Meta Analytical Study of the Role of Intramuscular Botulinum A Toxin Injection in the Treatment of Temporomandibular Joint (TMJ) Disorders

Original Article

Ayman Mohamed El-Kahky, Tarek Abdel-Hamid Hamdy, Mohamed El-Sayed Ahmed El-Tantawy, Anas Mohamed Askoura*

Department of Otorhinolaryngology Surgery, Faculty of Medicine, Ain Shams University, Egypt.

ABSTRACT

Introduction: Botulinum toxin is a neurotoxin produced by a gram-positive, anaerobic spore-forming bacterium called Clostridium botulinum recently used as an effective and safe line of treatment for the temporomandibular joint disorders (TMDs) through temporarily inhibition of the masticatory muscles. TMDs is a collective non-specific term used to describe disorders that involve the TMJ, masticatory muscles and/or associated structures.

Aim of the Work: A meta-analysis was conducted to evaluate the efficacy of intramuscular Botulinum toxin-A injection (BTX-A) in the treatment of myogenic temporomandibular joint (TMJ) disorders.

Patients and Methods: A systematic literature search was done to identify relevant studies published within the last 25 years on humans. Literature search had been done including PubMed, Medline, Scopus, Web of science, EBSCOhost and Cochrane databases. The study included published medical articles about intramuscular botulinum toxin-A injection in patients suffering from myogenic TMD. The results of the similar studies were pooled in the meta-analysis.

Results: Thirty-nine studies with 1538 participants were included in our systematic review and 23 of these studies were pooled in the meta-analysis. The current study showed that the difference of VAS (visual analogue scale) score at 1 and 3 months associated with intramuscular BTX-A injection (pre- and post-treatment) and BTX-A versus control is statistically significant. The difference of MMO (maximum mouth opening) at 1 and 3 months between BTX-A and control is not statistically significant. The difference of EMG amplitude at 1 month between BTX-A and control is not statistically significant while at 3 months is statistically significant. The change in maximum bite force at 3 and 6 months between BTX-A and control is statistically significant.

Conclusion: The available data favors the efficacy of usage of intramuscular BTX-A injection in cases of myogenic TMD, further randomized controlled studies must be conducted in the future.

Key Words: BTX-A, Temporomandibular joint, TMDs.

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Corresponding Author: Mohamed El-Sayed Ahmed El-Tantawy, MSc, Department of Otorhinolaryngology Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt. **Tel.:** 01022489947, **E-mail**: mohammed_tantawy51@yahoo.com

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INTRODUCTION

Temporomandibular joint disorders (TMDs) is a non-specific term used to describe orthopedic and myofascial disorders that affect the TMJ. The incidence rate of TMD is 4.6 % among adolescents and 3.9% among adult. No age group is immune but older age groups show slightly more TMD symptoms than the young.[1]

Many factors, alone or simultaneously, are responsible for the etiology of TMDs like; trauma, occlusal abnormalities and overloading of the joint structures such as parafunctions (bruxism). Also systemic, psychologic, structural and genetic factors may contribute to the pathogenesis of TMD.[2]

The American Academy of Orofacial Pain classifies TMDs into two groups: myofascial TMD, which is related to the masticatory muscles hyperactivity and arthrogenic TMD, which is more related to the TMJ itself. While the Research Diagnostic Criteria (RDC) categorizes TMD into three groups according to the common factors among conditions: group I is myofascial TMD, group II is disc displacement and group III is other TMD including osteoarthritis and osteoarthrosis.[3]

The most common TMD symptoms are pain in the region of the TMJ and clicking or popping sounds that is exacerbated by mouth movements. Moreover, the patient may also suffer from headache, facial pain, difficulty in opening the mouth wide, joint locking and some otological symptoms (hearing loss, tinnitus, dizziness or vertigo).[4]

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The diagnosis of TMD is based mainly on the medical history and physical examination findings. The TMD signs include one or more of the following; tender on palpation over the TMJ in the preauricular region anterior to the tragus, limited jaw opening or trismus, lateral deviation of the mandible and sounds (crepitus or clicking) with joint mobility. For confirmation of the diagnosis and assessment of the severity of TMD, a number of assessment tools have been proposed; the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), the Helkimo Index (HI), the Fonseca anamnestic index (FAI) and the American Academy of Orofacial Pain questionnaire (AAOPQ).[5]

There are several lines of treatment have been described for TMD that are categorized into invasive and non-invasive treatments. Reassurance of the patient, diet control, physiotherapy, warm compress, occlusal splints and pharmacological treatments are the noninvasive treatment of TMD. While, the invasive treatments include surgeries, dry needling and injection of drugs like botulinum toxin (A).[6]

