb.ufmg.br

tic resonance (NMR) of the encephalus, helps in the diagnosis of the vascular anatomical alterations, neoplasms and neurodegenerative diseases, which can be related to the development of TN[5]. From the etiopathogenic point of view, TN is a complex condition and the subjacent mechanisms are not completely clear. More recent studies show that the vascular microcompression is not essential to the development of TN, highlighting the relevance of other mechanisms in its development[6,7]. Several neurophysiologic phenomena, such as the activation of the peripheral receptor, transmission and projection of nociceptive information, afferent convergence in central neurons**,** demyelination, efactic transmission and interaction between several neurotransmitters and neuromodulators are an important role in the perception of pain[8].

The treatment for TN follows the guidelines of the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) which recommend pharmacologic treatment as the first choice. Carbamazepine (CBZ) and oxcarbazepine (OXC) anticonvulsants, which block the voltage--dependent sodium channels, are the most widely used drugs[9]. In cases of failure in pain control or when neurovascular conflict is evidenced by imaging studies, surgical procedures are the second line of treatment[9,10].

Botulinum neurotoxin (BoNT) is derived from the clostridium botulinum bacteria and is characterized by a group of homologous chain proteins with seven serotypes (A, B, C1, D, E, F and G). The active form consists of a light proteolytic chain of 50kDa attached to a heavy chain of 100kDa through a disulfide bond and non-covalent bonds. BoNT is known and used worldwide for aesthetic treatments and for the treatment of some disorders such as dystonia and muscle spasms[11,12].

Type A BoNT (BoNT/A) inhibits the release of acetylcholine (ACh) at the cholinergic nerve endings of the motor nerves by preventing ACh vesicles from binding to the membrane for release of content and subsequent binding to receptors on the postsynaptic membrane. This blockade leads to the desired aesthetic and therapeutic effect, as it weakens the muscle for a period of three to four months[13]. Besides this mechanism, it was suggested that BoNT/A could inhibit the liberation of local neuropeptides, such as the P substance, a peptide related to the calcitonin gene (CGRP) and glutamate. BoNT/A can also inhibit the neurogenic inflammation and the peripheral sensitization, although the mechanism of specific action is not yet completely clear. Due to these features, the use of BoNT/A is a potential treatment for pain[11].

Currently, its therapeutic use is exponentially expanding, including for the treatment of chronic pain conditions, mainly due to a better understanding of its mechanisms of action, as well as for efficacy and safety[14]. BoNT is safe and well tolerated when compared to conventional pharmacological therapies for chronic pain, mainly due to the adverse effects produced by the drugs[15].

Regarding the TN which is refractory to the conventional pharmacologic treatment, BoNT/A has been an interesting alternative. The results of clinical trials show effectiveness in most patients, with reduction or complete elimination of pain. Based on that, BoNT/A is considered a potential therapeutic option associated with the conventional pharmacologic treatment of TN, mainly in those patients that were not completely responsive to the initial therapy and/or presented contraindications for surgical procedures[14].

Despite the indications, the reliability of the studies is still questioned due to the diverse methodologies used in the clinical trials. Therefore, a comprehensive literature review is important for the elucidation of the available evidences, allowing for a critical view on the subject. Based on the above, this work had the objective of reviewing the literature and presenting available evidences for the use of BoNT/A in the treatment of pain in the TN.

CONTENTS

In order to critically analyze the scientific evidence regarding the use of BoNT/A for the treatment of TN, non-systematic searches were performed in the Pubmed and Scielo databases using the following descriptors: "trigeminal neuralgia" and "botulinum toxin". The inclusion criteria were: studies in humans (open-label study or double blind, randomized, placebo-controlled clinical trial) and literature reviews published in English, Spanish or Portuguese during the period of January 2008 to March 2020.

As shown in Figure 1, 105 articles were found, 21 of which fulfilled the inclusion criteria. From these, 14 articles are studies in humans and 7 are literature reviews. The 84 excluded articles consisted on case reports, letters to the editor, reviews of the BoNT use in chronic or neuropathic pain in general, technique descriptions, publications in other idioms or that were not available for access.

