REVIEW ARTICLE

Jaw muscles myofascial pain and botulinum toxin*

Dor miofascial dos músculos da mastigação e toxina botulínica

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ABSTRACT

BACKGROUND AND OBJECTIVES: Temporomandibular disorders (TMD) involve a set of craniofacial changes, which may involve temporomandibular joint (TMJ), jaw muscles and/or associated structures. Muscle TMD is the most frequent, and one of its subtypes is myofascial pain. Botulinum toxin type A (BoNT A), has been studied to control pain, including myofascial pain, and is related to pain relief mechanisms not only in neuromuscular junction receptors. This study aimed at evaluating articles addressing BoNT A to treat jaw muscles myofascial pain.

CONTENTS: Pubmed, LILACS and BVS databases were queried from 2000 to April 2012, crossing the following keywords: botulinum toxin type A, myofascial pain syndromes, facial pain, temporomandibular joint disorder syndrome, trigger-points, bruxism, temporomandibular joint, masseter muscle and temporalis muscle. Inclusion criteria were randomized double blind or blind studies, with 10 or more participants, with randomized methodological aspects, relating the use of botulinum toxin for jaw muscles TMD myofascial pain, more specifically masseter and temporalis muscles, and limited to the English language. Six articles were found and included in this study.

CONCLUSION: BoNT A was not more effective to treat myofascial pain than established conventional treatments. Because there are many uncontrolled variables in the few related studies, more studies with judicious methodologies are needed to make feasible its use in patients refractory to pain and previously submitted to conservative treatments.

Keywords: Botulinum toxin type A, Facial pain, Myofascial pain syndromes, Temporomandibular joint disorder syndrome.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Disfunção temporomandibular (DTM) abrange um conjunto de alterações craniofaciais, que pode envolver a articulação temporomandibular (ATM), os músculos da mastigação e/ou estruturas associadas. As DTM musculares são as mais frequentes e um dos seus subtipos compreende a dor miofascial. A toxina botulínica tipo A (BoNT A), tem sido objeto de estudos no controle da dor, incluindo dor miofascial, e está relacionada ao mecanismo de alívio da dor, não somente nos receptores da junção neuromuscular. O objetivo deste estudo foi acessar os artigos que abordam o uso da BoNT A no tratamento da dor miofascial nos músculos da mastigação.

CONTEÚDO: Foi realizada uma busca nas bases de dados Pubmed, LILACS e BVS, de 2000 a abril de 2012, cruzando-se os descritores: toxinas botulínicas tipo A, síndromes da dor miofascial, dor facial, síndrome da disfunção da articulação temporomandibular, pontos-gatilho, bruxismo, articulação temporomandibular, músculo masseter e músculo temporal. Como critérios de inclusão foram analisados estudos randomizados, duplamente encobertos ou encobertos, com 10 ou mais participantes, de aspectos metodológicos aleatórios, que relacionassem o uso da toxina botulínica na dor miofascial da DTM nos músculos da mastigação, mais especificamente masseter e temporal, limitados para o idioma inglês encontrando-se seis estudos que foram incluídos neste estudo.

CONCLUSÃO: O uso da BoNT A não se mostrou mais eficiente no tratamento da dor miofascial do que os tratamentos convencionais já estabelecidos. Por existirem diversas variáveis não controladas nos poucos estudos pertinentes, mais estudos, com metodologias criteriosas, são necessários para viabilizar sua aplicação em pacientes refratários à dor submetidos previamente a tratamentos conservadores.

Descritores: Dor facial, Síndrome da disfunção da articulação temporomandibular, Síndromes da dor miofascial, Toxinas botulínicas tipo A.

INTRODUCTION

Temporomandibular disorders (TMD) involve a set of craniofacial changes with multifactorial or biopsychosocial etiology, which may involve the temporomandibular joint (TMJ), masticatory muscles and/or musculoskeletal structures associated to head and neck. Its primary symptom is pain, but may also present with jaw movements limitation and joint noises.