Botulinum toxin-A is a neurotoxin produced by a gram-positive, anaerobic spore-forming bacterium called Clostridium botulinum. Its action is mediated through inhibition of acetylcholine release at the neuromuscular junction that leads to masticatory muscles weakness. Its administration is considered an effective, safe and minimally invasive technique for TMD. The Botox injection should be repeated after 8 - 20 weeks because single high dose or frequent injections will decrease the treatment effectiveness.[7]

Diffusion of BTX-A into adjacent or deeper musculature may result in both local and systemic side effects. Systemic side effects include transient flu-like symptoms, fatigue, nausea and pruritus. Local side effects are generally mild and transient including pain, edema, erythema and transient hypoesthesia at the site of injection. The patient also may experience facial muscle weakness, asymmetry of facial expression, transient dysphagia, restricted mouth opening, nasal regurgitation and nasal speech, difficulties in chewing and local injuries of the branches of the facial nerve.[8]

Contraindications related to BTX application are pregnancy and breast feeding, known sensitivity against BTX, pre-existing neuromuscular junction disease such as myasthenia gravis, amyotrophic lateral sclerosis, myopathies and theoretical drug interactions (aminoglycoside antibiotics, quinidine, calcium channel blockers, magnesium sulfate, succinylcholine and polymyxin).[9]

AIM OF THE WORK:

The aim of the present meta-analysis is to evaluate the efficacy of intramuscular BTX-A injection in the treatment of myogenic temporomandibular joint disorders (TMDs).

PATIENTS AND METHODS:

• Criteria of considering studies for this review:

Type of studies: Clinical trials, prospective cohort and retrospective studies that were conducted on humans and published in the last 25 years in English language.

Type of participants: Adults (>18 years) suffering from myofascial TMD based on the clinical examination, the recommendations of the RDC/TMD and/or other validated classification systems.

Types of intervention: Intra-muscular Botulinum toxin-A injection with any dose injected into any of the masticatory muscles (Masseter, Temporalis, Lateral or Medial pterygoids) compared with conservative treatment, placebo, no treatment or any other active intervention including low level laser, dry needling, acupuncture and any surgical intervention.

Type of outcome measures: The change in pain experience (VAS), changes in the frequency of bruxism events using the change in the masseter muscle EMG amplitude, changes in the maximum mouth opening (MMO) and change in the maximum bite force. We included all time-points reported by the studies, but we pooled the similar studies only in the meta-analysis.

• Search strategy for identification of study:

A systematic literature search was conducted to identify relevant medical studies published within the last 25 years on humans suffering from myofascial TMD and treated by intramuscular BTX-A injection. Literature search had been done by the authors through searching the PubMed, Medline, Scopus, Web of science, EBSCOhost and Cochrane databases using a combination of the following keywords: “Temporomandibular joint disorders”, “TMD”, “TMJ diseases”, “Severity of TMD”, “Botulinum toxin-A”, “Botox injection”, “BTX”, “Laser in TMD”, “Surgery in TMD” and “Treatment of TMD”.

• Methods of review:

Locating and selecting studies: We screened the title and abstracts of the yielded search seeking for the potentially matched articles. Then, full texts of the potentially included papers were reviewed searching for the most relevant articles.

Data extraction: The statistical data was derived from the finally pertinent publications. An excel sheet was constructed to collect the following items: author name and year, study design, number of patients, symptoms of TMD, type of intervention, follow-up duration and outcomes.

• Statistical considerations:

Statistical analysis was done using the Comprehensive Meta-Analysis© Software, Version 3 (Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013).

Assessment of heterogeneity:

Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests: Cochran Q chi square test and I-square (I2) index.

Evidence of publication bias:

The publication bias was assessed by: examination of funnel plots of the estimated effect size on the horizontal axis versus a measure of study size (standard error for the effect size) on the vertical axis, Begg-Mazumdar rank correlation test for funnel plot asymmetry, Egger's regression test for funnel plot asymmetry and Trim and Fill method.

Pooling of estimates:

Continuous outcomes are expressed as standardized mean difference (SMD) with 95% confidence intervals (95% CI). Estimates from included studies were pooled using the DerSimonian-Laird random effects method (REM).

RESULTS:

The electronic database search revealed 162 references. After the exclusion of the duplicate references, we screened 151 unique titles and abstracts, 82 references were excluded as they didn't fulfil the inclusion criteria, so 69 results were selected as potentially eligible. After full text reading, we excluded thirty studies, 18 studies of them included patients with arthrogenic TMDs and 12 were case reports.

