



**FACULTAD DE CIENCIAS DE LA SALUD
CARRERA PROFESIONAL DE ESTOMATOLOGÍA**

**“EFECTOS DE LA TOXINA BOTULÍNICA EN PACIENTES CON DOLOR
MIOFASCIAL RELACIONADO CON TRASTORNOS DE LA ARTICULACIÓN
TEMPOROMANDIBULAR: UNA REVISIÓN SISTEMÁTICA”**

Tesis para optar el Título de:
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INFORME DE REVISIÓN DE ORIGINALIDAD

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DEDICATORIA

A mi abuelito Oscar Ramos Medina por creer en mí y apoyarme en este logro profesional. A mi madre Ana María Herrada Aponte por ser mi inspiración de fortaleza y lucha constante. Y por último a mi querida hermana Jessica Ninoska Ramos Herrada por motivarme a ser una mejor persona cada día.

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Resumen

La toxina botulínica se utiliza como alternativa para el tratamiento del dolor miofascial crónico refractario derivado de los trastornos temporomandibulares (TMD). Es importante establecer los beneficios de la toxina botulínica en este tipo de sintomatología. El objetivo del estudio fue realizar una revisión sistemática para evaluar los efectos de la toxina botulínica en pacientes con dolor miofascial relacionado con trastornos temporomandibulares. La búsqueda se realizó de manera sistemática, sin limitaciones de idioma o año de publicación, hasta febrero de 2021. Las bases de datos buscadas incluyeron PubMed, Web of Science, Scopus, The Cochrane Library y Latin American and Caribbean Health Sciences Literature (LILACS). Se buscó literatura gris parcial utilizando Google Scholar, ClinicalTrials.gov, OpenGrey y las listas de referencias de los artículos seleccionados. Se incluyeron ensayos clínicos controlados aleatorios que evaluaron los efectos de la toxina botulínica en el tratamiento del dolor miofascial. El riesgo de sesgo se evaluó con la herramienta Cochrane RoB 2.0 y se utilizó el enfoque The Grading of Recommendations Assessment, Development and Evaluation (GRADE) para determinar la certeza de la evidencia científica. Se recuperaron un total de 900 estudios, de los cuales solo se seleccionaron 8 ensayos clínicos aleatorizados. De estos 8 estudios se obtuvieron los datos de un total de 314 pacientes, predominantemente mujeres, entre las edades de 18 a 75 años. Después de la evaluación de los estudios con la herramienta RoB 2.0, 7 estudios mostraron algunas preocupaciones con respecto a los resultados informados y solo uno tenía un bajo riesgo de sesgo general. El análisis de los estudios ha demostrado que dosis bajas de toxina botulínica son eficaces en el tratamiento del dolor miofascial refractario asociado a trastornos temporomandibulares. Los estudios presentaron evidencia de certeza media a baja.

Palabras clave: toxina botulínica, dolor miofascial, trastornos de la articulación temporomandibular.

Abstract

Botulinum toxin is used as an alternative for the treatment of refractory chronic myofascial pain derived from temporomandibular disorders (TMD). It is important to establish the benefits of botulinum toxin in this type of symptomatology. The aim of the study was to conduct a systematic review to assess the effects of botulinum toxin in patients with myofascial pain related to temporomandibular disorders. The search was performed systematically, without language or publication year limitations, up to February 2021. The databases searched included PubMed, Web of Science, Scopus, The Cochrane Library, and Latin American and Caribbean Health Sciences Literature (LILACS). Partial gray literature was searched using Google Scholar, ClinicalTrials.gov, OpenGrey and reference lists of selected articles. Randomized controlled clinical trials evaluating the effects of botulinum toxin in the treatment of myofascial pain were included. Risk of bias was assessed using the Cochrane RoB 2.0 tool and The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to determine the certainty of the scientific evidence. A total of 900 studies were retrieved, of which only 8 randomized clinical trials were selected. From these 8 studies, data were obtained from a total of 314 patients, predominantly women, between the ages of 18 and 75 years. After the evaluation of the studies with the RoB 2.0 tool, 7 studies showed some concerns with the reported results and only one had an overall low risk of bias. Analysis of studies has shown that low doses of botulinum toxin are effective in the treatment of refractory myofascial pain associated with temporomandibular disorders. The studies presented evidence of medium to low certainty.

Keywords: botulinum toxin, myofascial pain, temporomandibular joint disorders.

Effects of botulinum toxin in patients with myofascial pain related to temporomandibular joint disorders: a systematic review.

Introduction

The American Academy of Orofacial Pain (AAOP) defines temporomandibular disorder (TMD) as an umbrella term containing a number of clinical problems that affect the temporomandibular joint, masticatory muscles, and associated structures.^{1,2} Temporomandibular disorder has a multifactorial etiology involving biological, infectious, hormonal, psychological, social, and emotional factors.^{3, 4, 5, 6, 7, 8, 9, 10}

Patients with TMD present pain,^{11, 12, 13, 14, 15, 16, 17, 18, 19, 20} limitation of movement, dysfunction, fatigue, subjective weakness and stiffness of facial and masticatory muscles.²¹ In addition, there is a subgroup within the TMD that corresponds to musculoskeletal disorders, the most prevalent being localized myalgia and myofascial pain.¹⁷ Myofascial pain can present with acute to moderate intensity and is characterized by the presence of sensitive areas called trigger points, located in girdles, tendons and muscle fascicles, and which generate deep and localized pain in the tense muscle girdle. However, pain can also occur in other areas distant from the trigger point.^{17, 21, 22, 23}

Different treatment approaches have been proposed, including conservative therapies such as pharmacotherapy,^{4, 24, 25, 26} physiotherapy,^{14, 27, 28} ultrasound, transcutaneous electrical nerve stimulation,¹⁷ occlusal therapy (occlusal splints),^{29, 30, 31, 32} and psychotherapy.^{26, 33, 34, 35} On the other hand, more invasive procedures such as dry needling and acupuncture are also available.¹⁷ However, even after receiving these treatments, symptoms may partially persist. In this chronic condition, botulinum toxin type A (BTX-A) has recently been used as the alternative for longer relief of symptoms of refractory chronic myofascial pain.^{20, 28, 36, 37, 38}

BTX-A is an exotoxin synthesized by a spore-forming gram-negative anaerobic bacterium called *Clostridium botulinum*. This potent botulinum neurotoxin exerts its action on the presynaptic junction of alpha and gamma motor neurons by blocking Ca.³⁵ It has a dual mechanism of action on the neuromuscular junction such as inhibition of acetylcholine exocytosis of nerve plaques (temporary weakening of of nerve endings and consequent relaxation of muscle contraction or paralysis, depending on the dose, without any systemic effect) and inhibition of the release of

substance P and glutamate to reduce inflammatory pain.³⁹

Despite the factors mentioned, there is still a lack of unification and compilation of scientific information on the benefits of BTX-A therapy. Therefore, the aim of this systematic review was to assess the effects of botulinum toxin in patients with myofascial pain related to TMD.

Material and methods

Protocol and registration

This review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions,⁴⁰ and reported as suggested using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁴¹ Likewise, the study protocol was registered in the database of the PROSPERO Center for Reviews and Dissemination (CRD) of the University of York (Heslington, UK), and the National Institute for Health and Care Research (London, UK),⁴² under number: CRD42020168889.

Eligibility Criteria

To define the eligibility criteria, the acronym PICOS (Population, Intervention, Comparison, Outcomes and Study design) was used:

Population: adult patients with myofascial pain related to TMD;

Intervention – botulinum toxin injection treatment for myofascial pain;

Comparison: no treatment, placebo, or other specific treatment, including physical therapy, occlusal splints, pharmacotherapy, or acupuncture;

Primary outcome: changes in myofascial pain intensity due to botulinum toxin treatment;

Effect measures: changes from baseline to last available follow-up as measured by visual analogue scales or similar tools; Y

Study design: randomized clinical trials (RCTs) conducted in humans.

Exclusion criteria included studies in children or adolescents, studies on craniofacial anomalies or neuromuscular diseases, literature or systematic reviews, letters to the editor, pilot studies, case report studies, in vitro studies, and animal studies.

Information sources, search strategy and study selection

The search for studies was carried out regardless of language or year of publication in the following electronic databases: MedLine (via PubMed), Scopus, The Cochrane Library, Latin American and Caribbean Health Sciences Literature (LILACS), Embase, Web of Science. In addition, a partial gray literature search using specific keywords was performed up to February 2021 (detailed data is available from the corresponding author upon reasonable request), using Google Scholar,

OpenGrey, and ClinicalTrials.gov databases. The first 100 records were searched using Google Scholar. In addition, the reference lists of selected articles were checked to ensure that potential articles were not missed. Articles were managed using EndNote software (Thomson Reuters EndNote X7 ® ; New York,

Study selection was carried out independently in 2 phases by 2 reviewers (RMRH and KJAS). In the first phase, the reviewers reviewed the titles and abstracts identified from the results of the electronic database and additional sources. Studies with titles and abstracts that did not meet the inclusion criteria and duplicate studies were then removed. In the second phase, full-text studies were retrieved to confirm their eligibility, according to the inclusion criteria. The reference lists of the selected articles were also evaluated. Reviewers independently selected articles for inclusion in a qualitative synthesis. Disagreements were resolved by verbal discussion and consensus reached with the help of a third reviewer (LEAG),

Data collection process and data elements

Two reviewers (RMRH and KJAS) independently extracted data from included studies using a standardized Excel spreadsheet. The following data were extracted: study design, patient sex and age, sample size, TMD diagnosis, myofascial pain diagnosis, muscles involved, treatment approach, botulinum toxin application area, number of doses and time. of treatment. At the beginning of the study, it was planned to include the results on the quality of life of the patients. However, this was not possible as none of the studies selected for the review evaluated this variable. To clarify and resolve doubts about the studies, we contacted the authors by email.

Risk of bias in individual studies

Risk of bias (RoB) assessment of RCTs was performed using the Cochrane Risk of Bias tool (RoB 2.0; Cochrane, London, UK).⁴³ The following domains were considered: randomization process, deviations from planned interventions, missing outcome data, outcome measurement, and selection of reported outcome. Each domain was assessed as: low risk of bias, some concern, or high risk of bias. An overall RoB judgment was then assigned to each study as: low risk (if all domains had a low RoB), some concern (if at least one domain had some concern), or high risk (if one or more domains had some concern).⁴³

In addition, the degree of certainty of the evidence in the studies was evaluated using The Grading

of Recommendations Assessment, Development and Evaluation (GRADE) approach ⁴⁴ according to the categories (high, moderate, low and very low).

Both review authors (RMRH and KJAS) independently assessed the risk of bias and certainty of the evidence of the included studies. Discrepancies were resolved by verbal discussion and consultation with the third reviewer (LEAG).

Summary of measures

Primary outcome measures were based on quantitative data (efficacy of botulinum toxin therapy on TMD-related myofascial pain after botulinum toxin injection). Mean differences and 95% confidence intervals (CI) for changes were assessed based on patient responses, using a visual analog scale (VAS).

Synthesis of the results

The data collected from the included studies were synthesized and analyzed in a description table. After the evaluation and taking into account the differences between the botulinum toxin injection protocols, the sample size, the doses and the follow-up periods, it was considered that the methodology of the studies was not homogeneous. For this reason, no meta-analysis was performed.

Results

Selection of studies

In the first phase of the search strategy, a total of 787 studies were identified in the electronic databases (570 in PubMed, 5 in Scopus, 24 in LILACS, 15 in Embase, 60 in Web of Science and 113 in Cochrane Library). In addition, 113 studies were found during the partial gray literature search (100 in Google Scholar, 13 in ClinicalTrials.gov) published between 2008 and 2020. No studies were retrieved from OpenGrey or reference lists. A total of 890 studies were eliminated for being duplicates and not meeting the eligibility criteria after reading the titles and abstracts. Ten studies were retrieved for full text evaluation based on the inclusion and exclusion criteria. Two studies were excluded, of which one was excluded for not specifying the diagnosis of TMD and the other because the full text could not be obtained.^{45, 46} Finally, 8 studies were included in this systematic review. The complete sequence and search are detailed in the PRISMA flowchart (Figure 1). All 8 studies were RCTs.^{20, 47, 48, 49, 50, 51, 52, 53} Table 1 shows the characteristics of the included studies.

Study characteristics

A sample size of 314 patients was included in the analysis, the subjects being adults between 18 and 75 years of age, predominantly women, diagnosed with TMD-related myofascial pain, without complete relief of symptoms after receiving conventional treatment for at least 6 months. . The patients were treated with BTX-A in concentrations ranging between 100 U and 150 U diluted in 0.1 mL to 1.1 mL of sterile saline solution, injected into different muscles. In 6 of the 8 studies, BTX-A was injected into the masseter and temporalis muscles, while in only 2 studies BTX-A was injected into the masseter, temporalis, and pterygoid muscles. Each patient received a maximum of 25-150 U of BTX-A, with 5-50 U of BTX-A injected at 1, 2, or 3 sites.