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Whichever the nature of the pain, it brings changes in psychic behavior, with increased muscle tone e consequent presence of myofascial pain[1]. Conversely, long-lasting pain has no biological value and may become the major reason for patients' distress. In addition to neurophysiologic phenomena, psychological, cognitive, behavioral and social aspects are also involved[1-3].

Muscle pain is transmitted by nervous afferent fibers groups III and IV to the central nervous system, which processes noxious stimulation quantity, intensity, duration and location. The excessive use of a muscle by repetitive movements leads to traumas which generate localized muscle contraction and the release of algogenous substances promoting local pain[2-4]. This muscle disorder promotes excessive release of acetylcholine and an exacerbated crisis is perpetuated within the tight muscle band[5].

Muscle TMDs are the most frequent and one of its subtypes is myofascial pain, characterized by a state of chronic, regional musculoskeletal pain, with specific signs and symptoms as the presence of myofascial trigger points (TP). TPs are hyperirritable nodes located in a tight muscle, tendon or fascial band which, when palpated, produce local pain and referred pain outside the painful area[6,7]. The severity of symptoms caused by TPs varies from disabling and severe pain, to movement limitations and postural distortion[7].

Botulinum toxin type A (BoNT A), currently called *Onabotulinum* toxin A by the Food and Drug Administration (FDA), has been studied to control pain, including myofascial pain, and is related to pain relief mechanisms, not only in neuromuscular junction receptors, but also in the nociceptive receptors system[4,8-12].

Considered lethal for many centuries, its clinical and muscular symptoms were described in detail in the early 19th Century by the physician Justinus Kerner. However, *Clostridium botulinum* (C. botulinum), microorganism producing botulinum toxin, was only identified in 1895 in Belgium by Emile Pierre Marie Van Ermengem. BoNT is a neurotoxin produced by different microorganisms initially called *C. botulinum*. Depending on the environment where they develop and produce their spores, they affect different subsets of live species producing variants[13]. Its initial classification in seven strains, called from A to G, is currently not satisfactory, and now *C. botulinum* is divided in four physiological groups together with *Clostridium argentinense* (C. argentinense), and aggregating *Clostridium butyricum* (C. butyricum) and *Clostridium baratii* (C. baratii) strains[13].

BoNT A action mechanism propositions were suggested in mid 1950, showing that it blocked acetylcholine (ACh) release from motor nervous terminations[8,12]. Once inside the body, the toxin would reach neuromuscular junctions where, after its internalization, binding to its receptor by endocytosis, it may develop the activity of blocking nervous impulse transmission for 8 to 16 weeks[13,14].

As from the 1980's, with the use of BoNT A by Alan Scott to correct strabismus in apes, its clinical application for therapeutic use has started[15]. BoNT A has been used for some neurological, urological, gastrointestinal and proctologic disorders. It is also widely used in Ophthalmology, ENT, Dermatology and Gynecology[8,16]. It is indicated to treat Parkinson's disease[17] and is being widely used to manage pain[18]. Currently, BoNT therapeutic capacity is being determined by categorization and genetic engineering to act in changing binding sites, in catalysis and duration of the toxin, allowing specific effects and several therapeutic actions such as: in SNARE mediation during secreting processes involved with diabetes, in respiratory disorders and even in processes controlling immune and inflammatory disorders[19].

There are some restrictions to its use such as: drug allergy, pregnancy, lactation, difficult cooperation of patient (fear of the method), infection or inflammation in the proposed injection site, anatomic abnormalities making injection difficult or impossible (e.g., obesity or deformities), comorbidities (viral infection, chronic neuropathic pain), patients under anticoagulants or drugs which may interfere with muscular transmission, such as aminoglycosides, or with neuromuscular joint disorders (severe myasthenia, Lambert-Eaton syndrome, amyotrophic lateral sclerosis)[5,10,20,21]. Among adverse effects there are: flu-like symptoms which may last from one to two weeks, muscle weakness depending on the injection site. This depends on operator's technique and dose used. There may be change in facial expression and difficulties to chew and swallow related to masseter muscle injection[5,8].