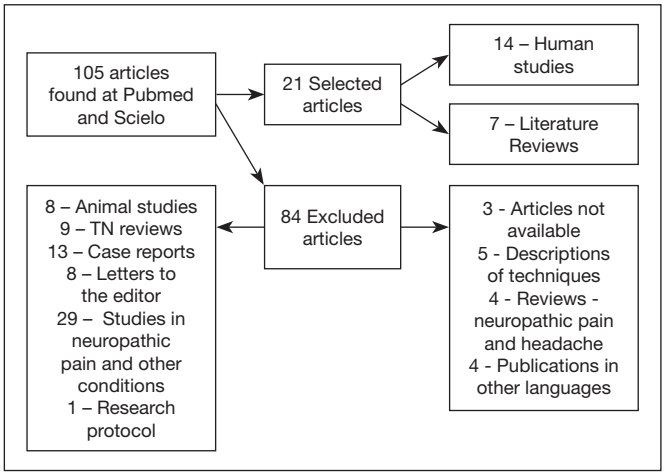

Figure 1. Flowchart of the selection process of studies

Clinical studies

From the clinical studies included in this review, 10 were open--label studies and four were double blind, randomized and placebo-controlled clinical trials, described in chronological order as follows.

One open label study evaluated the use of BoNT/A in the treatment of refractory TN in 12 patients. The protocol of application followed the subcutaneous injection of 20-50 U of BoNT/A in the trigger zones and, in cases where the mandibular branch of

the trigeminal nerve was affected, the BoTN/A was also applied to the masseter muscle. All patients were evaluated weekly for 8 weeks and the frequency of paroxysmal episodes and pain intensity using the visual analog scale (VAS) were analyzed. The results showed a reduction in pain intensity and paroxysmal episodes at the end of the assessment period[16].

Another study with a sample of 15 patients with refractory TN used the injection protocol of 50-100U of BoNT/A in each trigger zone. All patients were evaluated before the study, 1 week and 1 month after injections, when information on the intensity of pain through VAS, frequency of paroxysmal episodes and global response was collected. The results found showed that all patients presented significant improvement in the frequency of attacks and pain intensity up to 6 months after BoNT/A therapy[17].

A double-blind, randomized, placebo-controlled clinical trial assessed 42 patients with refractory TN. The patients were distributed in two groups: 22 patients received injection of 75U of BoNT/A in trigger zones and 20 received intradermal and/or submucous saline solution. The period of study was 13 weeks, being the first week designated for data collection and the other 12 weeks for evaluation after the administration of BoNT/A. The collected data was related to the intensity of pain measured by VAS, frequency of paroxysmal episodes per day and overall patient response.

The group that received BoNT/A presented a significant reduction on the daily episodes of pain since week one and intensity of pain from the second week forward, which was maintained throughout the study[18].

In a double-blind, randomized and placebo-controlled study, with 36 patients suffering from refractory TN, 50U of BoNT/A or 1mL of saline solution were applied subcutaneously to several sites along the path of the affected branch. In cases where the mandibular branch was affected, the masseter muscle received an injection of 10U of BoNT/A or placebo solution. All patients were evaluated 1, 2 and 3 months after the procedure, with a registry in intensity of pain and paroxysmal episodes frequency. The patients treated with BoNT/A presented significant results, with the reduction of the intensity of pain and frequency of pain episodes[19].

Twenty patients of a double-blind, randomized and placebo-controlled clinical trial received a subcutaneous injection of BoNT/A and saline solution, with total dosages of BoNT/A of 40U to 60U. The trigger zones were chosen as application sites and, in cases where the mandibular branch was affected, the masseter muscle was also included. All patients were assessed every two weeks, for 12 weeks, for intensity of pain through VAS and frequency of paroxysmal episodes. The results showed significant reduction in pain intensity and frequency in the group treated with BoNT/A[20].

An open-label study assessed 88 patients diagnosed with TN for 14 months and the BoNT/A was injected subcutaneously in the trigger zones present in the face and/or oral cavity. The total dosage applied to the patients was variable, which allowed for a division in three groups: ≤50U (43 patients), 50-100U (32 patients) and ≥100U (13 patients). Data related to pain intensity assessed by the VAS and frequency of paroxysmal episodes was registered. The analysis of the results found that after two months all patients presented reduction of pain episodes.

It was also found that BoNT/A presented gradual reduction of its effect after 3 months of application and only 25% of patients presented controlled TN at the 14th month[21].