Risk of bias within the study

The risk of bias assessment of the 8 included RCTs^{20, 47, 48, 49, 50, 51, 52, 53} was performed using the Cochrane RoB 2.0 tool.⁴³ Of the 8 studies, only one was at low risk of bias,⁵⁰ while in the remaining 7 studies some concerns have been raised regarding the selection of reported outcome in studies describing multiple outcome measures (scales and endpoints). time, among others). However, not all the data of the results obtained are shown in detail, evidencing a lack of information on the results.^{20, 47, 48, 49, 51, 52, 53} The evaluation of the studies is shown in Table 2 and Figure 2 .

Individual study results

All studies included in this systematic review evaluated changes in the range of pain intensity. Three studies compared BTX-A (study group) with saline injections (placebo group), ^{47, 51, 53} one study compared BTX-A (study group) with saline injections (placebo group) and lidocaine (placebo group). control), ⁴⁹ another study compared a low intensity laser (study group) with BTX-A ⁴⁸, another study compared BTX-A (study group) with the dry needling technique (control group), ⁵² another compared BTX- A (study group) with the technique of fascia manipulation technique (control group), ²⁰ and only one study compared 3 different concentrations of BTX-A with physiological saline solution (negative control group) and with oral appliance (negative control group). positive control). ⁵⁰

The study that evaluated the safety and efficacy of 3 different doses of botulinum neurotoxin type A (BoNT-A) (low-dose BoNT-A (BoNT-AL), medium-dose BoNT-A (BoNT-AM), and high-dose BoNT-A) BoNT-A (BoNT-AH)) showed a significant decrease in subjective pain intensity in all 3 groups, regardless of the administered dose. Furthermore, no significant differences were found between the 3 groups, ⁵⁰ showing that even at low doses, BoNT-A can be equally effective up to 6 months after administration. ^{49, 50}

Four of the studies comparing BTX-A with saline showed that BTX-A injections were clinically effective in reducing pain ^{47, 50, 51, 53} and increased pressure pain threshold more than saline. fifty

Another study evaluated the efficacy of BTX-A in the treatment of refractory masticatory myofascial pain syndrome (MMPS) and classified myofascial pain as localized (MP), nonlocalized, radiating, or referred (PR). The results showed that the changes in pain intensity values were statistically significant for the BTX-A group (all patients showed pain reduction from day 0 to day 180, except the saline and lidocaine groups). Likewise, when comparing the MP group with the PR group that received TXB-A, the reduction in pain according to the VAS was greater in the MP group, decreasing from 6 to 2 points and from 6.5 to 4 points, respectively. Although a significant decrease in pain was observed, very low values were not reached in the PR group. ⁴⁹

After comparing low-level laser therapy with BTX-A injections ⁴⁸ there were no statistically

significant differences between the 2 treatments with respect to pain at 30 days of follow-up. This study reported a baseline VAS of 7 points in both groups, with a decrease to 2.75 on day 12 in the laser group and to 2.86 in the BTX-A group on day 30, showing that both treatments were statistically effective. However, the effects of low-level laser therapy were more rapid compared to BTX-A injections (reduction observed at day 12 versus day 30, respectively). These results should be taken into account in future studies.⁴⁸

Another treatment compared to BTX-A injection was the dry needling technique,⁵² in which the efficacy on myofascial pain during chewing and at rest was evaluated. Both treatments achieved a significant improvement in VAS scores during the 6-week follow-up. However, regarding myofascial pain at rest, the relief was greater with the dry needling technique. One of the 8 included studies compared BTX-A with the fascial manipulation technique.²⁰ Both treatment protocols significantly improved and decreased the intensity of myofascial pain, with no relevant clinical differences between the 2 protocols during the 3-month follow-up.

When BoNT-A (regardless of dose) was compared to the oral device, the study showed that both treatments were equally effective in treating persistent myofascial pain at the 24-week follow-up and there was no statistical difference up to the last follow-up period. However, the author also reported a reduction in muscle activity and a decrease in muscle thickness and bone volume of the condyloid and coronoid processes as dose-related adverse effects of BoNT-A (higher doses). Therefore, BoNT-A in patients with myofascial pain should ideally be given in low doses.⁵⁰

A meta-analysis could not be performed due to the heterogeneity of the results (differences in botulinum toxin injection protocols, sample sizes, doses, and follow-up periods).

The evaluation of the level of evidence using the GRADE approach showed that the 8 included RCTs^{20, 47, 48, 49, 50, 51, 52, 53} presented evidence of moderate to low certainty. A detailed description is shown in Table 3.

Discussion

Currently, there is no consensus on the most appropriate treatment protocol for myofascial pain. A multidisciplinary approach and first-line treatment are recommended, starting with conventional therapy. However, some patients do not achieve complete pain relief and are diagnosed with refractory myofascial pain. Intramuscular injections with BTX-A have been proposed in the literature as an alternative treatment for these cases, since this neurotoxin induces a mechanism of action on the neuromuscular junction, inhibiting the exocytosis of acetylcholine from nerve end plates and causing relaxation. of muscle contraction and pain. relief. ³⁵Despite this, to date, the efficacy of this treatment is not very clear and, therefore,

In this systematic review, BTX-A injections were shown to be significantly effective in reducing the intensity of myofascial pain ^{20, 47, 48, 49, 50, 51, 52, 53} regardless of the dose used (high, medium, low). ⁵⁰ This is evidenced by studies comparing BTX-A with placebo, ^{47, 49, 50, 51, 53} which demonstrated clinically more efficient pain reduction with BTX-A compared with placebo. ^{49, 51} However, 2 studies found that the difference between the 2 treatments was not statistically significant. ^{47, 53}

The fascial manipulation technique has been shown to be more effective in immediate relief of self-reported pain compared to BTX-A treatment. ²⁰ However, the difference between the 2 treatment protocols was not clinically significant at 3-month follow-up, and both treatments were found to be equally effective in reducing pain. ²⁰ This difference could be due to the multiple sessions (3 ± 1) that the patients received compared to treatment with BTX-A that was only carried out in a single session. The relaxing and calming effect that the operator transmits when exerting deep digital pressure with the fingertips or elbows on the muscular zones (establishing a positive relationship) during the 50 min sessions could also have had a psychological influence, compared to BTX-A treatment, which has a cumulative effect. ²⁰ It should be noted that the evaluation of the immediate effect of BTX-A cannot be compared with other therapies. Said evaluation should be carried out days later when the effects appear, that is, their results should be compared in the medium and long term due to the cumulative effect of treatment with BTX-A. Similar results were obtained when low-level laser therapy was compared with BTX-A treatment. Their medium- and long-term results should be compared due to the cumulative effect of treatment with BTX-A. Similar results were obtained when low-level laser therapy was compared with BTX-A treatment. Their medium- and long-term results should be compared due to the cumulative effect of treatment with BTX-A. Similar

results were obtained when low-level laser therapy was compared with BTX-A treatment.

From the beginning to the last follow-up of the study, lidocaine injections were not significantly effective in treating myofascial pain.⁴⁹ In contrast, both the dry needling technique and the administration of BTX-A showed favorable results in relieving myofascial pain during chewing and at rest. Furthermore, myofascial pain relief at rest was statistically significant with the dry needling technique.⁵² Likewise, in a recently published study, De La Torre Canales et al. compared BoNT-A acupuncture treatment and saline administration. The researchers found that all 3 therapies significantly reduced self-perceived pain after 1 month of follow-up. However, there was no difference between acupuncture and BoNT-A.

Due to its non-invasive and reversible characteristics, the oral appliance is probably the most widely used therapy to reduce the symptoms of myofascial pain.⁵⁰ In our review, the oral device was equally effective as BoNT-A therapy. The study authors found no significant difference between the 2 treatments.⁵⁰ This could be because the effect of both treatments is observed days after the start of treatment, that is, it has a cumulative effect. Therefore, we can confirm that BTX-A compared to conventional treatments (oral appliances, fascial manipulation technique, low intensity laser therapy and dry needling technique) presents similar results. However, despite the aforementioned evidence, a definitive result cannot be stated as the certainty summary of the evidence using the GRADE approach showed moderate to low certainty in the evidence from the studies (see Table 3). Furthermore, the studies had limitations such as small sample sizes and short follow-up periods.

Therefore, more RCTs with larger sample sizes, longer follow-ups, and the inclusion of various control groups (occlusal splints, drug therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS, among others) are needed to determine the effectiveness of BTX-A in the long-term treatment of myofascial pain in patients with TMD.

Conclusions

- Based on the studies reviewed, botulinum toxin appears to be as effective in controlling TMD-related myofascial pain as conventional treatments (oral appliance, lidocaine injections, low-level laser therapy, dry needling technique, saline injections, and fascial manipulation technique).
- Botulinum toxin is a useful alternative clinical adjunct to existing conservative treatments for refractory myofascial pain related to TMDs.
- For the control of refractory myofascial pain related to TMDs, botulinum toxin should be administered in low doses to avoid adverse effects related to the administration of high doses.

Ethical approval and consent to participate

Does not apply.

data availability

All data analyzed during this study are included in this published article.

Consent to publication

Does not apply

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Table 1. Evidence for the effects of botulinum toxin (BTX-A) in patients with myofascial pain related to temporomandibular disorder (TMD).

<i>Author (Year)</i>	<i>Study design</i>	<i>Sample and Features</i>	<i>Muscle evaluated</i>	<i>Concentration BTX-A</i>	<i>Dosage and administratio n</i>	<i>follow-up</i>	<i>Relevant findings</i>
Ernberg (2011)	randomized clinical trial	21 patients Control group: saline solution isotonic.	Masseter	100 U TBX-A 1.0ml saline solution 100U maximum per patient 50U masseter muscle Control group: 1.0ml saline solution solution.	1 dose, 3 apps points on each muscles Control group: 1 dose	1 week before 1 months after and 3 months despues de.	No significant differences were found in pain reduction between BTX-A and saline injection in patients with persistent myofascial pain.
Guard (2012)	randomized clinical trial	30 patients 22 females 3 evils (age range 20-71 years). Control group: Driving technique Fascial.	Temporary Masseter	150 U BTX-A for each side treaty.	BTX-A 1 dose Multiple management points for muscle. Control group: Multiple 50 min sessions 150 minutes in all	Treatment initiation 1 hour later, and 3 months later.	The two treatments are equally effective in reducing pain in a follow-up of up to 3 months. The increase in mandibular range of motion was slightly greater after BTX-A injections.
Of Carly (2016)	randomized clinical trial	15 patients 13 females 2 evils Middle Ages	Temporary Masseter	500ml BTX-A 1.1 ml saline solution 0.9%	2 twos 2 management points in the masseter muscle	Before and After treatment.	Both treatments BTX-A like low level laser they were effective, there is no difference between both treatments regarding pain reduction 30 days later start treatment the low-level laser effect was faster (at 12 days)

		38 years BTX-A group (n = 7) Control group: low level laser (n = 8)		30 U first session 15 U seconds session	and 1 management point in the temporalis muscle.		than BTX-A (in 30 days).
Kütük et al (2019)	randomized prospective	40 patients 29 girls 11 men Mean age 33.8 (range, 20 to 60 years). study group n = 20, Control group: dry needling n = 20	Temporary Pterygoid Side.	500ml BTX-A 10 cc 0.9% NaCl 25 AU 150 AU per patient. 25 (0.5cc) at each trigger point	Study groups: 1 dose dry needling group: trigger point is injected 8 to 10 times.	Start of treatment and 6 weeks after treatment	Pain at rest was more effective with the dry needling technique after 6 weeks. Both treatments: BTX-A and dry the puncture produced significant pain relief and improved function in patients with myofascial pain.
Kurtoglu et al (2008)	randomized prospective	24 patients study group (n = 12) age mean of 29.6 years (range, 16 to 53 years), 10 females 2 evils. Placebo group (n = 12) mean age 23.4 years (range, 20 to 34 years), 10 females, 2 evils	Masseter Temporary	100 U BTX-A per patient. Study groups: BTX-A with 2 cc saline solution. Placebo group: 2cc solution Saline	1 dose 3 management points in the masseter muscle and 2 management points in the temporary muscle (10 U each)	Start of study, to 14 and 28 days thereafter	Pain relief and improvement of psychological state after the BTX-A injections and until the 28th day.
mounts (2020)	randomized clinical trial	60 patients age between 18-75 years BTA Group	Temporary and pterygoid masseter	Group BTA: 100-150 units 50 U in BTA 1.25ml of	1 dose in all groups. 3 management points in the	Before treatment and at 7, 14, 28, 60, 90 and 180 days	BTX-A significantly reduced pain compared to saline and lidocaine. The effects lasted up to 6 months and was more intense in patients with localized myofascial pain than in referred remote pain.

