

Botulinum Toxin Type A in the treatment of myofascial pain related to masticatory muscles

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ABSTRACT

Objective: To systematize the scientific evidence on the efficacy of botulinum toxin type A in the treatment of myofascial pain related to masticatory muscles. **Method:** A bibliographical search was made in the PubMed Central Journal and Allergan Product Literature databases - botulinum toxin (APL) encompassing the past 12 years, with the descriptors: "myofascial pain," "botulinum toxin," "treatment," "masticatory muscles". The methodological quality of the studies was evaluated through the Jadad scale. Four randomized, double-blind, clinical trial studies were selected. **Results:** It was found that the research on the use of botulinum toxin type A for myofascial pain contributed to improving the treatments that existed until that time for this clinical condition. **Conclusion:** The need for more studies and forms of evaluating precisely and quantitatively is essential in order to find a definitive answer on the efficacy and safety of this treatment.

Keywords: Myofascial Pain Syndromes, Temporomandibular Joint Disorders, Masticatory Muscles, Botulinum Toxins, Type A

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INTRODUCTION

By definition, orofacial pain is any pain associated with soft or mineralized tissues (skin, blood vessels, bones, teeth, glands, or muscles) in the oral cavity and of the face. Usually, this pain can be referred in the region of the head and/or neck or even be associated with cervicalgias, cephalaea, and rheumatic diseases such as fibromyalgia and rheumatoid arthritis.¹

The main sources of orofacial pain are represented by odontogenic problems, neurogenic pathologies, musculoskeletal pains, psychogenic pains, cancer, infections, autoimmune phenomena, and tissue trauma.¹

According to the American Academy of Orofacial Pain, the temporomandibular joint dysfunction (TMJD) is defined as a set of disorders that involve the masticatory muscles, the temporomandibular joint (TMJ), and associated structures.² Its characteristic symptoms are: facial pain, pain in the TMJ and/or masticatory muscles, headaches,^{3,2} and earaches.² Other symptoms reported by patients are otologic manifestations such as tinnitus, auricular plenitude, and vertigo.² The signs can include sensitivity of the muscles and of the TMJ to palpation, limitation and/or poor coordination of mandibular movements and joint noises.¹ These symptoms appear in more than 75% of the adult population afflicted by orofacial pain.³

Myofascial pain related to TMJ is normally treated in its initial phase, through guidance, rest, use of an interocclusal device, physiotherapy, and other conservative measures such as behavioral intervention, medications, postural training, and exercises. Despite the success of these treatments, some patients do not respond to them, which opens the possibility of medical treatment with low doses of tricyclic medications that can be considered.²

For various reasons, such as the more elevated cost of the application when compared to other treatments and the lack of information on the part of health professionals on the subject, some patients resist this treatment and applications of botulinum toxin type A (BTX-A), which can become a useful and efficient alternative.⁴ In order to present an alternative to this problem, the botulinum toxin type A is being studied as a therapeutic method for patients who suffer from orofacial pain.

OBJECTIVE

This study seeks to systematize the scientific evidence on the use of botulinum toxin type A in the treatment of myofascial pain related to masticatory muscles.

METHOD

For the selection of publications, a systematic review technique was adopted in October of 2013 to identify randomized and controlled clinical trials on the use of BTX-A for myofascial pain related to masticatory muscles. A bibliographical search was made in the PubMed Central Journal and Allergan Product Literature databases, encompassing the last 12 years, with the keywords: "myofascial pain", "botulinum toxin", "treatment", "masticatory muscles". Two researchers made the search independently and then compared their results.

The articles were first selected by their abstracts and, as the inclusion criteria, the randomized clinical trial type studies that had been published in Portuguese and English were chosen for this study. Studies that scored less than three on the Jadad quality scale were excluded.⁵

RESULTS

The bibliographical search resulted in 39 articles. After excluding articles that did not discuss clinical work on patients and those that did not focus on the myofascial pain related to the masticatory muscles as the main pathology, there were ten articles left. These articles were evaluated in their entirety, but only four articles scored 3 or higher on the Jadad scale (Chart 1).