Eighty-four patients participated in a double-blind, randomized, placebo-controlled study that used two different dosages of BoNT/A in the treatment of TN. The selected individuals were randomly divided into three groups: placebo (saline solution) and 25U or 75U of BoNT/A. The injections were intradermally and/or submucosally administered in the trigger zones. The patients were evaluated in relation to the intensity of pain through VAS and frequency of paroxysmal episodes. The results were statistically significant in both groups treated with BoNT/A in relation to the control group, without statistically significant differences between the BoNT/A groups[22].

An open-label study evaluated 87 patients that received intradermal BoNT/A in pain areas and trigger zones. The used dosage was not specified. The patients were evaluated 1 week before the application and weekly for 8 weeks after treatment in order to register pain intensity, anxiety, depression, quality of life and sleep disorders.

The results were statistically significant for the reduction of pain intensity, with an improvement in sleep, anxiety, depression and quality of life after 8 weeks of monitoring[23].

The single administration in comparison to repeated applications of BoNT/A was evaluated in an open-label study with 100 patients diagnosed with TN, randomly divided in two groups. The first group received a single 70-100U dosage of BoNT/A and the second group received two applications of 50-70U (totaling 100-140U). The administration was intradermal and/or submucous in the points of pain. The evaluation included intensity of pain and frequency of paroxysmal episodes and was made weekly during the first month and monthly up until the sixth month after application. The duration of the BoNT/A effect was longer in the single dosage group when compared to the other group, but no significant differences were identified in the comparison between the groups in the reduction of intensity of pain by the end of treatment[24].

Another open-label study assessed 27 patients with TN refractory to treatment. All patients received a total of 100U of BoNT/A, divided in 50U for the jaw root (pterygopalatine ganglion region) and 50U for the mandibular root (trigeminal ganglion region). The pain intensity frequency parameters were assessed by the VAS in the 24 hours prior to the applications, 1 week, 2 months and 6 months after the interventions. The results were statistically significant in all periods of registry and, by the end of the treatment, 24 patients presented a ≥50% reduction in pain intensity[25].

Twenty two individuals received intradermal BoNT/A, in trigger zones or pain areas, with a 15-50U dosage in an open-label study. These patients were assessed by VAS, 10, 20, 30, 60 and 90 days after treatment. The results found showed that the reduction in pain intensity was statistically significant in the 10, 30 and 60 days[26].

In a more recent open-label study, 43 patients with refractory TN were evaluated. The patients were divided into two groups:

the first with 14 patients aged ≥80 and the second with 29 patients aged <60. The administration was intradermal and/or submucous in the trigger zones and pain sites, the oldest group of patients received 45-150U and the other one 30-200U of BoNT/A. The patients were evaluated by VAS before and one month after treatment. The results showed statistically significant reduction in the intensity of pain in the two groups in comparison to the period prior treatment, with no statistical difference between the groups[27].

A sample of 104 patients, divided in groups according to age: <50 years (25 patients) and ≥50 years (79 patients), was evaluated in an open-label study. BoNT/A was administered intradermally and/or subcutaneously in the pain area and/or trigger zone with a dosage of 2.5U (subcutaneous) or 5U (intradermal) per site of application. The patients were evaluated weekly for 2 months and monthly for 12 months by the VAS. The results showed that 87 patients presented significant pain improvement[28].

Another open-label study was performed with 152 patients with intradermal and/or submucous administration of BoNT/A in trigger zones. Patients were divided into groups according to the received dosage: <40U (low), 40-70U (medium) and >70U (high). The assessment of pain was done by VAS during the period of 6 months to 28 months after treatment. The results showed a rate of symptom improvement of 89,4%, with maintenance of the BoNT/A effects during the first 6 months of monitoring[29].

The Tables 1 and 2 present the main features of studies described regarding the use of BoNT/A in the TN.