		(n = 20) Lidocaine group (n = 20) Placebo group: saline solution (n = 20)		saline solution to obtain 4 units of BTA per 0.1 ml of the injection liquid. Lidocaine group: lidocaine 2% with vasoconstrictor. Saline solution group: 0.9% saline solution;	temporarymus cle. 3 points on the masseter muscle. 1 point in the lateral pterygoid muscle	after treatment.	
De la Torre et al (2020)	randomized clinical trial	100 female patients Mean age = 36.8 ± 5.6. Low BONT-A group (n = 20) Group BONT- A medium (n = 20) High BONT-A group (n = 20) Positive control group: Oral administration (n = 20) Negative control group: Physiological serum (n = 20)	Previous Temporarily Masseter	BONT-A groups: 100 U of Botox diluted in different concentrations with 0.9% sterile saline solution. Saline solution group: 0.9% sterile saline solution.	1 dose of 1ml in all BONT-A and Saline groups. 5 administration points in each muscle. Oral administration group: Use during the night.	Before treatment and at 7, 14, 21, 28, 90 and 180 days thereafter.	BoNT-A (Regardless of dose) was more effective in the reduction of persistent myofascial pain than saline solution and was also as effective as the occlusal appliance after 14 days and up to 6 months of follow-up
Gupta et al (2016)	randomized clinical trial	24 patients Age range: 20 to 50 years. BTX-A group (n = 12)	Previous Temporarily Masseter	10U of BTX-A at 10 points 30MU for the masseter muscle. 20MU for	1 dose 3 administration points in each masseter muscle. 2 management	Before and at 14 and 28 days after treatment.	Statistically significant reduction in pain and improvement in function after the administration of BTX-A compared to the placebo that did not present a significant change in a follow-up of up to 8 months.

Control
group:
placebo (n =
12)

anterior temporal
muscle. points in each
temporal
muscle.

Control group:
isotonic saline

solution

Table 2. Assessment of risk of bias in randomized clinical trials. Cochrane Tool: RoB 2.0

<i>Author(s) / and</i>	<i>bias arising desde the randomization process</i>	<i>Bias due to deviations from intended intervention</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in the selection of the reported result</i>	<i>Overall</i>
Ernberg et al. 2011	low risk	low risk	low risk	low risk	Some concerns	Some concerns
Save et al 2012	Some concerns	low risk	low risk	low risk	Some concerns	Some concerns
De Carli et al 2016	low risk	low risk	low risk	Some concerns	Some concerns	Some concerns
Kütük et al 2019	low risk	Some concerns	low risk	low risk	Some concerns	Some concerns
Kurtoglu et al. 2008	low risk	low risk	low risk	low risk	Some concerns	Some concerns
Montes et al 2020	low risk	Some concerns	low risk	Some concerns	Some concerns	Some concerns
De la Torre et al. 2020	low risk	low risk	low risk	low risk	low risk	low risk
Gupta et al 2016	Some concerns	low risk	low risk	low risk	Some concerns	Some concerns

Table 3. Classification of the level of certainty of the evidence: Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

<i>Certainty assessment</i>							<i>Summary of findings</i>	<i>certainty</i>
<i>No. of studies (Patients)</i>	<i>Study design</i>	<i>Risk of bias</i>	<i>inconsistency</i>	<i>indirectness</i>	<i>Vagueness</i>	<i>Publication bias</i>		
BTX-A compared to saline injections								
3 (69)	RCTs	* Serious	Not serious	Not seriously	Not serious	Not suspected	BTX-A had a clinically significant effect on reducing pain in the 1- to 8-month follow-up compared to the saline group that did not present a statistically significant reduction.	⊕⊕⊕○ MODERATE
BTX-A compared to saline and lidocaine injections,								
1 (60)	RCT	* seriously	Not seriously	Not seriously	● seriously	Not suspected	BTX-A significantly reduced pain compared to saline and lidocaine. The effects lasted up to 6 months and was more intense in patients with localized myofascial pain than in those with referred remote pain.	⊕⊕○○ LOW
BTX-A compared to low-level lasers								
1 (15)	RCT	*serious	not serious	not serious	● seriously	Not suspected	Both treatments were effective, no difference between both treatments with respect to pain reduction 30 days after starting treatment.	⊕⊕○○ LOW
BTX-A compared to dry needling technique								

1 (40)	RCT	* seriously	Not seriously	Not seriously	● seriously	Not suspected	Both treatments showed significant pain relief at the 6-week follow-up.	⊕⊕○○ LOW
BTX-A compared to facial manipulation technique								
1 (30)	RCT	* seriously	Not seriously	Not seriously	● seriously	Not suspected	Both treatments were effective in reducing myofascial pain for up to 3 months of follow-up up.	⊕⊕○○ LOW
BTX-A (3 different concentrations) compared with saline and oral apparatus.								
1 (100)	RCT	Not serious	Not serious	Not seriously	● seriously	Not suspected	BoNT-A (Regardless of dose) was more effective in reducing persistent myofascial pain than physiological serum and was also equally effective as occlusal appliance at 14 days and up to 6 months of follow-up.	⊕⊕⊕○ MODERATE

RCT: randomized clinical trial. Reasons for evaluation: *The evidence was downgraded by one level due to some limitations. ● The evidence was downgraded by one level because the results were derived from a single study and few participants.

Complementary table 1. Electronic databases and keywords.

<i>Electronics database</i>	<i>Keywords</i>
PUBMED (n = 570)	Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia AND Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases AND Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A
SCOPUS (n = 5)	Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia AND Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases AND Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A
LILAS-VHL (n = 24)	(Myofacial Pain) OR (myofascial pain) AND (temporomandibular disorder) AND (Botulinum toxin) AND (Botulinum toxin)
BASE (n = 15)	((myofacial AND pain OR myofascial) AND pain AND syndromes OR pain) AND syndrome, AND myofascial AND (((temporomandibular AND joint AND disorders OR disorder,) AND temporomandibular AND joint OR joint) AND disorder, AND temporomandibular OR temporomandibular) AND joint AND disease AND (((((((botulinum AND toxins OR botulinum) AND toxins, AND type AND a OR 'bont a' OR pharmacotherapy OR neurotoxin) AND a, AND botulinum OR clostridium) AND botulinum AND a AND toxin OR clostridium) AND botulinum AND toxin AND type AND a OR botulinum) AND a AND toxin OR toxin,) AND botulinum AND a OR meditoxin OR neuronox OR oculinum OR 'btx a')
SCIENCE WEB (n = 60)	TS=(Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia) AND (Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases) AND (Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum

OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A)

THE COCHRANE LIBRARY
(n = 133)

"myofascial pain" AND "Temporomandibular Disorder" OR "TMJ disorder" AND "botulinum toxin-A" AND "BoNT-A"

ACADEMIC GOOGLE
(n = 100)

Myofascial Pain AND Temporomandibular Joint Disorders AND Botulinum Toxin

OPEN GRAY
(n = 0)

Myofascial Pain AND Botulinum Toxin / Myofascial Pain AND Botulinum Toxin

CLINICAL TRIALS
(n = 13)

Condition or disease: Botulinum toxin **Other terms:**
myofascial pain Study type: Interventional studies (clinical trials)

Supplementary Table 2. Reasons for excluding studies after full text assessment.

<i>Reasons for exclusion</i>	<i>Number of studies</i>
The study did not specify the diagnosis of temporomandibular disorder.	1
Study published in Russian language and I cannot access it.	1

Fig. 1. PRISMA flowchart (preferred reporting items for systematic reviews and meta-analyses)

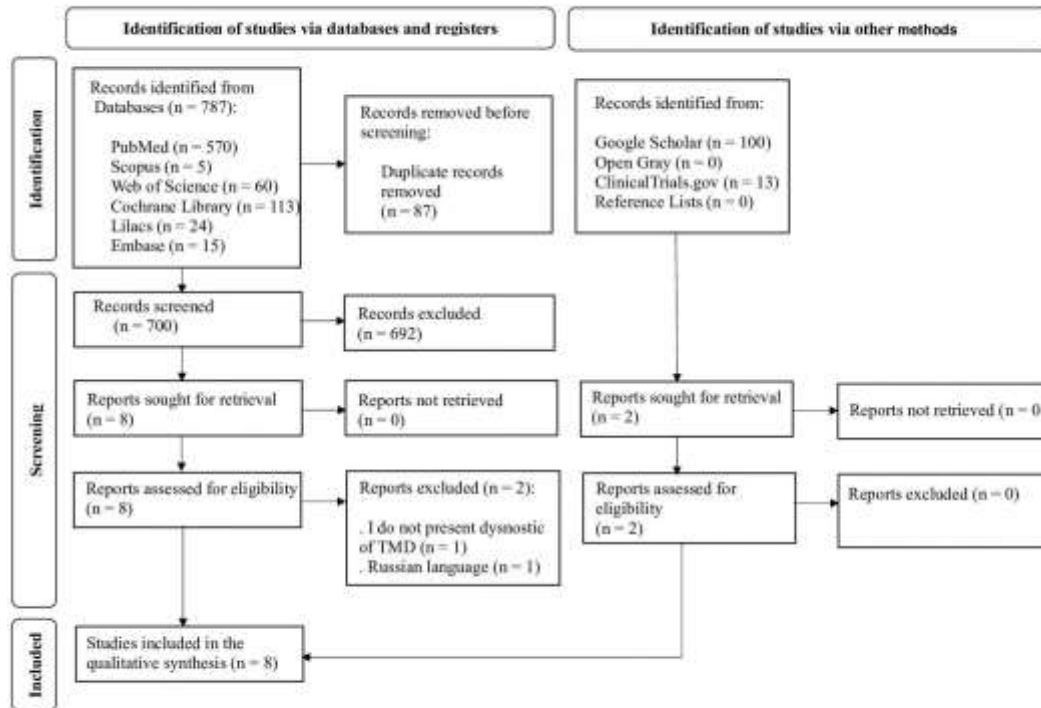
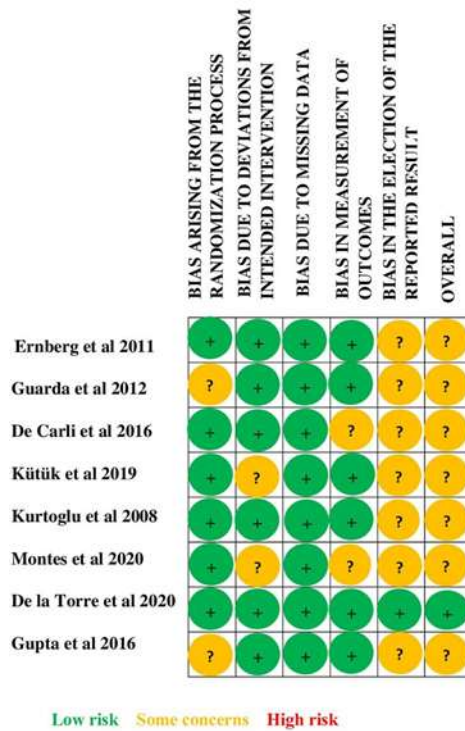


Figure 2. Assessment of included studies in terms of risk of bias



December 21, 2021

Letter to the editor

ID: DMP-02452-2021-01

Medical and dental problems

Title: Effects of botulinum toxin in patients with myofascial pain related to temporomandibular joint disorders: a systematic review

Authors: We welcome the reviewer's suggestions. Thank you for the opportunity to improve our manuscript. Based on your suggestions, some changes were made to the manuscript in this revised version.

Reviewer 1:

Temporomandibular joint disorder has to be replaced by Temporomandibular Disorder as it affects the Temporomandibular joint and neuromuscular complex (NOT dental occlusion!)

Authors: Thanks for the suggestion. Now, the authors have corrected the term throughout the article including the title as a suggestion of the reviewer.

The definition should be in accordance with the AAOP, especially since dental occlusion is no longer considered part of the musculoskeletal disorder.

Authors: Thanks for the suggestions. Now, we have changed the definition in the introduction. Likewise, the first two references were changed to improve the definition of TMD as a suggestion of the reviewer as follows:

" The American Academy of Orofacial Pain (AAOP) defines temporomandibular disorder (TMD) as a generic term that contains a series of clinical problems that affect the temporomandibular joint, masticatory muscles and associated structures. 1,2 It has a multifactorial etiology that involves biology, infectious, hormonal, psychological, social and emotional factors. 3-10"

Reference # 1: Reiter S, Goldsmith C, Emodi-Perlman A, Friedman-Rubin P, Winocur E.

Masticatory muscle disorders diagnostic criteria: the American Academy of Orofacial Pain versus

the research diagnostic criteria / temporomandibular disorders (RDC / TMD). J Oral Rehabil. 2012; 39 (12): 941-7. doi:10.1111 / j.1365-2842.2012.02337.x

Reference # 2: Griffiths RH. Report of the president's conference on examination, diagnosis and management of temporomandibular disorders. J Am Dent Assoc 1983; 106 (1): 75-77 doi:10.14219 / jada.archive.1983.0020

In the second paragraph of the introduction, the initial TMT should be replaced by TMD

Authors: Thanks for the suggestions. Now, TMT is replaced by TMD in the second paragraph

Reviewer 2:

Introduction: This part needs a better and more formulated description of the condition.