Finally, we included 39 studies in the systematic review that included 1538 participants in total, most of them were women. All studies were published in English between 1999 and 2021; twenty of the 39 studies were randomized control trials RCTs, three were cross-over trials, 13 were prospective studies and only 3 were retrospective studies.

All of the studies included participants with a clinical diagnosis of myogenic TMD or/and bruxism. Most participants had a history of a previous conservative treatment that had been unsuccessful. All participants in the intervention group received BTX-A with a total dose of 30 - 300 U, injected in two to three points of the masseter, temporalis and lateral pterygoid muscles either unilaterally or bilaterally. Results of twenty-three of these studies were pooled in the meta-analyses (Table 1).

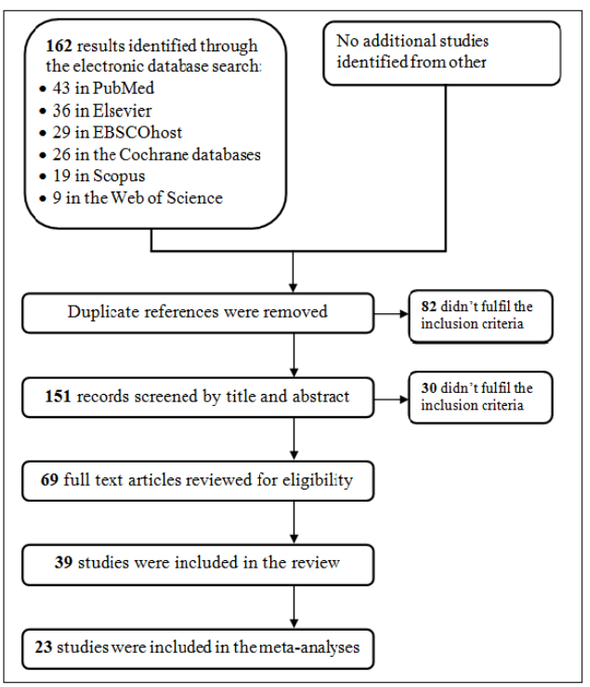

Fig. 1: Flow diagram of the process of study identification ad selection.

Table 1: Summary for the included studies in the meta-analysis.

N.	Author & year	Study design	Study group	Control group	Follow up
1	Freund *et al*., 1999.[10]	Prospective study	N = 15 (BTX-A)	---	1 and 2 months.
2	Freund *et al*., 2000.[11]	Prospective study	N = 46 (BTX-A)	---	1 and 2 months.
3	Freund & Schwartz, 2002.[12]	Prospective study	N = 60 (BTX-A)	---	1, 2 and 3 months.
4	Guarda-Nardini *et al*., 2008.[13]	RCT	N = 10 (BTX-A)	N = 100 (Placebo)	1st week, 1 and 6 months.

5	Kurtoglu *et al*., 2008. [14]	RCT	N = 12 (BTX-A)	N = 12 (Placebo)	14th day and 1 month.
6	Lee *et al*., 2010.[15]	RCT	N = 6 (BTX-A)	N = 6 (Placebo)	1, 2 and 3 months.
7	Ernberg *et al*., 2011.[16]	Cross-over RCT	N = 12 (BTX-A)	N = 9 (Placebo)	1 and 3 months.
8	Guarda-Nardini L. *et al*., 2012. [17]	RCT	N = 15 (BTX-A)	N = 15 (Facial massage)	1 and 3 months.
9	Kim *et al*., 2016. [18]	Prospective study	N = 21 (BTX-A)	---	3 months.
10	Zhang *et al*., 2016.[19]	RCT	N = 10 (BTX-A)	N = 10 (Placebo) N = 10 (Control)	4 weeks, 3 and 6 months.
11	Attia *et al*., 2017.[20]	Prospective study	N = 14 (BTX-A)	---	1st week, 1, 2 and 3 months.
12	Chaurand *et al*., 2017.[3]	RCT	N = 11 (BTX-A)	N = 11 (Conservative treatment)	1 month.
13	Jadhao *et al*., 2017.[21]	RCT	N = 8 (BTX-A)	N = 8 (Placebo) N = 8 (Control)	1st week, 3 and 6 months.
14	Khawaja *et al*., 2017.[22]	Retrospective study	N = 116 (BTX-A)	---	1 month.
15	Patel *et al*., 2017.[23]	Cross-over RCT	N = 10 (BTX-A)	N = 9 (Placebo)	1, 2, 3 and 4 months.
16	Pons *et al*., 2019.[24]	Prospective study	N = 6 (BTX-A)	---	3 months.
17	Thind, 2019.[25]	Prospective study	N = 11 (BTX-A)	---	1st week, 1, 2, 3 and 6 months.
18	Hosgor & Altindis, 2020.[26]	Retrospective study	N = 44 (BTX-A)	---	1, 3 and 6 months.
19	Montes-Carmona *et al*., 2020. [27]	RCT	N = 20 (BTX-A)	N = 19 (Placebo) N = 20 (Lidocaine)	1, 2, 3 and 6 months.
20	Silva *et al*., 2020.[28]	RCT	N = 15 (BTX-A)	N = 15 (Placebo)	1, 2, 3, 4, 5 and 6 months.
21	Kef, 2021.[29]	Prospective study	N = 37 (BTX-A)	---	1, 2 and 6 months.
22	Meral *et al*., 2021.[30]	Prospective study	N = 25 (BTX-A)	---	1 month.
23	Miotto *et al*., 2021.[31]	RCT	N = 20 (BTX-A)	N = 20 (Conservative treatment)	1 month.