In the end, four randomized, double-blind studies were included in this systematic review. Details of the four studies are shown in Chart 2.

DISCUSSION

In 2004, the International Classification of Headache Disorders (ICHD), from the International Headache Society (IHS), included a

specific type of cephalaea secondary to TMJD in its 11th category (IHS 11.7 - cephalaea or facial pain attributed to TMJ dysfunction).¹⁶

The term temporomandibular dysfunction is used to unify a group of diseases that afflict the masticatory muscles, the temporomandibular joints, and adjacent structures. This dysfunction is highly debilitating and alters the performance of some essential tasks such as chewing foods or speaking appropriately. Its incidence in the population has been increasing considerably, especially among middle-aged women, with 80% of the patients being female.¹⁷

Recent studies concluded that the TMJD has multifactorial origin, with the most frequent being trauma, psychosocial factors, and physiopathological factors.¹ Some factors of the occlusal relationship are cited as a predisposal to TMJD, however, studies have shown that the correction of these factors in symptomatic individuals has little efficacy in controlling TMJD.^{18,19} This conclusion does not diminish the importance of occlusion for the odontological practice. According to Carrara et al.¹ the oral surgeon must dedicate special attention to occlusion, when giving a physical examination or when performing any clinical procedure in patients, for the occlusal pathologies bring relevant consequences to the masticatory system in the esthetic and functional aspects.

As their main symptom, TMJD patients present myofascial pain provoked by spasms in the masticatory muscles, associated with altered mandibular function and that can be triggered by distension, contraction, or muscle fatigue.¹⁷ These are generally caused by muscular hyperactivity, corresponding to 80% of the etiology of TMJD. The main cause of muscular hyperactivity is the practice of parafunctional habits (bruxism and the habit of biting nails, among others), being aggravated and influenced by emotional stress.¹⁷

The diagnosis is established with anamnesis and the clinical exam itself. The most common way to identify the location of the myofascial pain is muscular palpation.²⁰ This pain is transmitted by afferent nerve fibers to the central nervous system that processes the amount, intensity, duration, and location of the noxious stimulus. Excess use of a musculature through repetitive movements causes traumas that generate a localized muscle contraction and the

Chart 1. Quality evaluation of the selected clinical studies, according to the Jadad scale

	Was the study defined as random?	Was the randomization method appropriate?	Was the study double-blind?	Was the masking method appropriate?	Was there a description of losses and exclusion?	Score	Formulation
Nixdorf et al. ⁶	Yes	Yes	Yes	Yes	Yes	5	Onabotulinumtoxin A
Freund & Schwartz ⁷	No	No	No	No	No	-2	Onabotulinumtoxin A
De Andrés et al. ⁸	No	No	No	No	Yes	-1	Onabotulinumtoxin A
Von Lindern et al. ⁹	Yes	No	Yes	Yes	No	3	Onabotulinumtoxin A
Lee KM et al. ¹⁰	No	No	No	No	No	-2	Onabotulinumtoxin A
Guarda-Nardini L et al. ¹¹	Yes	Yes	Yes	Yes	No	4	Onabotulinumtoxin A
Ernberg M et al. ¹²	Yes	Yes	Yes	Yes	Yes	5	Onabotulinumtoxin A
Guarda-Nardini et al. ¹³	Yes	Yes	No	No	Yes	2	Onabotulinumtoxin A
Sidebottom AJ ¹⁴	No	No	No	No	No	-2	Onabotulinumtoxin A
Venancio et al. ¹⁵	Yes	Yes	No	No	Yes	2	Onabotulinumtoxin A

Chart 2. Methodological characteristics of the studies selected on the use of botulinum toxin type A in the treatment of myofascial pain related to masticatory muscles