Authors: The authors welcome the reviewer's suggestions. Now, the authors have expanded the description as the reviewer's suggestion. As follows:

“The American Academy of Orofacial Pain (AAOP) defines temporomandibular disorder (TMD) as a generic term that contains a series of clinical problems that affect the temporomandibular joint, masticatory muscles and associated structures. 1,2 It has a multifactorial etiology that involves biology, infectious, hormonal, psychological, social and emotional factors. 3-10 Patients with TMD present with pain, 11-20 limitation of movement, dysfunction, fatigue, subjective weakness, and stiffness of the facial and chewing muscles. 21 In addition, within the TMD is the subgroup corresponding to musculoskeletal disorders, the most prevalent of which are localized myalgia and myofascial pain. 17 Myofascial pain can present with acute to moderate intensity and is characterized by the presence of sensitive areas called trigger points, located in bands, tendons and muscle fascicles, generating deep and localized pain in the tense muscular band. However, pain can also occur in other areas distant from the trigger point.17,21-23”

A description of the intervention (Botox-A) and its mode of action is missing. I would suggest reading the following article as an example (José L. de-la-HozMD et al. Efficacy of botulinum toxin type A in the management of Chewing Myofascial Pain: A Retrospective Clinical Study The Journal of the American Dental Association, November 8, 2021)

Authors: Thanks for the suggestions. Now, we have added the definition and mode of action of botulinum toxin. We also decided to add the reference suggested by the reviewer and another reference to complement the requested information.

“Different treatment approaches have been proposed including conservative therapies such as pharmacotherapy, 4,24-26 physical therapy, 14,27,28 ultrasound, transcutaneous electrical nerve stimulation, 17 occlusal therapy (occlusal splints) 29-32 and psychotherapy.26,33 -35 On the other hand, more invasive procedures such as dry needling and acupuncture, 17 however, even after receiving these treatments, the symptoms may persist partially. In this chronic condition, botulinum toxin type A (BTX-A) has recently been used as alternatives for the longer relief of the symptoms of refractory myofascial pain. 20, 28,36,37,38

BTX-A is an exotoxin protease synthesized by a spore-forming gram-negative anaerobic bacterium called Clostridium botulinum. This powerful botulinum neurotoxin performs its action at the presynaptic junction of alpha and gamma motor neurons by blocking Ca. 35 It has a dual mechanism of action on the neuromuscular junction such as the inhibition of acetylcholine exocytosis of the nerve end plates (temporary weakening of nerve endings and consequent relaxation of muscle contraction or paralysis, depending on the dose, without any systemic effect) and inhibits the release of substance P and glutamate to reduce inflammatory pain. 39

Despite the aforementioned, there is still a lack of unification and collection of scientific information on the benefits of BTX-A therapy. Therefore, the objective of this systematic review was to assess the effects of botulinum toxin in patients with myofascial pain related to temporomandibular disorder. ”

Reference # 36: Torres Huerta JC, Hernández Santos JR, Ortiz Ramírez EM, Tenopala Villegas S. Botulinum toxin type A for pain management in patients with chronic myofascial pain syndrome. Rev Soc Esp Pain. 2010; 17 (1): 22-7. Available at: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1134-80462010000100004&lng=es.

Reference # 39: Villa S, Raoul G, Machuron F, Ferri J, Nicot R. Improvement in quality of life after botulinum toxin injection for temporomandibular disorder. Journal of stomatology, oral and maxillofacial surgery. 2019; 120 (1): 2-6. doi: 10.1016 /j.jormas.2018.10.007

Lines 9 and 10 TMT? he meant TMD.

Authors: Thanks for your question. Yes, it is TMD. Now, we have fixed the error in the translation.

Material and methods: Eligibility criteria: If I understood correctly: the only outcome measure was the first: a subjective measure of pain intensity improvement as reported by the patient without an objective measure such as range of motion, etc..

Authors: Thanks for your question. Yes, only the assessment of the intensity of pain perceived by the patient was considered. Most studies measured it with the visual analog scale (subjective measure).

Study search and selection strategy: “Regardless of language”, how would you judge the suitability of the article? please elaborate.

Authors: The possibility of analyzing articles without taking into account the language of writing allowed us to evaluate the more global context of this problem. Therefore, to control the level of evidence, the risk of bias and the quality of evidence were assessed.

Data collection process and data elements: Was there any homogeneity in the way patients were diagnosed with TMD / MFP?

Authors: Thanks for your question. Some of the studies included in the systematic review mention that they made the diagnosis of TMD and MFP using the research diagnostic criteria for temporomandibular disorders (RDC / TMD). However, there were also studies that did not mention it. So, we could not determine if they presented a homogeneity in the form of evaluation.

Were they refractory from the patient? Or is it the first time you've been diagnosed with this condition?

Authors: Thanks for your question. Yes, all the studies included in the review patients presented a diagnosis of refractory myofascial pain. They previously received treatment with conventional therapies for at least 6 months. You can view it in the characteristics of the studies.

Study characteristics

“The total sample size of the studies was 314 patients, the subjects being predominantly female, adults between 18 and 75 years of age, all diagnosed with TMD-related myofascial pain, without

complete relief of symptoms after receiving conventional treatment for at least 6 months. The patients were treated with botulinum toxin type A (BTX-A) in concentrations ranging from 100 U to 150 U diluted in 0.1 ml to 1.1 ml of sterile saline, injected into different muscles. In 6 of the 8 studies, BTX-A was injected into the masseter and temporal muscles, whereas in only 2 studies BTX-A was injected into the temporal, masseter, and pterygoid muscles. Each patient received a maximum of 25 to 150 U of BTX-A, with injection of 5 to 50 U at 1, 2, or 3 sites. "

Results of the individual studies: Line 158b: could it be due to different action periods of the 2 different modalities? (One point for the discussion part).

Authors: We cannot determine it, although the study mentions that the application of botulinum toxin was performed once for each patient and the dry needling technique consisted of rapidly puncturing 8 to 10 times at the point of activation of the muscle band with the tip of the needle. We could not be totally sure as the study does not specify whether it was just a dry needling session.

“Injected into the predetermined trigger point in the lateral pterygoid muscle under the US guide after cleansing the skin with an antiseptic. A sterile 22 g 1.5 inch syringe was advanced to reach the trigger point and 25 (0.5 cc) of Dysport was injected intramuscularly for each trigger point after negative aspiration. This practice was carried out once for each patient. The botulinum toxin injections were manufactured in volumes ranging from 25 U to 150 U, not to exceed 150 U in total. For 20 patients in the dry needling treatment, 38 mm long a needle with a green tip was used (Fig. 1). Following proper skin preparation, the needle was held perpendicular to the skin and the subcutaneous tissue was quickly entered. The needle was inserted into the muscle until the trigger point where the muscle band with the tip was found. The same point was rapidly punctured 8-10 times with the needle tip mounted on the empty syringe. The following clinical parameters were assessed at baseline and at 6 weeks, and the findings were compared within each group and between groups. The injection was carried out by the first author, who had experience in this field ”

Discussion: Lines 209-210 need a reference.

Authors: We added this reference.

“Due to its non-invasive and reversible characteristics, the oral appliance is probably the most widely used therapy to reduce the symptoms of myofascial pain. 50 In our review, the oral appliance was equally effective as BoNT-A therapy; The study authors found no significant differences between the two treatments, 50 this could be due to the fact that the effect in both treatments is

observed days after the start of treatment, that is, it has a cumulative effect. Therefore, we can point out that BTX-A compared with conventional treatments (oral appliances, fascial manipulation technique, low-level laser and dry needling) presents similar results. However, despite the aforementioned lines, a definitive result cannot be established since from the summary of certainty of the evidence using GRADE, the studies showed moderate to low certainty in the evidence (see Table 3). They also had limitations such as: RCTs with small sample sizes and short follow-up periods."

References:

ref 6: skip the parentheses and add a. before the name of the magazine.

ref 11: correct Doi to doi.

ref 26: correct the doi.

ref 33: correct the page numbering as was done for the other ref.

ref 37: correct the page numbering as was done for the other ref.

ref 42: correct the page numbering as was done for the other ref.

ref 49: missing doi.

ref 50: correct the page numbering as was done for the other ref.

Authors: Thanks for your suggestion. Now, the authors have modified and updated (some of these references have been renumbered for the reason that references were added to expand the requested definitions) these references as follows:

6. *Khudoroshkov YG, Ishmurzin PV, Danilova MA. The impact of interna TMJ disorders on quality of life of patients with malocclusion. Stomatology. 2015; 94 (5): 55-7. doi: 10.17116 / stomat201594555-57*
11. *Lavigne GJ, Sessle BJ. The Neurobiology of Orofacial Pain and Sleep and Their Interactions. J Dent Res. 2016; 95 (10): 1109-16. doi: 10.1177 / 0022034516648264*
26. *Wieckiewicz M, Boening K, Wiland P, Shiau YY, Paradowska-Stolarz A. Reported concepts for the treatment modalities and pain management of temporomandibular disorders. J Headache Pain. 2015; 16 (1): 106. doi:https://doi.org/10.1186/s10194-015-0586-5*

References that have been renumbered:

Before ref. 49 now ref. 51

51. Gupta A, Aggarwal A, Aggarwal A. *Effect of botulinum toxin A on myofascial pain in temporomandibular disorders: a randomized, double-blind, placebo-controlled study. Indian J Pain. 2016; 30 (3): 166-70. doi: 10.4103 / 0970-5333.198013*

ref 37: correct the page numbering as was done for the other ref. (now ref. 38)

ref 42: correct the page numbering as was done for the other ref. (now ref. 44)

ref 50: correct the page numbering as was done for the other ref. (now ref. 52)

Reviewer 3:

Line 9 has a typo: it should be TMD; and you should add “patients”: TMD patents present....

Authors: Thanks for the suggestion. Now, the authors have corrected the error in the translation.

Likewise, the word patients was added in the paragraph as follows:

“Patients with TMD present with pain, 11-20 limitation of movement, dysfunction, fatigue, subjective weakness, and stiffness of the facial and chewing muscles.²¹ In addition, within the TMD is the subgroup corresponding to musculoskeletal disorders, the most prevalent of which are localized myalgia and myofascial pain. 17 Myofascial pain can present with acute to moderate intensity and is characterized by the presence of sensitive areas called trigger points, located in bands, tendons and muscle fascicles, generating deep and localized pain in the tense muscular band . However, pain can also occur in other areas distant from the trigger point.^{17,21-23} ”

Line 10 another typo

Authors: Thanks for the suggestion. Now, we have fixed the error in the translation as follows:

“Patients with TMD present with pain, 11-20 limitation of movement, dysfunction, fatigue, subjective weakness, and stiffness of the facial and chewing muscles.²¹ In addition, within the TMD is the subgroup corresponding to musculoskeletal disorders, the most prevalent of which are localized myalgia and myofascial pain. 17 Myofascial pain can present with acute to moderate intensity and is characterized by the presence of sensitive areas called trigger points, located in bands, tendons and muscle fascicles, generating deep and localized pain in the tense muscular band . However, pain can also occur in other areas distant from the trigger point.^{17,21-23} ”

Line 47: delete point after post

Authors: Thanks for the suggestion. Now, we have corrected the misspelling as follows:

“The search for studies was carried out regardless of the year or language of publication in the following electronic databases: MedLine (via PubMed), Scopus, The Cochrane Library, Health”

Line 50: period after parentheses. Also, should you say complementary as you used for table 1 or as complementary you used for table 2? Make sure it's consistent. Maybe it just says Appendix 1 and 2?

Authors: Thanks for the suggestion. Now, we have corrected the spelling error.

“The search for studies was carried out regardless of the year or language of publication in the following electronic databases: MedLine (via PubMed), Scopus, La Biblioteca Cochrane, Salud de América Latina y el Caribe (LILACS), Embase, Web of Science and a partial search of gray literature using keywords up to the date February 2021 (Supplementary Table 1). In addition, to”

In Results- Characteristics of the study, it would be informative to know in the text what type of journals were published. You can have more than 1 selected study published in a specific journal....

Authors: Thanks. We controlled that. First Table 1 describe the type of study selected. Also, the reference lists of the selected articles were checked to ensure that no potential articles were lost. Articles were saved and managed in EndNote software (EndNote X7® BasicThomson Reuters, NewYork, USA) to avoid possible duplication. Furthermore, Study selection was carried out by two reviewers (RMRH and KJAS) independently in two phases. In the first phase, the authors screened titles and abstracts identified from the results of the electronic database and additional sources, then studies with titles and abstracts that did not meet the inclusion criteria and duplicate studies were removed.