Studies were arranged according to publication year.
The total number of patients in the study groups (injected with BTX-A) in all the studies included in the meta-analysis were 544 patients and 234 participants in the control groups.

• The outcome measures:

A) Pain intensity (VAS):

Eighteen of the 23 studies assessed the TMJ pain reduction using visual analogue scale (VAS) score (higher values indicate more pain). First, the effect of intramuscular injection of BTX-A on VAS score was assessed through comparison of VAS score pre- and post-injection of the study groups. The results of all 18 studies (studies 1, 2, 3, 4, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 19, 21, 22 & 23) were pooled in the meta-analysis: 14 studies at one month and 11 studies at three months post-treatment as shown in (Figures 2, 3, 4 & 5).

Twelve of the 23 studies were RCTs that compared BTX-A versus control that include conservative treatment, placebo and facial manipulation. Seven of them assessed the TMJ pain reduction using (VAS), we pooled the results of four RCTs (studies 4, 7, 13 & 15) in the meta-analysis at two time points: 3 studies at one month and 3 studies at three months post-treatment as mentioned in (Figures 6, 7, 8 & 9).

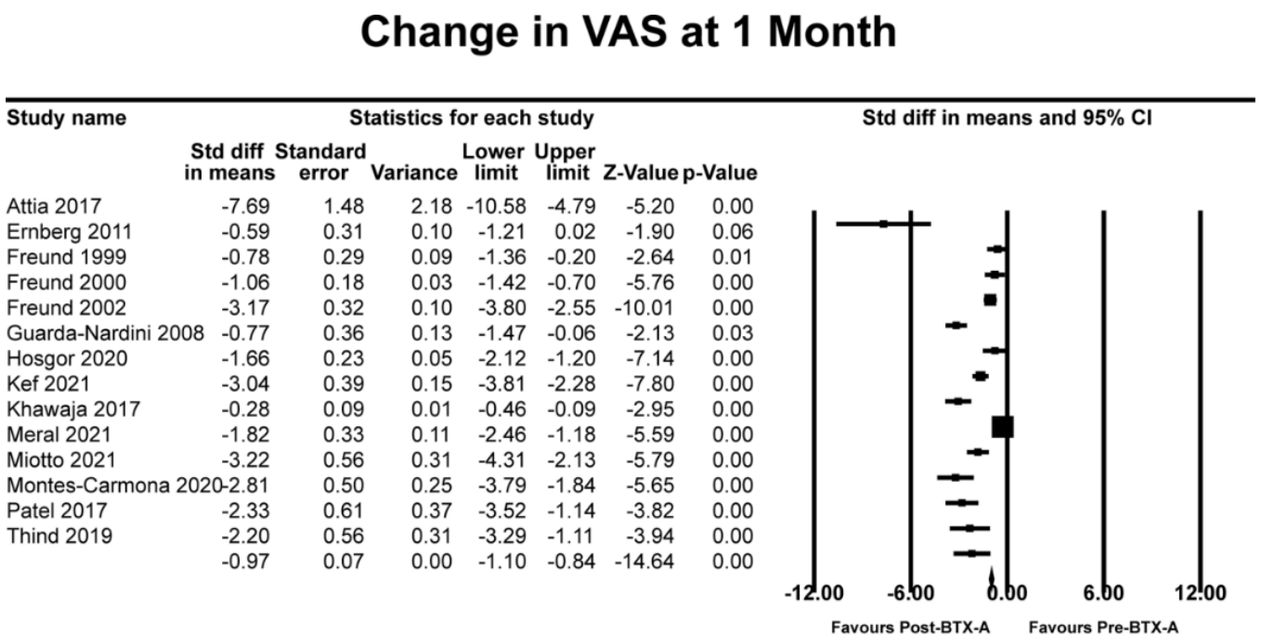

Fig. 2: Forest plot for the change in VAS associated with BTX-A (pre- and post-treatment) at 1 month. The decrease in VAS is statistically significant. Standardized mean difference = -0.97, 95% CI = -1.10 to -0.84, *p-value < 0.01*. There is considerable heterogeneity across studies (I-squared = 93.8%, Cochran Q = 208.46, df = 13, *p-value < 0.01*).