Table 1. Comparison between the main features of the open label studies on the use of BoNT/A for the treatment of trigeminal neuralgia

Authors	Number of patients	Site and route of administration	BoNT/A dose (Total)	Evaluation period	Results	Adverse effects
Zuñiga et al.[16]	12	Trigger zones and masseter/subcutaneous route	20 – 50U	Weekly during 8 weeks after application	Reduction of paroxysmal episodes and pain intensity; 10 patients presented immediate relief or in a couple of minutes after the injection of BoNT/A	Facial asymmetry
Bohluli et al.[17]	15	Trigger zones/ does not report administration route	50-100U in each trigger zone	Base period (1 week) and 1 and 6 months after application	All patients presented reduction of paroxysmal episodes and intensity of pain; 3 patients returned responding to the pharmacological therapy with anticonvulsants	Transitory paresthesia of the facial nerve
Li et al. [21]	88 divided in three groups 43 (BoNT/A ≤ 50U) 32 (BoNT/A 50-100U) 13 (BoNT/A ≥ 100U)	15-20 trigger zones/subcutaneous and/or submucous route (4 - 10 zones)	≤50U 50-100U ≥100U	Weekly for 2 months and monthly until 14 months after application	All patients presented effective improvement after 2 months of treatment; reduction of the effect of BoNT/A after 3 months; absence of significant differences between groups treated with different dosages	Edema and muscle relaxation
Xia et al.[23]	87	15-20 trigger zones or pain sites / intradermal route	Does not mention used dosage	Base period (1 week) and weekly during 8 weeks after application	The results were significant for the reduction of pain intensity by the end of 8 weeks; improvement in anxiety (90.32%), depression (96.77%) and sleep disorders was also registered	Edema and muscle relaxation
Zhang et al.[24]	100 divided in two groups 50 (single dose) 50 (two doses)	15-20 points of pain / intradermal and/or submucous route	70 – 100 U (single dose) 100 – 140 U (two doses)	Weekly for 1 month and monthly until 6 months after application	The duration of the BoNT/A effect was greater in the single dosage group; both groups presented significant results for the reduction of pain intensity and no differences were identified in the comparison between groups	Not specified
Borü et al.[25]	27	Maxillary and mandibular root	100 U	Base period (1 day) and 1 week, 1 and 6 months after application	Significant results for the reduction of pain intensity, frequency of paroxysmal attacks and improvement perception; by the end of treatment, 24 patients presented a reduction of ≥50% in pain intensity	Muscle weakness
Caldera et al.[26]	22	Trigger zones or pain sites/intradermal route	15 – 50 U	10, 20, 30, 60 e 90 days after the application	The patients who received the BoNT/A presented significant reduction in pain intensity; no significant differences were found in the comparisons of pain intensity reduction according to different dosages and sites of application.	Not reported

Continue...

Table 1. Comparison between the main features of the open label studies on the use of BoNT/A for the treatment of trigeminal neuralgia – continuation

Authors	Number of patients	Site and route of administration	BoNT/A dose (Total)	Evaluation period	Results	Adverse effects
Liu et al.[27]	43 14 (≥80 years) 29 (<60 years)	Trigger zones and pain sites / intradermal and/or submucous route	45 – 150 U (≥80 years) 30 – 200 U (<60 years)	1 month after application	The results of the two groups were significant for the reduction of pain intensity; the comparison of results between the two groups was not statistically significant.	Facial palsy and eyelid ptosis
Wu et al. [28]	104 25 (<50 years) 79 (≥50 years)	Trigger zones and/or pain sites/intradermal and/or submucous route	5U for each point (intradermal route) 2,5 U for each point (submucous route)	Weekly for 2 months and monthly for 12 months	The results show that 87 patients presented significant improvement in pain; the group assessment showed good pain control in 83.3% (≥50anos) and 57.7% (<50 years).	Facial asymmetry
Zhang et al.[29]	152	15-25 Trigger zones and pain sites/intradermal and/or submucous route	1,25 – 5 U for each trigger zone <40 U 40-70 U >70 U	Minimum monitoring of 6 months and maximum of 28 months	Results show a general efficacy rate of 89.4%, maintaining the effects of BoNT/A during the first 6 months of monitoring.	Facial asymmetry

BoNT/A = type A botulinum neurotoxin; U = units.