Item	Nixdorf et al. ⁶	Von Lindern et al. ⁹	Guarda-Nardini et al. ¹¹	Ernberg M et al. ¹²
Methodological design	Randomized, controlled, double-blind clinical trial	Randomized, controlled, blind clinical trial	Randomized, controlled, double-blind clinical trial	Randomized, controlled, double-blind, crossed clinical trial
Sample	15 females (placebo and TBA) (18-45 years)	60 (verum) +30 (placebo) (Age not reported)	10 (verum) +10 (placebo) (25-45 years)	12 (verum) +9 (placebo) (> 18 years)
Monitoring	Monitoring: beginning, 8, 16, and 24 weeks. Monitoring rate: 66%	Monitoring: between 1 and 3 weeks. Monitoring rate: not reported	Monitoring: 1 week, 1 and 6 months. Monitoring rate: not reported	Monitoring: 1 and 3 months and after the crossing another 1 and 3 months. Monitoring rate: 90% of the cases
Treatment	Group 1 = 25U TBA in each temporalis muscle 50U TBA in each masseter muscle (3 points) Group 2: saline solution	Group 1 = 35U TBA in each side of the temporalis, masseter, and medial pterygoid muscles. Group 2: saline solution	Group 1: 30U TBA in each masseter 20UI Botox in each anterior temporalis muscle Group 2: saline solution	Group 1: 50U TBA in each masseter Group 2: saline solution
Evaluation	Visual Analogue Scale	Visual Analogue Scale	Visual Analogue Scale	Visual Analogue Scale
Result	No significant differences were found between TBA and the placebo	Improvement of 91% in the group that received TBA and only improvement of local pain in the placebo group	Significant reduction of pain in mastication and improvement of subjective efficacy when compared with the saline solution group	Significant reduction of pain (30%) one month after the application of TBA
Safety	Reports adverse effects	Reports adverse effects	Not reported	Reports adverse effects

release of algogenic substances that promote local pain. This muscular dysfunction provokes excessive release of acetylcholine and an exacerbated energy crisis is perpetuated within the tense muscular band.²¹

All the articles mentioned in this review discuss the use of botulinum toxin type A as an alternative to the treatment of myofascial pain. Those works that met the quality criteria of the Jadad scale were selected for discussion.⁵ The quality of a systematic review is defined by the criteria adopted in its planning, execution, and analysis in order to minimize biases.

Nixdorf et al.⁶ analyzed the efficacy of botulinum toxin type A in the treatment of 15 women with moderate to intense chronic pain in the mastication muscles in a randomized, double-blind, placebo-controlled, cross-over study. Into each right and left temporalis muscle 25U (onabotulinumtoxin A) was applied

and 50U was applied to each right and left masseter muscle at three different locations per muscle. The data was collected every week and crossed for 16 weeks. The visual analogue scale (VAS) was used to measure the intensity of pain as a primary variable. The secondary variables used included: maximum opening without pain, muscular palpation at 12 points, and four general questions. Only 10 patients concluded the study and no significant differences were found between the botulinum toxin type A and the placebo. The result showed that there was no support for the use of botulinum toxin, probably due to the high dropout rate (34%) of the patients. Four patients showed unilateral incapacity to move the zygomaticus major muscle, which resulted in an asymmetrical smile. The authors reported using electromyography by needling to locate the mandibular elevating muscles

and these effects were justified as being provoked either by diffusion of the product or by direct injury to the muscle while inserting the needle. The use of electromyography by needling to locate the masseter and temporalis muscles is not necessary because of the ease in locating the musculature through palpation.

An error in the location of the application points in the masseter or a dispersion of the material during the application due to the speed of the injection should be added to the incapacity to move the zygomaticus major muscle. Ten patients reported pain increasing after the first applications and four of those patients reported the same after the second application. According to the authors, the patients may have had difficulty understanding the difference between pain intensity and discomfort and pain and, therefore, some patients may have answered differently than others.