I think in the Discussion section the cumulative effect of BTX and the comparisons with other therapies should be clearer. We cannot assume that the effect of BTX is not better due to the cumulative effect. Evaluation of the effect of BTX should be done after a few days (when it shows effect) and then compared with other therapies. This should be made clearer. You may add that the evaluation of the immediate effect of BTX cannot be compared with other therapies. Only the

medium and long-term effect should be compared due to the cumulative effect. It appears that BTX and facial manipulation or laser had the same effect after 3 months. Also, 2 studies found no significant difference compared to placebo. And there are no differences with acupuncture

Authors: Thanks for the suggestion. Now, the authors have modified the description as a suggestion of the reviewer. As follows:

“The fascial manipulation technique has been shown to be more effective in the immediate relief of self-reported pain compared to BTX-A treatment. 20 However, the difference between the two treatment protocols was not clinically significant at 3-month follow-up, and both treatments were found to be equally effective in reducing pain. 20 This difference could be due to the multiple sessions (3 ± 1) that patients received compared to BTX-A treatment that was only performed in a single session. The relaxing and calming effect that the operator transmits by exerting deep digital pressure with the fingertips or elbows on the muscle areas (establishing a positive relationship) during the 50-minute sessions could also have had a psychological influence, compared to BTX -A, which has a cumulative effect. 20 It should be noted that the evaluation of the immediate effect of BTX- A cannot be compared with other therapies. It should be done days later when the effects appear, that is, its results should be compared in the medium and long term due to the cumulative effect. Similar results were found when low-level laser was compared to BTX-A”

Add more information on the facial manipulation technique used.

Authors: Thanks for the suggestion. Now, the authors have expanded the information on the fascial manipulation technique as follows:

“The fascial manipulation technique has been shown to be more effective in the immediate relief of self-reported pain compared to BTX-A treatment. 20 However, the difference between the two treatment protocols was not clinically significant at 3-month follow-up, and both treatments were found to be equally effective in reducing pain. 20 This difference could be due to the multiple sessions (3 ± 1) that patients received compared to BTX-A treatment that was only performed in a single session. The relaxing and calming effect that the operator transmits by exerting deep digital pressure with the fingertips or elbows on the muscle areas (establishing a positive relationship) during the 50-minute sessions could also have had a psychological influence, compared to BTX -A, which has a cumulative effect. 20 It should be noted that the evaluation of the immediate effect of BTX- A cannot be compared with other therapies. It should be done days later when the effects

appear, that is, its results should be compared in the medium and long term due to the cumulative effect. Similar results were found when low-level laser was compared to BTX-A ”

Line 205: compared instead of bought?

Authors: Thanks for the suggestion. Now, we have corrected the spelling error.

*“Therefore, we can point out that BTX-A **compared** with conventional treatments (oral appliances, fascial manipulation technique, low-level laser and dry needling) presents similar results. ”*

In conclusion: "Botulinum toxin appears to be as effective in controlling myofascial pain related to temporomandibular disorders as conventional treatments." It would be more informative to include the types of conventional treatments. Consider adding: "based on studies with moderate to low methodological quality". Explain better: "However, as it does not depend on the collaboration of the patient"

Authors: Thanks for the suggestion. Now, we have mentioned the conventional therapies of the included articles. We also place the methodological quality and improve the explanation of our conclusions as a suggestion of the reviewer as follows:

Conclusions

Based on studies with moderate to low methodological quality, it is concluded:

- *Botulinum toxin appears to be as effective in controlling myofascial pain related to temporomandibular disorders as conventional treatments (**oral appliance, lidocaine injections, low intensity laser, dry needling technique, saline injections and facial manipulation technique**).*
- *Botulinum toxin is a useful clinical alternative as an adjunct to existing conservative treatments for the treatment of refractory myofascial pain related to temporomandibular disorder.*
- *For the control of refractory myofascial pain related to temporomandibular disorders, botulinum toxin should ideally be administered in low doses to avoid adverse effects related to high doses.*

Be clearer also in the summary.

Authors: Thanks for the suggestion. Now, we have modified our summary as the reviewer's suggestion as follows:

Summary

Botulinum toxin is used as an alternative for the treatment of refractory myofascial pain derived from temporomandibular disorders. It is important to establish the benefits of botulinum toxin in this type of symptomatology. The objective was to conduct a systematic review to evaluate the effects of botulinum toxin in patients with myofascial pain related to temporomandibular disorders. The search was carried out systematically, without limitations of language or year of publication until February 2021. The databases included were PubMed, Web of Science, Scopus, The Cochrane Library and Lilacs. Partial gray literature was also searched using Academic Google, ClinicalTrials.gov, Open Gray, and the reference lists of selected articles. Randomized controlled clinical trials evaluating the effects of botulinum toxin in the treatment of myofascial pain were included. Risk of bias was assessed with the Cochrane RoB 2.0 tool and GRADE was used to determine the certainty of the scientific evidence. A total of 900 studies were retrieved, of which only 8 randomized clinical trials were selected. From these 8 studies a total of 314 patients, predominantly women, between the ages of 18 to 75 years were obtained. After assessment of the studies with the RoB 2.0 tool, seven studies showed some concerns regarding the reported results and only one was at low risk of overall bias. Low doses of botulinum toxin are effective for the treatment of refractory myofascial pain associated with temporomandibular disorders. The studies presented medium to low-certainty evidence.

Supplemental Table 2 may not be needed. You can add that information in text.

Authors: Thanks for the suggestion. Now, we have text the reasons for exclusion of the 2 studies.

All of these changes were highlighted in red in the final manuscript as follows:

“Two studies were excluded, of which 1 was excluded for not specifying the diagnosis of temporomandibular disorder and the other because it could not be obtained in full text. 45-46 Eight studies were finally included in this systematic review, and the sequence and complete search are detailed in the PRISMA flow chart (Figure 1). ”

Efectos de la toxina botulínica en pacientes con dolor miofascial relacionado con trastornos de la articulación temporomandibular: una revisión sistemática

Introducción

La Academia Estadounidense de Dolor Orofacial (AAOP) define el trastorno temporomandibular (TMD) como un término genérico que contiene una serie de problemas clínicos que afectan la articulación temporomandibular, los músculos masticatorios y las estructuras asociadas.^{1,2} El trastorno temporomandibular tiene una etiología multifactorial que involucra factores biológicos, infecciosos, hormonales, psicológicos, sociales y emocionales.^{3, 4, 5, 6, 7, 8, 9, 10}

Los pacientes con TMD presentan dolor,^{11, 12, 13, 14, 15, 16, 17, 18, 19, 20} limitación del movimiento, disfunción, fatiga, debilidad subjetiva y rigidez de los músculos faciales y masticatorios.²¹ Además, existe un subgrupo dentro de la TMD que corresponde a los trastornos musculoesqueléticos, siendo los más prevalentes las mialgias localizadas y el dolor miofascial.¹⁷ El dolor miofascial puede presentarse con intensidad aguda a moderada y se caracteriza por la presencia de zonas sensibles denominadas puntos gatillo, ubicadas en fajas, tendones y fascículos musculares, y que generan un dolor profundo y localizado en la faja muscular tensa. Sin embargo, el dolor también puede ocurrir en otras áreas distantes del punto gatillo.^{17, 21, 22, 23}

Se han propuesto diferentes abordajes de tratamiento que incluyen terapias conservadoras como la farmacoterapia,^{4, 24, 25, 26} fisioterapia,^{14, 27, 28} ultrasonido, electroestimulación nerviosa transcutánea,¹⁷ terapia oclusal (férulas oclusales),^{29, 30, 31, 32} y psicoterapia.^{26, 33, 34, 35} Por otro lado, también están disponibles procedimientos más invasivos como la punción seca y la acupuntura.¹⁷ Sin embargo, incluso después de recibir estos tratamientos, los síntomas pueden persistir parcialmente. En esta condición crónica, la toxina botulínica tipo A (BTX-A) se ha utilizado recientemente como la alternativa para el alivio más prolongado de los síntomas del dolor miofascial crónico refractario.^{20, 28, 36, 37, 38}

La BTX-A es una exotoxina sintetizada por una bacteria anaeróbica gramnegativa formadora de esporas llamada *Clostridium botulinum*. Esta potente neurotoxina botulínica ejerce su acción en la unión presináptica de las neuronas motoras alfa y gamma mediante el bloqueo del Ca.³⁵ Tiene un mecanismo de acción dual sobre la unión neuromuscular como la inhibición de la exocitosis de la acetilcolina de las placas nerviosas (debilitamiento temporal de las terminaciones nerviosas y consecuente relajación de la contracción muscular o parálisis, dependiendo de la dosis, sin ningún

efecto sistémico) y la inhibición de la liberación de sustancia P y glutamato para reducir el dolor inflamatorio.³⁹

A pesar de los factores mencionados, aún falta unificación y recopilación de información científica sobre los beneficios de la terapia con BTX-A. Por lo tanto, el objetivo de esta revisión sistemática fue evaluar los efectos de la toxina botulínica en pacientes con dolor miofascial relacionado con TMD.

Material y métodos

Protocolo y registro

La presente revisión se llevó a cabo siguiendo el Manual Cochrane para Revisiones Sistemáticas de Intervenciones,⁴⁰ y se informó según lo sugerido utilizando las pautas de Elementos de informe preferidos para revisiones sistemáticas y metanálisis (PRISMA).⁴¹ Asimismo, el protocolo del estudio fue registrado en la base de datos del PROSPERO Center for Reviews and Dissemination (CRD) de la Universidad de York (Heslington, UK), y del National Institute for Health and Care Research (Londres, UK),⁴² bajo el número: CRD42020168889.

Criterio de elegibilidad

Para definir los criterios de elegibilidad se utilizó el acrónimo PICOS (Population, Intervention, Comparison, Outcomes and Study design):

Población: Pacientes adultos con dolor miofascial relacionado con TMD.

Intervención: Tratamiento de inyección de toxina botulínica para el dolor miofascial.

Comparación: Ningún tratamiento, placebo u otro tratamiento específico, incluida la fisioterapia, las férulas oclusales, la farmacoterapia o la acupuntura.

Resultado primario: Cambios en la intensidad del dolor miofascial debido al tratamiento con toxina botulínica.

Medidas de efecto: Cambios desde la línea de base hasta el último seguimiento disponible medidos por escalas analógicas visuales o herramientas similares; y

Diseño del estudio: Ensayos clínicos aleatorizados (ECA) realizados en humanos.

Los criterios de exclusión incluyeron estudios en niños o adolescentes, estudios sobre anomalías cráneo faciales o enfermedades neuromusculares, literatura o revisiones sistemáticas, cartas al editor, estudios piloto, estudios de informes de casos, estudios in vitro y estudios en animales.

Fuentes de información, estrategia de búsqueda y selección de estudios

La búsqueda de estudios se realizó independientemente del idioma o año de publicación en las siguientes bases de datos electrónicas: MedLine (vía PubMed), Scopus, The Cochrane Library, Latin American and Caribbean Health Sciences Literature (LILACS), Embase, Web of Science. Además, se realizó una búsqueda parcial de literatura gris utilizando palabras clave

específicas hasta febrero de 2021 (los datos detallados están disponibles del autor correspondiente a pedido razonable), utilizando las bases de datos Google Scholar, Open Grey y ClinicalTrials.gov. Los primeros 100 registros se buscaron utilizando Google Scholar. Además, se revisaron las listas de referencias de los artículos seleccionados para asegurar que no se perdieran artículos potenciales. Los artículos se gestionaron mediante el software EndNote (Thomson Reuters EndNote X7 ®; Nueva York, EE. UU.) para evitar posibles duplicidades.

La selección de estudios se llevó a cabo de forma independiente en 2 fases por 2 revisores (RMRH y KJAS). En la primera fase, los revisores revisaron los títulos y resúmenes identificados a partir de los resultados de la base de datos electrónica y fuentes adicionales. Luego, se eliminaron los estudios con títulos y resúmenes que no cumplieran con los criterios de inclusión y los estudios duplicados. En la segunda fase, se recuperaron los estudios de texto completo para confirmar su elegibilidad, de acuerdo con los criterios de inclusión. También se evaluaron las listas de referencias de los artículos seleccionados. Los revisores seleccionaron de forma independiente los artículos para incluirlos en una síntesis cualitativa. Los desacuerdos se resolvieron mediante discusión verbal y se llegó a un consenso con la ayuda de un tercer revisor (LEAG), cuando fue necesario.

Proceso de recopilación de datos y elementos de datos

Dos revisores (RMRH y KJAS) extrajeron de forma independiente los datos de los estudios incluidos mediante una hoja de cálculo de Excel estandarizada. Se extrajeron los siguientes datos: diseño del estudio, sexo y edad del paciente, tamaño de la muestra, diagnóstico de TMD, diagnóstico de dolor miofascial, músculos implicados, abordaje del tratamiento, zona de aplicación de la toxina botulínica, número de dosis y tiempo de tratamiento. Al inicio del estudio, se planificó incluir los resultados sobre la calidad de vida de los pacientes. Sin embargo, esto no fue posible ya que ninguno de los estudios seleccionados para la revisión evaluó esta variable. Para aclarar y resolver dudas sobre los estudios, contactamos a los autores por correo electrónico.