Table 2. Comparison between the main features of the double-blind, randomized and placebo-controlled clinical trials on the use of BoNT/A for the treatment of trigeminal neuralgia

Authors	Number of patients	Site and route of administration	BoNT/A dosage (Total)	Evaluation period	Results	Adverse effects
Wu et al. [18]	42 divided in two groups 22 (BoNT/A) 20 (Placebo)	15 trigger zones/ intradermal and/or submucous route	75 U 5 U in each trigger zone	Base period (1 week) and weekly during 12 weeks after application	Reduction of the paroxysmal episodes and pain intensity; 15 patients presented reduction of >50% in the VAS scores; 17 patients reported improvement after therapy with BoNT/A	Edema and facial asymmetry
Zuñiga et al.[19]	36 divided in two groups 20 (BoNT/A) 16 (Placebo)	Points in the area innervated by the affected branch and masseter/submucous route	50 U	1, 2 and 3 months after application	Reduction of paroxysmal episodes and pain intensity in the group treated with BoNT/A	Hematoma and facial asymmetry
Shehata et al.[20]	20 divided in two groups 10 (BoNT/A) 10 (Placebo)	Trigger zones and masseter/ submucous route	40 – 60 U 5U in each trigger zone	Each two weeks during the period of 12 weeks after application	Reduction of paroxysmal episodes, pain intensity and use of drugs; improvement of quality of life	Hematoma, facial asymmetry, and pain in the application site
Zhang et al.[22]	84 divided in three groups 25 (BoNT/A –25U) 28 (BoNT/A–75U) 27 (Placebo)	20 trigger zones/ intradermal and/or submucous route	25 U e 75 U	Base period (1 week) and weekly during 8 weeks after application	Reduction of pain intensity in groups treated with BoNT/A; absence of significant differences between groups treated with different doses	Edema and facial asymmetry

BoNT/A = type A botulinum neurotoxin; U = units.

Of the seven review articles included below in chronological order, three were systematic reviews and one performed meta-analysis. In one of the literature reviews, 5 studies that used BoNT/A in the treatment of TN were evaluated. Therapeutic success was observed; however, careful evaluation is necessary in establishing this therapy[30].

A systematic review analyzed the efficacy of BoNT/A in the treatment of TN, as well as its safety and tolerability. The authors selected randomized clinical trials and semi-trials (case-control study, open-label study and case series) which reported reduction of, at least, 50% in the frequency and intensity of pain. The results showed that more than 60% of patients were benefited from the therapy and that up to 80% of patients presented reduction of pain intensity in 8-12 weeks[31]. Available evidence on the use of BoNT/A for treating TN and the most indicated injection technique were described in a literature review. The results of the groups treated with BoNT/A were statistically significant when compared to the placebo group and all studies considered BoNT/A as an effective alternative. The routes of administration chosen in the studies were sub-

cutaneous or intradermal, and the intradermal route would be more interesting because it allows direct contact with non-myelinated sensitive nerve endings[32].

In another review, the conclusion was that there are not sufficient evidences for the recommendation of BoNT/A as a treatment alternative for TN, but that it can be considered a promising therapy. New randomized, placebo-controlled studies are necessary[33].

In a systematic meta-analysis review, 6 studies on the use of BoNT/A for treating TN and postherpetic neuralgia were analyzed. The results showed safety and efficacy of BoNT/A in the diminishing of pain. According to the authors, there is moderate evidence that support the use of BoNT/A, but new studies are necessary for more final reccomendations[34].

A systematic meta-analysis review evaluated 4 randomized, placebo-controlled studies and observed that the treated group presented patients with >50% reduction in pain intensity, decrease of paroxysmal episodes and pain scores at the end of treatment compared to the placebo group[35].

Nineteen studies were selected in a literature review on the available evidence on BoNT/A for the treatment of TN. According to the authors, BoNT/A may be a safe and effective alternative for refractory patients, but new studies need to be conducted[36].

The revised studies presented different methodologies, inclusion and exclusion criteria, routes of administration, application sites, BoNT/A dosage, therapeutic effect evaluation criteria and duration. Nevertheless, all studies evaluated the intensity of pain through VAS and frequency of paroxysmal episodes after treatment with BoNT/A.

In general, despite the differences and methodological flaws, the studies observed the therapeutic efficacy of BoNT/A characterized by the significant reduction of the paroxysmal episodes and the intensity of pain in most patients with TN. Nonetheless, there are some limitations in the studies and gaps in the literature that are relevant and deserve to be mentioned.