In addition, only one point of measuring in time, which was based on the patient's memory, was considered to represent his or her pain. All the adverse effects were temporary and reversible.

Von Linder et al.,⁹ in a randomized, blind, placebo-controlled study, investigated the application of botulinum toxin type A in patients with chronic pain resulting from hyperactivity of the masticatory muscles, parafunctional movements, and hypermobility disorders. The indication for the treatment with botulinum toxin was determined in accordance with the evaluation and functional analysis of the mandibular movement, joint function, muscular hyperactivity, and pain. These patients had been previously treated with the appropriate conservative methods from 3 to 34 months, with no significant results. As a protocol, they received an application of botulinum toxin type A (Onabotulinumtoxin A) at a dosage of 35U (or saline solution as a placebo) in the masseter, temporalis, and medial pterygoid muscles. The pain symptoms were evaluated by the VAS before and after the treatment and the observation period was from one to three months. The results showed an improvement in local pain of 3.2 points (91%) on the VAS in the group where the botulinum toxin had been applied and only an improvement of 0.4 points in the VAS in the placebo group. They concluded that the botulinum toxin A was an innovative and efficient method for chronic facial pain associated with the muscular hyperactivity in patients who had not responded to the conventional treatment methods. The adverse effects reported were difficulty in deglutition and temporary paralysis of one muscle of facial expression in only one patient, which completely reverted after four weeks.

Guarda-Nardini et al.¹¹ made a double-blind, randomized, placebo-controlled study in which they compared the efficacy of the botulinum toxin A in relation to the saline solution on the reduction of bruxism and myofascial pain in the masticatory muscles of 20 patients. The levels of pain while at rest and masticating were evaluated through the VAS, on a scale of 0-10, before and after the application with botulinum toxin. The authors injected 30U of onabotulinumtoxin A into the masseter muscles and 20U into the anterior temporalis muscle of 10 patients. The clinical parameters were evaluated in the beginning, after one week, one month, and six months later. After six months of monitoring, the botulinum toxin group showed a significantly greater pain reduction during mastication than

the placebo group. It was concluded that the onabotulinumtoxin A was efficacious in reducing the symptoms of myofascial pain in patients with bruxism. No adverse effects were reported.

In a randomized, double-blind, placebo-controlled, cross-over clinical trial, Ernberg et al.¹² evaluated the effects of onabotulinumtoxin A on the pain conditions of 20 patients with persistent muscular TMJD. The patients had TMJD with no relief of pain after the conventional treatment. The botulinum toxin was applied in one group and the saline solution, on the control group; 50U were applied at three pre-defined points on each side of the masseter muscle. Monitoring was made after one month and after three months through the VAS. After that period, the data was crossed and evaluated for pain, physical function, emotional function, global improvement, and the side effects aside from the need for analgesics, limitation to opening the mouth, pain of palpation of masticatory muscles (20 locations), pain threshold to pressure, and pain tolerance. There was significant pain reduction (30%) one month after the application of botulinum toxin but not with the saline solution. As adverse effects, some patients reported muscle weakness or increase of pain after BTX-A injections, as much for saline solution as for BTX-A. All the effects were temporary and not significant.

The botulinum toxin type A has been the object of study in the control of pain, including myofascial pain, and it is related to the mechanism of pain relief, not only in the neuromuscular junction receptors, but also in the nociceptive receptors system.²² Intramuscular applications of BTX-A are an effective treatment for a great variety of movement afflictions.²³ The neurochemical blockage inhibits the exocytotic release of acetylcholine in the motor nerve endings, leading to a decrease in muscular contraction. This property makes it useful, clinically and therapeutically, in a series of conditions where there is excessive muscular contraction.²⁴