Riesgo de sesgo en estudios individuales

La evaluación del riesgo de sesgo (RoB) de los ECA se realizó mediante la herramienta Cochrane Risk of Bias (RoB 2.0; Cochrane, Londres, Reino Unido).⁴³ Se consideraron los siguientes dominios: proceso de aleatorización, desviaciones de las intervenciones planificadas, datos de resultados faltantes, medición de resultados y selección del resultado informado. Cada dominio se evaluó con: bajo riesgo de sesgo, algunas preocupaciones o alto riesgo de sesgo. Luego, se asignó

un juicio RoB general a cada estudio como: bajo riesgo (si todos los dominios tenían un RoB bajo), algunas preocupaciones (si en al menos un dominio hubo algunas preocupaciones) o alto riesgo (si en uno o más dominios hubo algunas preocupaciones).⁴³

Además, el grado de certeza de la evidencia en los estudios se evaluó mediante el enfoque The Grading of Recommendations Assessment, Development and Evaluation (GRADE)⁴⁴ según las categorías (alta, moderada, baja y muy baja).

Ambos revisores (RMRH y KJAS) evaluaron de forma independiente el riesgo de sesgo y la certeza de la evidencia de los estudios incluidos. Las discrepancias se resolvieron mediante discusión verbal y consulta con el tercer revisor (LEAG).

Resumen de medidas

Las medidas de resultado primarias se basaron en datos cuantitativos (eficacia de la terapia con toxina botulínica en el dolor miofascial relacionado con TMD después de la inyección de toxina botulínica). Las diferencias de medias y los intervalos de confianza (IC) del 95 % para los cambios se evaluaron en función de las respuestas de los pacientes, utilizando una escala analógica visual (VAS).

Síntesis de los resultados

Los datos recopilados de los estudios incluidos se sintetizaron y analizaron en una tabla de descripción. Tras la evaluación y teniendo en cuenta las diferencias entre los protocolos de inyección de toxina botulínica, el tamaño de la muestra, las dosis y los periodos de seguimiento, se consideró que la metodología de los estudios no era homogénea. Por esta razón, no se realizó un metanálisis.

Resultados

Selección de estudios

En la primera fase de la estrategia de búsqueda, se identificaron un total de 787 estudios en las bases de datos electrónicas (570 en PubMed, 5 en Scopus, 24 en LILACS, 15 en Embase, 60 en Web of Science y 113 en Cochrane Library). Además, se encontraron 113 estudios durante la búsqueda parcial de la literatura gris (100 en Google Scholar, 13 en ClinicalTrials.gov) publicados entre 2008 y 2020. No se recuperaron estudios de OpenGrey ni de las listas de referencia. Un total de 890 estudios fueron eliminados por estar duplicados y no cumplir con los criterios de elegibilidad después de la lectura de los títulos y resúmenes. Se obtuvieron diez estudios para evaluación de texto completo según los criterios de inclusión y exclusión. Se excluyeron dos estudios, de los cuales uno se excluyó por no especificar el diagnóstico de TMD y el otro porque no se pudo obtener el texto completo.^{45, 46} Finalmente, 8 estudios fueron incluidos en esta revisión sistemática. La secuencia y búsqueda completa se detallan en el diagrama de flujo PRISMA (Figura 1). Los 8 estudios fueron ECA.^{20, 47, 48, 49, 50, 51, 52, 53} La tabla 1 muestra las características de los estudios incluidos.

Características del estudio

Se incluyó en el análisis un tamaño de muestra de 314 pacientes, siendo los sujetos adultos entre 18 y 75 años, predominantemente mujeres, diagnosticados con dolor miofascial relacionado con TMD, sin alivio completo de los síntomas después de recibir tratamiento convencional durante al menos 6 meses. Los pacientes fueron tratados con BTX-A en concentraciones que oscilaban entre 100 U y 150 U diluidas en 0,1 ml a 1,1 ml de solución salina estéril, inyectadas en diferentes músculos. En 6 de los 8 estudios, se inyectó BTX-A en los músculos masetero y temporal, mientras que en solo 2 estudios se inyectó BTX-A en los músculos masetero, temporal y pterigoideo. Cada paciente recibió un máximo de 25-150 U de BTX-A, con una inyección de 5-50 U de BTX-A en 1, 2 o 3 sitios.

Riesgo de sesgo dentro del estudio

La evaluación del riesgo de sesgo de los 8 ECA incluidos^{20, 47, 48, 49, 50, 51, 52, 53} se realizó mediante la herramienta Cochrane RoB 2.0.⁴³ De los 8 estudios, solo uno tenía un bajo riesgo de sesgo,⁵⁰ mientras que en los 7 estudios restantes se han planteado algunas preocupaciones con respecto a la selección del resultado informado en los estudios que describen múltiples medidas de resultado (escalas y puntos de tiempo, entre otros). Sin embargo, no se muestran en detalle todos los

datos de los resultados obtenidos, evidenciando una falta de información sobre los resultados.^{20, 47, 48, 49, 51, 52, 53} La evaluación de los estudios se muestra en la tabla 2 y la figura 2 .

Resultados de estudios individuales

Todos los estudios incluidos en la presente revisión sistemática evaluaron cambios en el rango de intensidad del dolor. Tres estudios compararon BTX-A (grupo de estudio) con inyecciones de solución salina (grupo placebo),^{47, 51, 53} un estudio comparó BTX-A (grupo de estudio) con inyecciones de solución salina (grupo placebo) y lidocaína (grupo control),⁴⁹ otro estudio comparó un láser de baja intensidad (grupo de estudio) con BTX-A⁴⁸ , otro estudio comparó BTX-A (grupo de estudio) con la técnica de punción seca (grupo control)⁵² , otro comparó BTX-A (grupo de estudio) con la técnica de fascia técnica de manipulación (grupo de control),²⁰ y solo un estudio comparó 3 concentraciones diferentes de BTX-A con solución salina fisiológica (grupo de control negativo) y con aparato bucal (grupo de control positivo).⁵⁰

El estudio que evaluó la seguridad y eficacia de 3 dosis diferentes de neurotoxina botulínica tipo A (BoNT-A) (dosis baja de BoNT-A (BoNT-AL), dosis media de BoNT-A (BoNT-AM) y dosis alta de BoNT-A (BoNT-AH)) mostró una disminución significativa en la intensidad del dolor subjetivo en los 3 grupos, independientemente de la dosis administrada. Además, no se encontraron diferencias significativas entre los 3 grupos⁵⁰ , lo que demuestra que incluso a dosis bajas, la BoNT-A puede ser igualmente efectiva hasta 6 meses después de la administración.^{49, 50}

Cuatro de los estudios que compararon BTX-A con solución salina mostraron que las inyecciones de BTX-A fueron clínicamente efectivas para reducir el dolor^{47, 50, 51, 53} y aumentaron el umbral del dolor a la presión más que la solución salina.⁵⁰

Otro estudio evaluó la eficacia de BTX-A en el tratamiento del síndrome de dolor miofascial masticatorio refractario (MMPS) y clasificó el dolor miofascial como localizado (MP), no localizado, irradiado o referido (PR). Los resultados mostraron que los cambios en los valores de intensidad del dolor fueron estadísticamente significativos para el grupo BTX-A (todos los pacientes mostraron una reducción del dolor desde el día 0 hasta el día 180, excepto los grupos de solución salina y lidocaína). Asimismo, al comparar el grupo MP con el grupo PR que recibió TXB-A, la

reducción del dolor según la EVA fue mayor en el grupo MP, disminuyendo de 6 a 2 puntos y de 6,5 a 4 puntos, respectivamente. Aunque se observó una disminución significativa del dolor, no se alcanzaron valores muy bajos en el grupo PR. ⁴⁹

Tras comparar la terapia con láser de baja intensidad con las inyecciones de BTX-A ⁴⁸, no hubo diferencias estadísticamente significativas entre los 2 tratamientos con respecto al dolor a los 30 días de seguimiento. Este estudio reportó una EVA basal de 7 puntos en ambos grupos, con una disminución a 2,75 el día 12 en el grupo láser y a 2,86 en el grupo BTX-A el día 30, demostrando que ambos tratamientos fueron estadísticamente efectivos. Sin embargo, los efectos de la terapia con láser de bajo nivel fueron más rápidos en comparación con las inyecciones de BTX-A (la reducción observada en el día 12 frente al día 30, respectivamente). Estos resultados deben tenerse en cuenta en futuros estudios. ⁴⁸

Otro tratamiento comparado con la inyección de BTX-A fue la técnica de punción seca ⁵², en la que se evaluó la eficacia sobre el dolor miofascial durante la masticación y el reposo. Ambos tratamientos lograron una mejora significativa en las puntuaciones de la EVA durante las 6 semanas de seguimiento. Sin embargo, con respecto al dolor miofascial en reposo, el alivio fue mayor con la técnica de punción seca. Uno de los 8 estudios incluidos comparó la BTX-A con la técnica de manipulación fascial. ²⁰ Ambos protocolos de tratamiento mejoraron y disminuyeron significativamente la intensidad del dolor miofascial, sin diferencias clínicas relevantes entre los 2 protocolos durante los 3 meses de seguimiento.

Cuando se comparó la BoNT-A (independientemente de la dosis) con el dispositivo oral, el estudio mostró que ambos tratamientos fueron igualmente efectivos en el tratamiento del dolor miofascial persistente durante el seguimiento de 24 semanas y no hubo diferencia estadística hasta el último período de seguimiento. -arriba. Sin embargo, el autor también informó una reducción en la actividad muscular y una disminución en el grosor muscular y el volumen óseo de los procesos condiloide y coronoides como efectos adversos relacionados con la dosis de BoNT-A (dosis más altas). Por lo tanto, la BoNT-A en pacientes con dolor miofascial debe administrarse idealmente en dosis bajas. ⁵⁰

No se pudo realizar un metanálisis debido a la heterogeneidad de los resultados (diferencias en los protocolos de inyección de toxina botulínica, tamaños de muestra, dosis y períodos de seguimiento).

La evaluación del nivel de evidencia mediante el enfoque GRADE mostró que los 8 ECA incluidos ^{20, 47, 48, 49, 50, 51, 52, 53} presentaron evidencia de certeza moderada a baja. En la Tabla 3 se muestra una descripción detallada .

Discussion

Actualmente, no existe un consenso sobre el protocolo de tratamiento más adecuado para el dolor miofascial. Se recomienda un abordaje multidisciplinario y un tratamiento de primera línea, comenzando con la terapia convencional. Sin embargo, algunos pacientes no logran un alivio completo del dolor y son diagnosticados con dolor miofascial refractario. Las inyecciones intramusculares con BTX-A han sido propuestas en la literatura como una alternativa de tratamiento para estos casos, ya que esta neurotoxina induce un mecanismo de acción sobre la unión neuromuscular, inhibiendo la exocitosis de acetilcolina de las placas terminales nerviosas y provocando la relajación de la contracción muscular y el dolor. ³⁵A pesar de esto, hasta la fecha, la eficacia de este tratamiento no está muy clara y, por lo tanto, el objetivo de esta revisión sistemática fue sintetizar la información actual sobre los efectos de la toxina botulínica en pacientes con dolor miofascial relacionado con los TMD.

En la presente revisión sistemática, las inyecciones de BTX-A demostraron ser significativamente efectivas para reducir la intensidad del dolor miofascial ^{20, 47, 48, 49, 50, 51, 52, 53} independientemente de la dosis utilizada (alta, media, baja). ⁵⁰ Esto se evidencia en estudios que comparan BTX-A con placebo, ^{47, 49, 50, 51, 53} que demostraron una reducción del dolor clínicamente más eficiente con BTX-A en comparación con placebo. ^{49, 51} Sin embargo, 2 estudios encontraron que la diferencia entre los 2 tratamientos no fue estadísticamente significativa. ^{47, 53}

La técnica de manipulación fascial ha demostrado ser más efectiva en el alivio inmediato del dolor autoinformado en comparación con el tratamiento con BTX-A. ²⁰ Sin embargo, la diferencia entre los 2 protocolos de tratamiento no fue clínicamente significativa a los 3 meses de seguimiento, y se encontró que ambos tratamientos eran igualmente efectivos para reducir el dolor. ²⁰ Esta diferencia podría deberse a las múltiples sesiones (3 ± 1) que recibieron los pacientes frente al tratamiento con BTX-A que solo se realizó en una única sesión. El efecto relajante y calmante que transmite el operador al ejercer una profunda presión digital con la yema de los dedos o los codos sobre las zonas musculares (estableciendo una relación positiva) durante las sesiones de 50 min también podría haber tenido una influencia psicológica, en comparación con el tratamiento con BTX-A, que tiene un efecto acumulativo. ²⁰ Cabe señalar que la evaluación del efecto inmediato de la BTX-A no se puede comparar con otras terapias. Dicha evaluación se debe realizar días después cuando aparecen los efectos, es decir, se deben comparar sus resultados a mediano y largo plazo debido al efecto

acumulativo del tratamiento con BTX-A. Se obtuvieron resultados similares cuando se comparó la terapia con láser de baja intensidad con el tratamiento con BTX-A.