Some studies detailed the drugs used in the conventional treatment associated with BoNT/A or after application,

Table 3. Comparison between the main features of the literature reviews on the use of BoNT/A for the treatment of trigeminal neuralgia

Authors	Objective	Database	Articles	Conclusions
Verma[30]	Evaluate available evidences on the use of BoNT/A for the treatment of TN	Does not mention the used databases	4 open label studies and 1 placebo-controlled, randomized, double-blind clinical trial	Data available in the literature is insufficient to indicate the use of BoNT/A as an alternative treatment, and new studies with larger samples are necessary.
Hu et al.[31]	Evaluate the efficacy, safety and tolerability of BoNT/A for the treatment of TN	PubMed, EMBASE (OVID), Cochrane and Web of Science	5 open label studies and 1 placebo-controlled, randomized, double-blind clinical trial	Results available in the literature show that BoNT/A is a promising alternative for the treatment of TN, but new studies are necessary in order to evaluate the optimal dosage, time of therapeutic efficacy and registry of adverse effects
Guardiani et al.[32]	Evaluate the available evidence on BoNT/A for the treatment of TN and description of the most indicated administration technique	Google Scholar and Medline	5 open label studies and 2 placebo-controlled, randomized, double-blind clinical trials	BoNT represents a new alternative for the treatment of TN. The most appropriate route of administration is intradermal.
Kowacs et al. [33]	Evaluate available evidences on the use of BoNT/A for the treatment of TN	Does not mention the used databases	7 clinical trials, 2 case series, 5 open label studies, 4 placebo-controlled, randomized, double-blind clinical trials and 1 citation	There are no significant evidences for the recommendation of BoNT/A as a successful alternative for the treatment of TN, but it was considered a promising therapy and new randomized and placebo-controlled studies are necessary.
Shackleton et al.[34]	Evaluate available evidences on the use of BoNT/A for the treatment of TN and post-herpetic neuralgia	Medline, Web of Science e Cochrane	6 double-blind, randomized, placebo-controlled clinical trials (4 TN and 2 post-herpetic neuralgia)	There are moderate evidences to support the use of BoNT/A as a potential therapeutic alternative, but new randomized, placebo-controlled studies are necessary.
Morra et al.[35]	Evaluate the efficacy and safety of the use of BoNT/A for the treatment of TN	10 data bases (Pubmed, Web of Science, Scopus, Google Scholar, WHO Global Health Library and others)	4 double-blind, randomized, placebo-controlled clinical trials	BoNT/A is an alternative for the treatment of TN, but in order to expand evidences, new randomized and placebo-controlled studies are necessary.
Castillo-Alvarez, Bárcena e Marzo-Sola[36]	Evaluate available evidences on the use of BoNT/A for the treatment of TN	Does not mention the used databases	8 clinical cases, 7 open label studies and 4 double-blind, randomized, placebo-controlled clinical trials	BoNT/A may be a safe and effective alternative, but to detail the therapeutic protocol new studies are necessary.

BoNT/A = type A botulinum neurotoxin; TN = trigeminal neuralgia.

while others didn't present any description in that regard. However, all patients selected for the studies were refractory to the conventional treatment and/or surgery because they had crisis that were not controlled using drugs and/or surgical treatment.

Regarding the administration route, some authors used the subcutaneous route[16,19,20], while others opted for the intradermal and/or submucous[18,22,24,27-29]. Although there are positive results observed in studies that used the subcutaneous route, one of the reviews suggest that the most suitable administration route would be intradermal because it allows for a direct contact to the non-myelinated sensitive nerve endings[32].

Another difference between the works was the application site of BoNT/A. Some recommend the direct injection only in trigger zones[16-18,20-22,29] or in areas of pain[24], according to exams and patients' reports. However, other studies adopted an application protocol for BoNT/A in both trigger zones as well as areas of pain[23,26-28]. In addition to that, some authors performed additional injections in the masseter muscle, in cases where the trigeminal mandibular branch was affected[19,20].

The dosage of BoNT/A used in the treatment varied considerably. Some authors opted for lower dosages of 20-75U[16,18-20,22,26,29], and others opted for higher dosages of up to 200U[21,24,25,27]. Despite of this great variation, most patients presented similar benefits, independently of the used dosage[21,22]. Similarly, more than one application also did not provide an advantage over the single application[24]. It is worth noting, thus, that smaller dosages, as well as the smaller number of applications, should be prioritized in order to minimize possible adverse effects and the possibility of developing tolerability to BoNT/A.