Recent studies were published showing possible antinociceptive effects of BoNT A to treat pain not necessarily originated by excessive muscle use[9,22]. This possible antinociceptive mechanism could 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 create a complex environment responsible for neurogenic inflammation[8,11,23,24].

BoNT A specificity for cholinergic neurons in the presence of specific receptors makes it inhibit other neurotransmitters such as norepinephrine in motor and neuromediator nerves, including epinephrine, norepinephrine and CGRP, bringing benefits to painful symptoms. BoNT A also suppresses the release of substance P, a peptide involved in neurogenic inflammation and pain disorders genesis, and the release of glutamate, another neurotransmitter involved with peripheral nociception and spinal cord dorsal horn[11,24,25].

For myofascial pain of masticatory muscles, recommended doses in the literature are: masseter (superficial and deep portion) 40-60 U per injected muscle in two or three sites of superficial masseter muscle, taking care with facial nerve motor part, and temporalis muscle (anterior, median and posterior portions) 30-50 U per muscle, injected in four sites of anterior, median and posterior bands of such muscle. Total dose should not exceed 200 U for masticatory muscles[20].

Because more than 70% of general population have at least one TMD symptom, and orofacial patients suffer its resulting clinical effects, and due to its physical, psychological and social impact, this study aimed at searching articles addressing BoNT to treat orofacial pain of masticatory muscles.

CONTENTS

Literature search strategies

Pubmed, LILACS and BVS databases were queried from 2000 to April 2012, crossing the following keywords: botulinum toxin type A versus myofascial pain versus facial pain versus temporo-

mandibular joint disorder syndrome, versus trigger-points versus bruxism, versus temporomandibular joint versus masseter muscle versus temporalis muscle. Inclusion criteria were randomized, double blind or blind studies with 10 or more participants, with randomized methodological aspects, relating the use of BoNT for TMD myofascial pain of masticatory muscles, more specifically masseter and temporalis, limited to the English language.

Review articles, clinical reports, open label studies, animal model studies, articles not related to TMD myofascial pain, disk displacement, tension headache, migraine and muscle movement disorders were excluded. After crossing keywords in all possible manners and applying inclusion and exclusion criteria, six studies were included and are summarized in table 1.

Description of selected literature

In a crossover randomized double-blind placebo-controlled study, the efficacy of BoNT A was analyzed to manage moderate to severe chronic pain in masticatory muscles where 25 U were injected in each left and right temporalis muscle and 50 U in each right and left masseter muscle in three different sites per muscle[26]. Data were collected every week and were crossed in 16 weeks. Visual analog scale (VAS) was used to measure pain intensity as primary variable. Secondary variables were: maximum painless mouth opening, muscle palpation in 12 points and four general questions. Only 10 patients have finished the study and there were no statistically significant differences between BoNT A and placebo. The study has not supported the use of BoNT[26].

In a different randomized, blind and placebo-controlled study, patients received BoNT injection in masticatory muscles: masseter, temporalis and medial pterygoid[27]. All patients had chronic pain resulting from masticatory muscles hypermobility and had been previously treated with adequate conservative methods from 3 to 34 months. Pain symptoms were evaluated by VAS before and after treatment and the observation period was of three months, were 35 U BoNT A in saline, and NaCI solution as placebo were administered in temporalis and masseter muscles. Results have shown 91% improvement in the BoNT A group and just local pain improvement in the placebo group. The conclusion was that BoNT A is an innovative and effective method for chronic facial pain associated to muscle hyperactivity in patients not responding to conventional treatments[27].

Another publication was a double-blind, randomized, placebo-controlled study where patients had bruxism and masticatory muscles myofascial pain[28]. Treatment protocol was muscular administration of four BoNT A (Botox, Allergan Inc., Irivine, CA) in masseter muscles on both sides and in anterior temporalis muscles on both sides, in a total of 100 U. Injections were controlled with topography and ultrasound. Clinical parameters were evaluated at baseline, one week, one month and six months after treatment and included pain at rest and during chewing, chewing efficiency, maximum mouth opening, protrusion and lateral protrusion, jaw movements limitation, subjective efficacy and tolerance to treatment. Results have shown improvement with BoNT A of jaw movements amplitude and pain at rest and during chewing. Clinical results variables were better with Botox as compared to placebo. Patients treated with BoNT A had better perception of treatment efficacy than those of the placebo group. Differences were not significant in some cases due to the small sample size. Authors have concluded

Table 1 - Articles adressing the use of BoNT to manage masticatory muscles fascial pain.