Desde el comienzo hasta el último seguimiento del estudio, las inyecciones de lidocaína no fueron significativamente efectivas en el tratamiento del dolor miofascial.⁴⁹ Por el contrario, tanto la técnica de punción seca como la administración de BTX-A mostraron resultados favorables en el alivio del dolor miofascial durante la masticación y en reposo. Además, el alivio del dolor miofascial en reposo fue estadísticamente significativo con la técnica de punción seca.⁵² Asimismo, en un estudio publicado recientemente, De La Torre Canales et al. comparó el tratamiento de acupuntura con BoNT-A y la administración de solución salina. Los investigadores encontraron que las 3 terapias redujeron significativamente el dolor autopercibido después de 1 mes de seguimiento. Sin embargo, no hubo diferencia entre la acupuntura y la BoNT-A. Ambas terapias fueron efectivas y superiores a la solución salina.⁵⁴

Debido a sus características no invasivas y reversibles, el aparato oral es probablemente la terapia más utilizada para reducir los síntomas del dolor miofascial.⁵⁰ En nuestra revisión, el dispositivo oral fue igualmente efectivo que la terapia con BoNT-A. Los autores del estudio no encontraron diferencias significativas entre los 2 tratamientos.⁵⁰ Esto podría deberse a que el efecto de ambos tratamientos se observa días después del inicio del tratamiento, es decir tiene un efecto acumulativo. Por lo tanto, podemos confirmar que la BTX-A comparada con los tratamientos convencionales (aparatos orales, técnica de manipulación fascial, terapia con láser de baja intensidad y técnica de punción seca) presenta resultados similares. Sin embargo, a pesar de la evidencia antes mencionada, no se puede establecer un resultado definitivo ya que el resumen de certeza de la evidencia utilizando el enfoque GRADE mostró certeza moderada a baja en la evidencia de los estudios (ver **Tabla 3**). Además, los estudios tenían limitaciones como tamaños de muestra pequeños y períodos de seguimiento cortos.

Por lo tanto, se necesitan más ECA con tamaños de muestra más grandes, seguimientos más prolongados y la inclusión de varios grupos de control (férulas oclusales, terapia con medicamentos, acupuntura, estimulación nerviosa eléctrica transcutánea (TENS, entre otros) para determinar la efectividad de BTX-A en el tratamiento a largo plazo del dolor miofascial en pacientes con TMD.

Conclusiones

- Según los estudios analizados, la toxina botulínica parece ser tan eficaz para controlar el dolor miofascial relacionado con los TMD como los tratamientos convencionales (aparato oral, inyecciones de lidocaína, terapia con láser de bajo nivel, técnica de punción seca, inyecciones de solución salina y técnica de manipulación fascial).
- La toxina botulínica es un complemento clínico alternativo útil a los tratamientos conservadores existentes del dolor miofascial refractario relacionado con los TMD.
- Para el control del dolor miofascial refractario relacionado con los TMD, la toxina botulínica debe administrarse en dosis bajas para evitar efectos adversos relacionados con la administración de dosis altas.

Aprobación ética y consentimiento para participar

No aplica.

Disponibilidad de datos

Todos los datos analizados durante este estudio se incluyen en este artículo publicado.

Consentimiento para publicación

No aplica

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Table 1. Evidence for the effects of botulinum toxin (BTX-A) in patients with myofascial pain related to temporomandibular disorder (TMD).

<i>Author (Year)</i>	<i>Study design</i>	<i>Sample and Features</i>	<i>Muscle evaluated</i>	<i>Concentration BTX - A</i>	<i>Dosage and administratio n</i>	<i>Follow up</i>	<i>Relevant findings</i>
Ernberg (2011)	Randomized clinical trial	21 patients Control group: Saline solution Isotonic.	Masseter	100 U BTX- A 1.0 ml Saline solution solution 100 U maximum per patient 50U masseter muscle	1 dose, 3 application points on each muscle Control group: 1 dose	1 week before 1 months after and 3 months after.	No significant differences were found in pain reduction between BTX-A and saline injection in patients with persistent myofascial pain.
Guarda (2012)	Randomized clinical trial	30 patients 22 females 3 males (age range 20-71 years). Control group: Driving technique Fascial.	Temporary Masseter	150 U BTX- A for each side treaty.	BTX- A 1 dose Multiple administration points for muscle. Control group: Multiple 50 min sessions 150 min in total	Treatment initiation 1 hour after, and 3 months later.	The two treatments are equally effective in reducing pain in a follow-up of up to 3 months. The increase in mandibular range of motion was slightly greater after BTX-A injections.
Del Carli (2016)	randomized clinical trial	15 patients 13 females 2 males Middle Ages	Temporary Masseter	500 ml BTX-A 1.1 ml saline solution 0.9%	2 doses 2 administration points in the masseter muscle	Before and After treatment.	Both treatments BTX-A like low level laser they were effective, no there is a difference between both treatments regarding pain reduction 30 days later start treatment the low-level laser effect was faster (at 12 days)

		38 years BTX-A group (n = 7) Control group: low-level laser (n = 8)		30 U first session 15 U seconds session	and 1 administration point in the temporalis muscle.		than BTX-A (in 30 days).
Kütük et al (2019)	Randomized prospective	40 patients 29 women 11 men Mean age 33.8 (range, 20 to 60 years). Study group n = 20, Control group: dry needling n = 20	Temporary Pterygoid Side.	500 ml BTX-A 10 cc 0.9% NaCl 25 UA 150 U per patient. 25 (0.5cc) at each trigger point	Study group: 1 dose Dry needling group: The trigger point is injected 8 to 10 times.	Start of treatment and 6 weeks after treatment	Pain at rest was more effective with the dry needling technique after 6 weeks. Both treatments: BTX-A and dry the puncture produced significant pain relief and improved function in patients with myofascial pain.
Kurtoglu et al (2008)	Randomized prospective	24 patients Study group (n = 12) age mean of 29.6 years (range, 16 to 53 years), 10 females 2 males. Placebo group (n = 12) mean age 23.4 years (range, 20 to 34 years), 10 females, 2 males	Masseter Temporary	100 U BTX- A per patient. Study group: BTX-A with 2 cc saline solution. Placebo group: 2 cc solution Saline	1 dose 3 administration points in the masseter muscle and 2 administration points in the temporal muscle (10 U each)	Start of study, to 14 and 28 days thereafter	Pain relief and improvement of psychological state after the BTX- A injections and until the 28th day.
Montes (2020)	Randomized clinical trial	60 patients Age between 18- 75 years BTA Group	Temporal and pterygoid masseter	Group BTA: 100-150 U 50 U in BTX-A 1.25 ml of	1 dose in all groups. 3 administration points in the	Before treatment and at 7, 14, 28, 60, 90 and 180 days	BTX-A significantly reduced pain compared to saline and lidocaine. The effects lasted up to 6 months and was more intense in patients with localized myofascial pain than in referred remote pain.

		(n = 20) Lidocaine group (n = 20) Placebo group: saline solution (n = 20)		solution saline to obtain 4 units of BTA per 0.1 ml of the injection liquid. Lidocaine group: lidocaína 2% with vasoconstrictor. Saline solution group: 0.9% saline solution;	temporal muscle. 3 points on the masseter muscle. 1 point in the lateral pterygoid muscle	after treatment.	
De la Torre et al (2020)	Randomized clinical trial	100 female patients Mean age = 36.8 ± 5.6. Low BONT-A group (n = 20) Group BONT- A medium (n = 20) High BONT-A group (n = 20) Positive control group: Oral administration (n = 20) Negative control group: Physiological serum (n = 20)	Anterior Temporal Masseter	BONT-A groups: 100 U of Botox diluted in different concentrations with 0.9% sterile saline solution. Saline solution group: 0.9% sterile saline solution.	1 dose of 1ml in all BONT-A and Saline groups. 5 administration points in each muscle. Oral administration group: Use during the night.	Before treatment and at 7, 14, 21, 28, 90 and 180 days thereafter.	BoNT-A (Regardless of dose) was more effective in the reduction of persistent myofascial pain than saline solution and was also as effective as the occlusal appliance after 14 days and up to 6 months of follow-up
Gupta et al (2016)	Randomized clinical trial	24 patients Age range: 20 to 50 years. BTX-A group (n = 12)	Anterior Temporal Masseter	10 U of BTX-A at 10 points 30MU for the masseter muscle. 20MU for	1 dose 3 administration points in each masseter muscle. 4 administration	Before and at 14 and 28 days after treatment.	Statistically significant reduction in pain and improvement in function after the administration of BTX-A compared to the placebo that did not present a significant change in a follow-up of up to 8 months.

Control group:
placebo (n =
12)

anterior temporal
muscle. points in each
temporal
muscle.

Control group:
isotonic saline

solution

Table 2. Assessment of risk of bias in randomized clinical trials. Cochrane Tool: RoB 2.0

<i>Author (s) / and</i>	<i>Bias arising from the randomization process</i>	<i>Bias due to deviations from intended intervention</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in the selection of the reported result</i>	<i>Overall</i>
Ernberg et al 2011	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Guarda et al 2012	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
De Carli et al 2016	Low risk	Low risk	Low risk	Some concerns	Some concerns	Some concerns
Kütük et al 2019	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
Kurtoglu et al 2008	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Montes et al 2020	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
De la Torre et al 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gupta et al 2016	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns

Tabla 3. Clasificación del nivel de certeza de la evidencia: Sistema Grading of Recommendations Assessment, Development and Evaluation (GRADE)

<i>Certainty assessment</i>							<i>Summary of findings</i>	<i>Certainty</i>
<i>N ° of studies (Patients)</i>	<i>Study design</i>	<i>Risk of bias</i>	<i>Inconsistency</i>	<i>Indirectness</i>	<i>Imprecision</i>	<i>Publication Bias</i>		
BTX-A compared to saline injections								
5 (69)	RCTs	* Serious	Not serious	Not serious	Not serious	Not suspected	BTX-A had a clinically significant effect on reducing pain in the 1- to 8-month follow-up compared to the saline group that did not present a statistically significant reduction.	⊕⊕⊕○ MODERATE
BTX-A compared to saline and lidocaine injections,								
1 (60)	RCT	* Serious	Not serious	Not serious	● Serious	Not suspected	BTX-A significantly reduced pain compared to saline and lidocaine. The effects lasted up to 6 months and was more intense in patients with localized myofascial pain than in those with referred remote pain.	⊕⊕○○ LOW
BTX-A compared to low-level lasers								
1 (15)	RCT	*Serious	Not serious	Not serious	● Serious	Not suspected	Both treatments were effective, no difference between both treatments with respect to pain reduction 30 days after starting treatment.	⊕⊕○○ LOW

BTX-A compared to dry needling technique

1 (40)	RCT	* Serious	Not serious	Not serious	● Serious	Not suspected	Both treatments showed significant pain relief at the 6-week follow-up.	⊕⊕○○ LOW
BTX-A compared to facial manipulation technique								
1 (30)	RCT	* Serious	Not serious	Not serious	● Serious	Not suspected	Both treatments were effective in reducing myofascial pain for up to 3 months of follow-up up.	⊕⊕○○ LOW
BTX-A (3 different concentrations) compared with saline and oral apparatus.								
1 (100)	RCT	Not serious	Not serious	Not serious	● Serious	Not suspected	BoNT-A (Regardless of dose) was more effective in reduction of persistent myofascial pain than physiological serum and was also equally effective as occlusal appliance at 14 days and up to 6 months of follow-up.	⊕⊕⊕○ MODERATE

RCT: randomized clinical trial. Reasons for evaluation: *The evidence was downgraded by one level due to some limitations. ● The evidence was downgraded by one level because the results were derived from a single study and few participants.

Complementary table 1. Electronic databases and keywords.