During the first years of treatment with botulinum toxin for motor conditions, investigators noticed a significant benefit in the pain symptoms, which exceeded the effects of muscular relaxation, and which not necessarily corresponded to the neuromuscular regions affected.²⁵ That suggested that the effects on pain were independent from the muscular effects and could have independent mechanisms of action.²⁴ These mechanisms of action included local neurons, spinal cord, and

suprasegmental brain centers involving the autonomic and somatic nervous systems,²⁵ and could be explained by the injured cells and primary afferent fibers releasing a series of chemical mediators, including the substance P, a peptide related to the calcitonin gene (PRGC), that have direct effects on the excitability of sympathetic sensory fibers. These chemical mediators contribute to form a complex environment responsible for the neurogenic inflammation.^{26,27}

The studies examined had small samples, varying from 15 to 90 participants, as well as patients who dropped out during the studies. The age of participants varied from 18 to 45 years.

All the studies that met the established quality criteria used onabotulinumtoxin A and the doses varied from 30U to 50U per side for the masseter and from 20U to 35U per side for the temporalis, at one to three points in the masseter and at one point in the anterior temporalis muscle. The work by Von Lindern et al.⁹ did not report the technique used in the application to the pterygoid medial muscle. According to Clark,²⁸ for myofascial pain of the masticatory muscles the doses recommended in the literature are: for the masseter (superficial and deep portions) - 40-60U per muscle, injected into two or three locations of the superficial part of the muscle, being careful of the motor portion of the facial nerve, and for the temporalis muscle (anterior, medial, and posterior portions) - 30-50U per muscle, injected into four locations of the anterior, medial, and posterior bands of this muscle. The total dose per procedure must not surpass 200U in the masticatory muscles. The patient must be examined by the professional before the application of botulinum toxin to determine an ideal dosage, according to the case presented. Especially among females, a complaint about the discomfort generated by the excessive decrease in the masticatory strength after an application was clinically observed in patients' reports, reinforcing the need for minimum and maximum intervals between doses so that the professional may establish the dosage for each patient individually.

No reliable diagnostic and measuring method for the presence and severity of temporomandibular dysfunctions exists yet that can be used without restrictions by researchers and clinicians. In order to diagnose and treat individual cases, the anamnesis is still the most important step in the formulation of the patient's diagnosis.¹

The physical exam, palpating the muscles and the TMJ, measuring the active mandibular movement, and analyzing the joint noises are, when performed by trained professionals, an instrument of great value in diagnosing and formulating therapeutic proposals, as well as in monitoring the efficacy of the treatments.²

Two of the examined studies evaluated patients only through the VAS.^{9,11} This scale is a unidimensional instrument to evaluate pain intensity. It is a line with extremes numbered from 0 to 10. At one end of the line, it is marked "no pain" and at the other, "worst pain imaginable". The patient is asked to evaluate and mark on the line the pain felt at that moment.²⁹ This method, although easy for the patient to understand and quick to apply, analyzes only the intensity of pain, not considering any of its other aspects. It would be necessary to use methods that evaluate the results from other aspects such as location of the pain, sensory and affective characteristics, impact of the pain on the well-being of the patient, the use of pain medications and their usefulness, and many other characteristics that are possibly analyzed on multidimensional scales.

CONCLUSION

The clinical studies have shown that applications of botulinum toxin can reduce the levels of pain and satisfy patients with their efficacy in this pathology, in addition to not having significant adverse effects. The muscles to be injected are the masseter and the anterior temporalis muscle (Figure 1).

According to the four works discussed, the doses vary from 30U to 50U per side for the masseter muscle and from 20U to 35U per side for the temporalis muscle, injected into one to three points in the masseter and one point in the anterior temporalis muscle. The patient should be examined again 15 days after the application, and should return for control after three to four months after the application for a new exam and application, if needed. Thus, according to the literature examined, the use of botulinum toxin type A for myofascial pain contributed to improving the treatments that existed up until then, but it is indispensable that a greater number of studies with quality and more precise and quantitative forms of evaluation be made to reach a definitive conclusion on its efficacy and safety.



Figure 1. Points for the application of botulinum toxin, according to the literature cited

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