It is also possible to observe differences in relation to the monitoring period of patients after treatment. Most studies performed monitoring for short periods of 2 - 3 months[16,18-20,22,23,26] to 6 months[17,24,25], and only a few for periods greater than or equal to 1 year[21,28,29]. The monitoring for short periods does not allow the assessment of the long term effect or the necessity of a new application for the management of the desired therapeutic effects.

Considering the different methodologies and existent gaps, the necessity for new studies on the use of BoNT/A for the treatment of TN is evident. One of the great advantages for the designing and execution of further studies is based on the fact that the adverse effects reported, related directly to the mechanism of action of BoNT/A and to the trauma resulting from the injection, are transitory, have spontaneous resolution and don't compromise the patients' health[16,18-23,25,27].

Therefore, the absence of systemic adverse effects is an important aspect for enabling the continuation of the studies with BoNT/A on the relief of pain in the TN, with important potential benefits mainly for those patients that make use of several drugs or present associated comorbidities. Studies with more methodological rigor, as the randomized and placebo-controlled clinical trials, are still necessary for the determination of the adequate dosage and most indicated administration route of BoNT/A, as well as the establishment of a treatment protocol based in more robust evidence. A larger time of monitoring after treatment is also fundamental, allowing for a long-term evaluation of BoNT/A and constituting a subsequent protocol of applications for the management of the desired therapeutic effects.

CONCLUSION

The studies available in the literature have shown that BoNT/A is interesting and promising as an association therapy with conventional pharmacological treatment of patients with refractory NT, since most studies have shown satisfactory results regarding the control of pain intensity, decrease paroxysmal episodes and improved quality of life. Nevertheless, the studies presented important methodological differences and there are gaps in the literature that need clarification before the BoNT/A therapy is established as a completely safe and effective therapeutic alternative.

REFERENCES

1. Headache Classification Committee of International Headache Society (IHS)The International Classification of Headache Disorders, 3rd ed. Cephalalgia. 2018;38(1):1-211.
2. Ibrahim S. Trigeminal neuralgia: diagnostic criteria, clinical aspects and treatment outcomes. A retrospective study. Gerodontology. 2012;31(2):89-94.
3. Katusic S, Williams BD, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945-1984. Neuroepidemiology. 1991;10(5-6):276-81.
4. IASP. Part III: Pain Terms, a current list with definitions and notes on usage. 2011.
5. Shakur SF, Bhansali A, Mian AY, Rosseau GL.Neurosurgical treatment of trigeminal neuralgia. Dis Mon. 2011;57(10):570-82.
6. Lee A, McCartney S, Burbidge C, Raslan AM, Burchiel KJ. Trigeminal neuralgia occurs and recurs in the absence of neurovascular compression. J Neurosurg. 2014;120(5):1048-54.
7. Burchiel KJ. Trigeminal neuralgia: new evidence for origins and surgical treatment. Neurosurgery. 2016;63(1):52-5.
8. Montano N, Conforti G, Di Bonaventura R, Meglio M, Fernandez E, Papacci F. Advances in diagnosis and treatment of trigeminal neuralgia. Ther Clin Risk Manag. 2015;11:289-99.
9. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepina or oxcarbazepine in a tertiary centre for neuropathic pain. J Headache Pain. 2014;15:34.
10. Zakrzewska JM, McMillan R. Trigeminal neuralgia: the diagnosis and management of this excruciating and poorly understood facial pain. Postgrad Med J. 2011;87(1028):410-6.
11. Oh HM, Chung ME. Botulinum toxin for neuropathic pain: a review of the literature.toxins. 2015;7(8):3127-54.
12. Guo BL, Zheng CX, Sui BD, Li YQ, Wang YY, Yang YL.A closer look to botulinum neurotoxin type A-induced analgesia. Toxicon. 2013;71:134-9.
13. Nayyar P, Kumar P, Nayyar PV, Singh A.Botox: broadening the horizon of dentistry. Botox: broadening the horizon of dentistry. 2014;8(12):25-9.
14. Persaud R, Garas G, Silva S, Stamatoglou C, Chatrath P, Patel K.Anevidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions. JRSM Short Rep. 2013;4(2):10.
15. Colhado OC, Boeing M, Ortega LB. Botulinumtoxin in paintreatment. Rev Bras Anestesiol. 2009;59(3):366-81.
16. Zúñiga C, Díaz S, Piedemonte F, Micheli F. Beneficial effects of botulinum toxin type A in trigeminal neuralgia. ArqNeuropsiquiatr. 2008;66(3):500-3.
17. Bohluli B, Motamedi MH, Bagheri SC, Bayat M, Lassemi E, Navi F, et al. Use of botulinum toxin A for drug-refractory trigeminal neuralgia: preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(1):47-50.
18. Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Chang N, et al.Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double blind, placebo-controlled trial. Cephalalgia. 2012;32(6):443-50.
19. Zúñiga C, Piedemonte F, Díaz S, Micheli F. Acute treatment of trigeminal neuralgia with onabotulinum toxin A. Clin Neuropharmacol. 2013;36(5):146-50.
20. Shehata HS, Tamawy MS, Shalaby NM, Ramzy G. Botulinum toxin-type A: could it be an effective treatment option in intractable trigeminal neuralgia? J Headache Pain. 2013;14:92.