<i>Electronic database</i>	<i>Keywords</i>
PUBMED (n = 570)	Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia AND Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases AND Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A
SCOPUS (n = 5)	Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia AND Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases AND Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A
LILAS- BVS (n = 24)	(Myofacial Pain) OR (dolor miofascial) AND (temporomandibular disorder) AND (Botulinum toxin) AND (Toxina botulínica)
EMBASE (n = 15)	((myofacial AND pain OR myofascial) AND pain AND syndromes OR pain) AND syndrome, AND myofascial AND (((temporomandibular AND joint AND disorders OR disorder,) AND temporomandibular AND joint OR joint) AND disorder, AND temporomandibular OR temporomandibular) AND joint AND disease AND (((((((botulinum AND toxins OR botulinum) AND toxins, AND type AND a OR 'bont a' OR pharmacotherapy OR neurotoxin) AND a, AND botulinum OR clostridium) AND botulinum AND a AND toxin OR clostridium) AND botulinum AND toxin AND type AND a OR botulinum) AND a AND toxin OR toxin,) AND botulinum AND a OR meditoxin OR neuronox OR oculinum OR 'btx a')
SCIENCE WEB (n = 60)	TS=(Myofacial Pain OR Myofascial Pain Syndromes OR Pain Syndrome, Myofascial OR Myofascial Trigger Point Pain OR Trigger Point Pain OR Facial Pain OR Facial Neuralgia) AND (Temporomandibular Joint Disorders OR Disorder, Temporomandibular Joint OR Joint Disorder, Temporomandibular OR Temporomandibular Joint Disease OR Temporomandibular Disorders OR Temporomandibular Dysfunction OR Temporomandibular Pain OR Temporomandibular Joint Dysfunction Syndrome OR Joint Syndrome, Temporomandibular OR Syndrome, TMJ OR Costen Syndrome OR Costen's Syndrome OR TMD Diseases) AND (Botulinum Toxins OR Botulinum Toxins, Type A OR BoNT-A OR Pharmacotherapy OR Neurotoxin A, Botulinum

	OR Clostridium botulinum A Toxin OR Clostridium Botulinum Toxin Type A OR Botulinum A Toxin OR Toxin, Botulinum A OR Meditoxin OR Neuronox OR Oculinum OR BTX-A)
THE COCHRANE LIBRARY (n = 133)	"myofascial pain" AND "Temporomandibular Disorder" OR "TMJ disorder" AND "botulinum toxin-A" AND "BoNT-A"
ACADEMIC GOOGLE (n = 100)	Myofascial Pain AND Temporomandibular Joint Disorders AND Botulinum Toxin
OPEN GRAY (n = 0)	Myofacial Pain AND Botulinum Toxin / Myofascial Pain AND Botulinum Toxin
CLINICAL TRIALS (n = 13)	Condition or disease: Botulinum toxin Other terms: myofascial pain Study type: Interventional studies (clinical trials)

Supplementary Table 2. Reasons for excluding studies after full text assessment.

<i>Reasons for exclusion</i>	<i>Number of studies</i>
The study did not specify the diagnosis of temporomandibular disorder.	1
Study published in Russian language and I cannot access it.	1

Fig. 1. Diagrama de flujo de PRISMA (elementos de informe preferidos para revisiones sistemáticas y metanálisis)

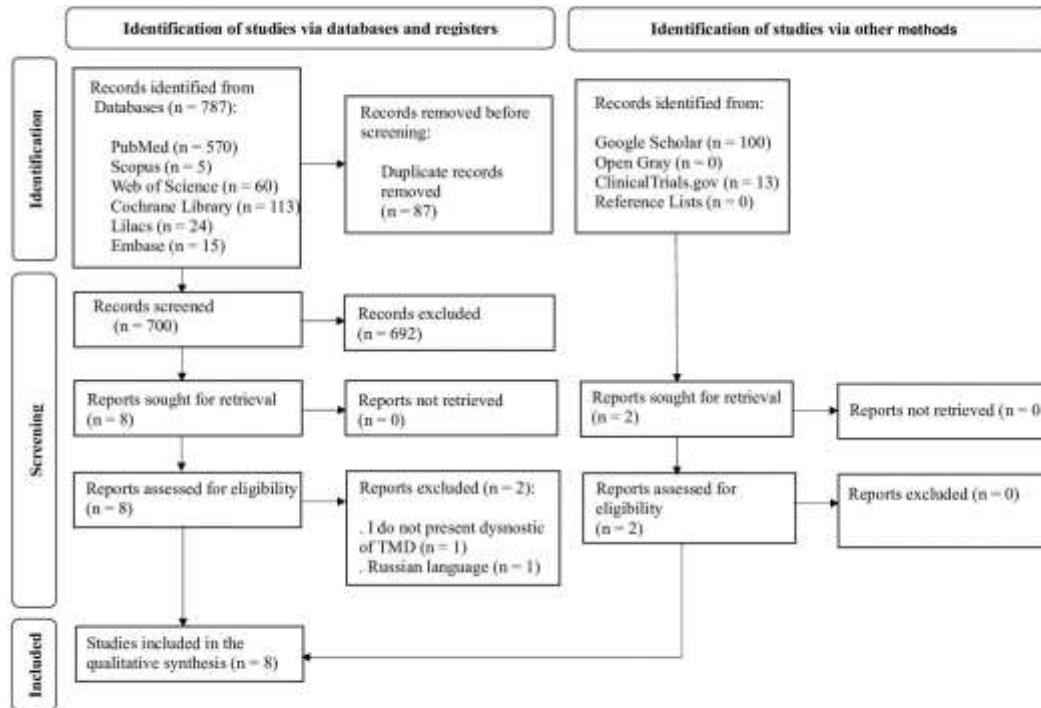
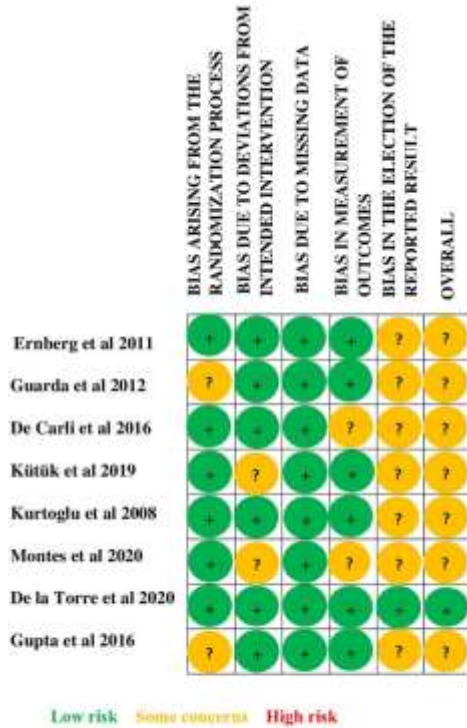


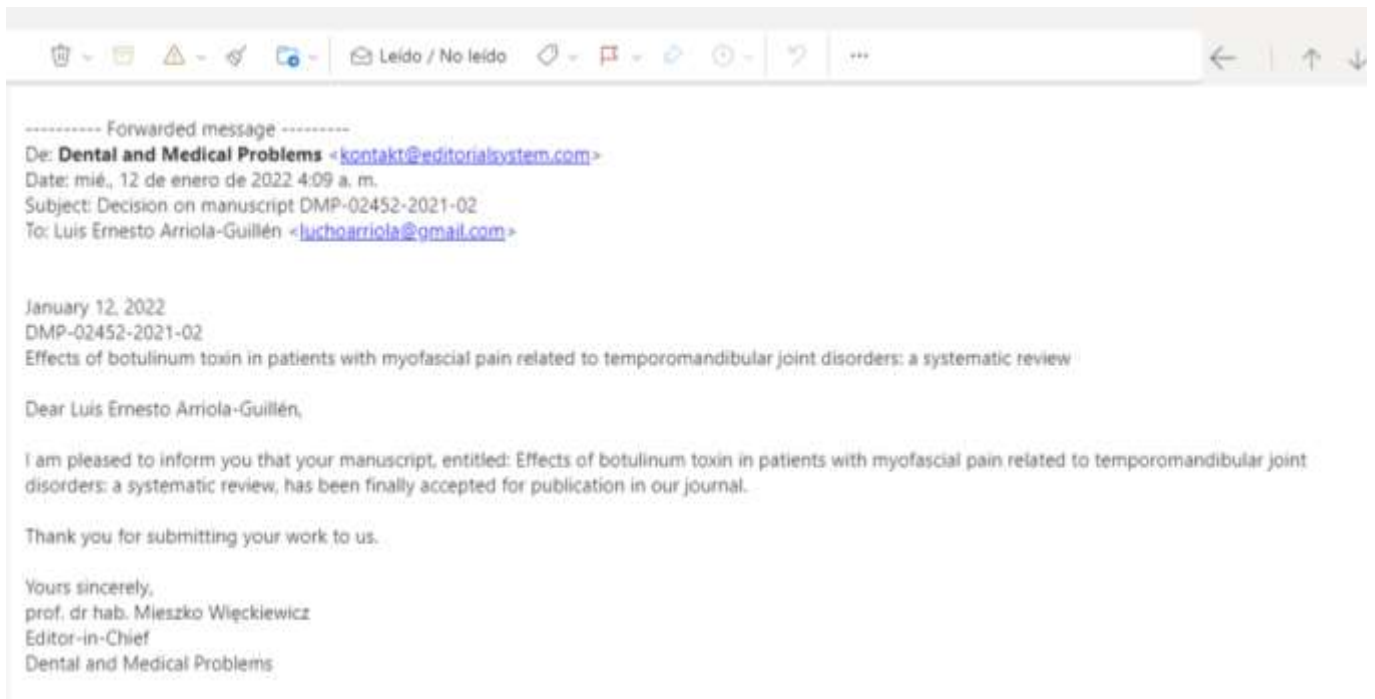
Figura 2. Evaluación de los estudios incluidos en términos de riesgo de sesgo



Abreviaturas

ABREVIATURA	
AAOP	La Academia Estadounidense de Dolor Orofacial
TMD	Trastorno temporomandibular.
BTX-A	Toxina botulínica tipo A.
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
CRD	Center for Reviews and Dissemination
PICOS	Population, Intervention, Comparison, Outcomes and Study design
ECA	Ensayos clínicos aleatorizados
LILAS- BVS	Latin American and Caribbean Health Sciences Literature
RMRH	Rosa Marina Ramos Herrada
KJAS	Katherine Joselyn Atoche-Socola
LEAG	Luis Ernesto Arriola-Guillén
RoB 2.0	Una herramienta Cochrane de riesgo de sesgo revisada para ensayos aleatorios
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
IC	Intervalos de confianza
VAS	Escala analógica visual
U	Unidad de medida.
ml	Mililitros
BoNT-A	Neurotoxina botulínica tipo A
BoNT-AL	Dosis baja de BoNT-A
BoNT-AM	Dosis media de BoNT-A
BoNT-AH	Dosis alta de BoNT-A
MMPS	Síndrome de dolor miofascial masticatorio refractario
MP	dolor miofascial localizado
PR	dolor miofascial no localizado, irradiado o referido.
TENS	Estimulación nerviosa eléctrica transcutánea
RCTs	Randomized Controlled Trials
PROSPERO	International prospective register of systematic reviews
TMDs.	Trastornos temporomandibulares

Anexos 1 Carta de aceptación del artículo



ANEXO 2

**SOLUCIÓN DIRECTORAL DE ACEPTACIÓN DEL PROYECTO DE TESIS Y
NOMBRAMIENTO DEL ASESOR**

**RESOLUCIÓN DIRECTORAL DE LA CARRERA DE ESTOMATOLOGÍA N° 009-
POSG-DACE-DAFCS-U. CIENTÍFICA-2022**

Lima, 02 de julio del 2022

VISTO:

La solicitud de el/la tesista, asesor/a y la evaluación del Responsable de Investigación de la Carrera de Estomatología y de acuerdo a la RESOLUCIÓN DIRECTORAL No. 012-DGIDI-CIENTIFICA-2021 sobre Normas de precisiones de exoneración del Comité de Ética. Se aprueba el registro N° **725-2019-POS8** del proyecto de Tesis Titulado: **“TRATAMIENTO DEL DOLOR MIOFACIALEN EL TRASTORNO TEMPOROMANDIBULAR UTILIZANDO TOXINA BOTULÍNICA: UNA REVISIÓN SISTEMÁTICA”** presentado por **RAMOS HERRADA ROSA MARINA**.

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y los reglamentos de pre/posgrado para obtener el Título de **SEGUNDA ESPECIALIDAD EN REHABILITACIÓN ORAL** en la Carrera de Estomatología de la Universidad Científica del Sur, se debe desarrollar un trabajo de investigación.

Que, de acuerdo con la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de Carrera.

SE RESUELVE:

ART. 1°: APROBAR E INSCRIBIR el Proyecto de Tesis titulado: **“TRATAMIENTO DEL DOLOR MIOFACIAL EN EL TRASTORNO TEMPOROMANDIBULAR UTILIZANDO TOXINA BOTULÍNICA: UNA REVISIÓN SISTEMÁTICA”** de la **CD. RAMOS HERRADA ROSA MARINA** con registro: **N° 725-2019-POS8** y establecer la vigencia de aprobación de este documento de dieciocho (18) meses (hasta el 02 de enero del 2024), periodo en el que puede desarrollarse el proyecto de investigación.

ART. 2°: NOMBRAR Asesor/a del trabajo de tesis señalado, a al/la **Dr. Arriola Guillén, Luis Ernesto**.

Regístrese, comuníquese y archívese.



Dr. Claudio Peña Soto
Director Académico de la Carrera de Estomatología