Authors	Types of Study	Samples	Evaluated Variables	Study Duration	Methodology	Result*
Nixdorf, Heo and Major[26]	Crossover, double-blind, randomized controlled study.	n=15 females; age -18 to 45 years; myofascial pain according to RDC/TMD	PAIN - by VAS; maximum mouth opening amplitude; pain at palpation and 4 general questions.	24 weeks	SG= 25U m.R temporal, 25U m. L temporal, 50U R masseter m., 50U L masseter m. Doses divided in three sites for each muscle (=0.2 cm^3). CG= 0.9% saline. Application of 0.2 cm^3 in each of the three sites of each muscle. Data collection: baseline, 8, 16 and 24 weeks.	SG = CG
Von Linder et al.[27]	Double-blind, randomized controlled study.	n = 90 individuals; refractory to conservative treatment	PAIN - by VAS	12 weeks	SG = 35U in 0.7 mL de NaCl injected in each side of temporal, masseter and medial pterygoid muscles. CG= 0.7 mL of NaCl injected in each side of temporal, masseter and medial pterygoid muscles. Data collection: baseline and 4 weeks.	SG > CG

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Authors	Types of Study	Samples	Evaluated Variables	Study Duration	Methodology	Result*
Guarda-Nardini et al.[28]	Double-blind, randomized controlled study.	n=20 individuals; (10 females and 10 males) age - 25 to 45 years; myofascial pain according to RDC/TMD	PAIN - by VAS; maximum mouth opening amplitude; mastictory efficiency - by VAS and efficacy and tolerabilityto treatment.	24 weeks	SG = 20U R temporal m., 20U L temporal m., 30U R masseter m, 30U L masseter m. Doses divided in three temporal m. sites and 4 masseter m. sites. CG= 0.9% saline. Application in each site corresponding to SG in each muscle. Data collection: baseline,1, 4 and 24 weeks.	SG > CG
Venâncio, Alencar and Zamperini[29]	Randomized controlled study.	n = 45 individuals; (40 females and 5 males) age - 18 to 65 years; headache according to IHS induced by trigger-points in masseter and temporal muscles.	Modified symptoms severity index (SSI); trigger points palpation; pain diary and pain questionnaire.	12 weeks	SG1 = 0.2 mL of 25% lidocaine without vasoconstrictor in 1 to 3 trigger points. SG2= 25U or 50 U BoNT in 1 to 3 trigger points. CG = Dry needling in 1 to 3 trigger points. Data collection: baseline, 10 min after, 1,4 and 12 weeks.	SG1 = SG2 = CG
Ernberg et al.[30]	Crossover, double-blind, randomized controlled study.	n = 21 individuals; (19 females and 2 males) mean age - 38 years; myofascial pain according to RDC/TMD; refractory to conservative treatment	Use of IMMPACT; use of analgesics; painless mouth opening amplitude; apin at palpation; pressure pain threshold and tolerability.	26 weeks	SG = 100U in 1.0 mL of 9% saline, 0.1 mL deep part, 0.2 mL fixed insertion and 0.2 mL mobile insertion of each L and R masseter. CG=1.0 mL of 0.9% saline. 0.1 mL deep part, 0.2 mL fixed insertion and 0.2 mL mobile insertion of each R and L masseter. Data collection: baseline, 4,12,14,18 and 26 weeks.	SG = CG
Guarda-Nardini et al.[14]	Double-blind, randomized controlled study.	n = 30 individuals; (22 females and 8 males) age - 23 to 69 years; myofascial pain according to RDC/TMD; refractory to conservative treatment	PAIN - by VAS and maximum mouth opening amplitude.	12 weeks	SG = 150U in each side of masseter and temporal muscles by the Manfredini et al.[31] technique CG = Fascial manipulation. Data collection: baseline and 12 weeks.	SG = CG