21. Li S, Lian YJ, Chen Y, Zhang HF, Ma YQ, He CH, et al. Therapeutic effect of botulinum toxin-A in 88 patients with trigeminal neuralgia with 14-month follow-up. J Headache Pain. 2014;15:43.
22. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014;15:65.
23. Xia JH, He CH, Zhang HF, Lian YJ, Chen Y, Wu CJ, et al. Botulinum toxin A in treatment of trigeminal neuralgia. Int J Neurosci. 2016;126(4):348-53.
24. Zhang H, Lian Y, Xie N, Chen C, Zheng Y. Single-dose botulinum toxin type a compared with repeated-dose for treatment of trigeminal neuralgia: a pilot study. J Headache Pain. 2017;18(1):81.
25. TürkBörü Ü, Duman A, Bölük C, Coskun Duman S, Taşdemir M. Botulinum toxin in the treatment of trigeminal neuralgia 6-month follow-up. Medicine. 2017;96(39):e8133.
26. Caldera MC, Senanayake SJ, Perera SP, Perera NN, Gamage R, Gooneratne IK. Efficacy of botulinum toxin type A in trigeminal neuralgia in a south Asian cohort. J Neurosci Rural Pract. 2018;9(1):100-5.
27. Liu J, Xu YY, Zhang QL, Luo WF. Efficacy and safety of botulinum toxin type A in treating patients of advanced age with idiopathic trigeminal neuralgia. Pain Res Manag. 2018;2018:7365148.
28. Wu S, Lian Y, Zhang H, Chen Y, Wu C, Li S, et al. Botulinum toxin A for a refractory trigeminal neuralgia in older patients: a better therapeutic effect. J Pain Res. 2019;12:2177-86.
29. Zhang H, Lian Y, Xie N, Cheng X, Chen C, Xu H, et al. Factors affecting the therapeutic effect of botulinum toxin A on trigeminal neuralgia: A follow-up retrospective study of 152 patients. Exp Ther Med. 2019;18(5):3375-82.
30. Verma G. Role of botulinum toxin type-A (BTX-A) in the management of trigeminal neuralgia. Pain Res Treat. 2013;2013:831094.
31. Hu Y, Guan X, Fan L, Li M, Liao Y, Nie Z, et al. Therapeutic efficacy and safety of botulinum toxin type A in trigeminal neuralgia: a systematic review. J Headache Pain. 2013;14:72.
32. Guardiani E, Sadoughi B, Blitzer A, Sirois D. A new treatment paradigm for trigeminal neuralgia using botulinum toxin type A. Laryngoscope. 2014;124(2):413-7.
33. Kowacs PA, Utiumi MA, Nascimento FA, Piovesan EJ, Teive HA. On a botulinum toxin A for trigeminal neuralgia: a review of the available data. ArqNeuropsiquiatr. 2015;73(10):877-84.
34. Shackleton T, Ram S, Black M, Ryder J, Clark GT, Enciso R. The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(1):61-71.
35. Morra ME, Elgebaly A, Elmaraezy A, Khalil AM, Altibi AM, Vu TL, et al. Therapeutic efficacy and safety of botulinum toxin A therapy in trigeminal neuralgia: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2016;17(1):63.
36. Castillo-Alvarez F, Bárcena IG, Marzo-Sola ME. Botulinum toxin in trigeminal neuralgia. Med Cli. 2017;148(1):28-32.