RDC/TMD = *Research Diagnostic Criteria for Temporomandibular Disorder*; VAS = visual analog scale; IHS = *International Headache Society*; IMMPACT = *Initiative on Methods, Measurement and Pain Assesssment in Clinical Trials*; SG = Study Group; CG = Control Group.
*Evaluated result was with regard to pain and movement amplitude improvement.

that BoNT A was effective to decrease myofascial pain symptoms in patients with bruxism[28].

A randomized study with patients with myofascial pain and TP-associated headache has used lidocaine and dry-needling in the referred TP[29]. Patients were divided in three groups: G1 dry-needling, G2 0.25% lidocaine without vasoconstrictor and G3 25 U or 50 U of BoNT. The following parameters were evaluated during 12 weeks: pain intensity levels, frequency, duration and sensitivity after injection, length of relief and use of rescue analgesics. All groups had favorable results for evaluated requisites, except for the use of rescue medication and sensitivity after injection, which was better for G3. Authors have concluded that, considering its low cost, lidocaine could be adopted as the substance of choice and BoNT would be reserved for refractory cases where expected ef-

fects of other therapies could not be reached[29].

Another crossover randomized double-blind and placebo-controlled study has evaluated the effect of BoNT A on persistent muscle TMD pain[30]. Patients had TMD without adequate pain relief after conventional treatment and received BoNT injection; the control group received isotonic saline solution. Both drugs were randomly injected in three standardized sites of the masseter muscle on both sides. Patients were followed after one and three months. After this period, the following parameters were evaluated: pain, physical function, emotional function, overall improvement and side-effects, in addition to the need for analgesics, mouth opening limitation, pain at palpation of masticatory muscles on 20 sites, pressure pain threshold and tolerance to pain. There has been significant pain improvement (30%) one month after BoNT injection, but this was not true for saline solution injection, as shown by other studies. The conclusion was that this improvement is regardless of its muscle relaxation effects, because the relief may precede this relaxation, being also present outside the areas of BoNT injection. There has been no primary difference between drugs, and results have not shown a relevant clinical effect of BoNT A to treat persistent TMD myofascial pain or to bring about emotional changes[30].

A randomized controlled study has compared the effectiveness of BoNT and the treatment with fascial manipulation of masseter and bilateral temporal muscles[14]. All patients had myofascial pain and were distributed in Group A receiving BoNT in a single session and Group B receiving multiple muscle fascia manipulation sessions. Evaluated parameters were maximum pain level by VAS, maximum mouth opening, right and left protrusion and laterality in the beginning, at the end and one month later. Follow up time was three months. There has been pain improvement in both cases and BoNT was better with regard to jaw movement amplitude[14].

Refractory patients are common in chronic diseases. Accurate myofascial pain diagnosis is difficult because its symptoms may be mistaken for other diseases, and basically depends on history and palpation exams, in addition to well trained professionals. BoNT is used to treat pain induced by spasm and dystonia because it paralyzes the overloaded muscle, but it is known that its analgesic effect is not only related to muscle relaxation and may be independent of it. So, hypothetically, BoNT A could be used to relieve myofascial pain due to its antinociceptive properties.

However, current studies still have several uncontrolled variables such as: small sample size, waiver of patients during the study, use of rescue drugs, differences in injection sites and doses used, which make these studies not reproducible. It is also necessary to investigate which would be its therapeutic benefits for these disorders, in addition to considering time between injections, the formation of antibodies and the complications of its use.

CONCLUSION

BoNT A was not more effective to treat myofascial pain than already established conventional treatments because there are few randomized, double-blind or placebo-controlled studies, which brings lots of controversies about its effectiveness. Further studies are needed to enhance the understanding of long-lasting pain pathophysiology and the mechanisms through which BoNT may change pain, in addition to the feasibility of its application in refractory myofascial pain patients, simultaneously with physical therapies.

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