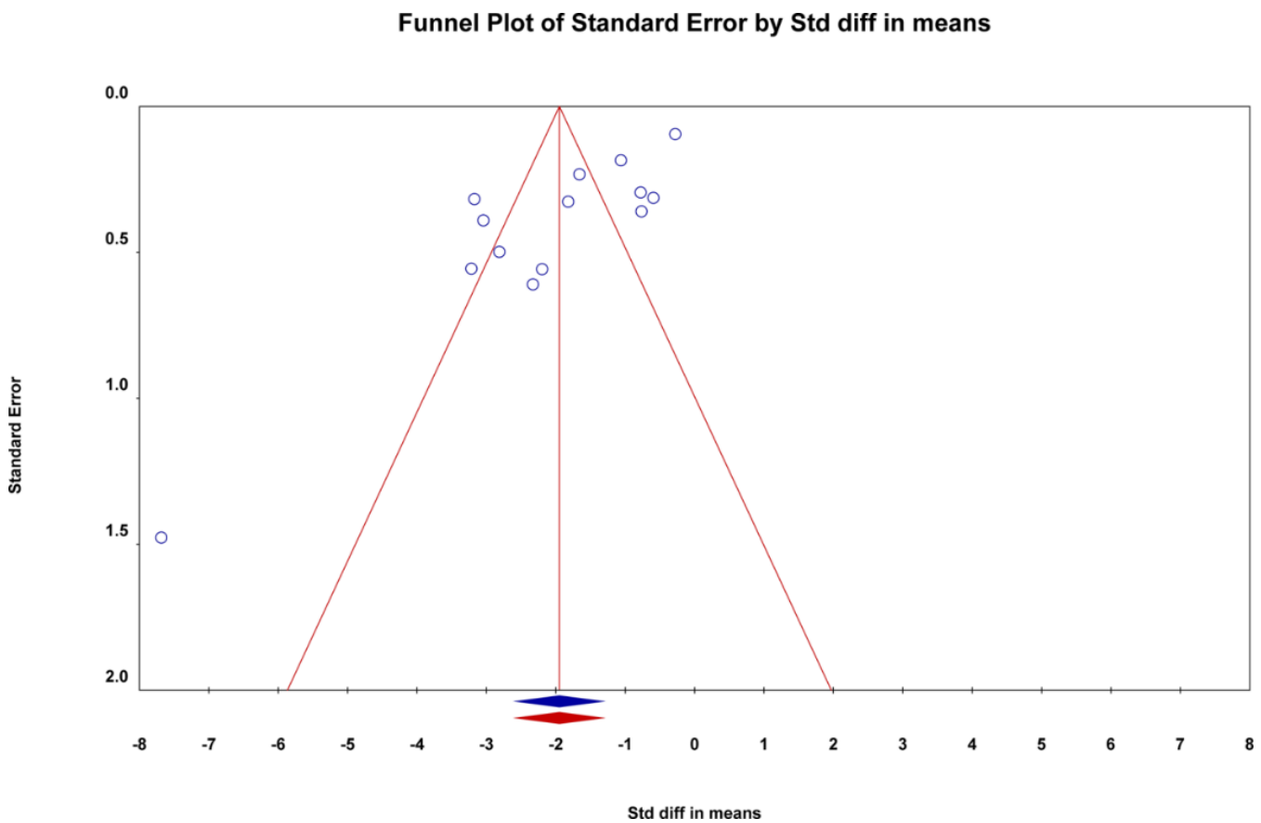

Fig. 3: Funnel plot for the change in VAS associated with BTX-A (pre- and post-treatment) at 1 month. There is no evidence of publication bias. The rank correlation test is not statistically significant (*p-value = 0.05*) but the regression test for funnel plot asymmetry is statistically significant (*p-value < 0.01*). Under the random effects model the point estimate and 95% confidence interval for the combined studies is -1.95 (-2.56, -1.33). However, using Trim and Fill these values are unchanged.

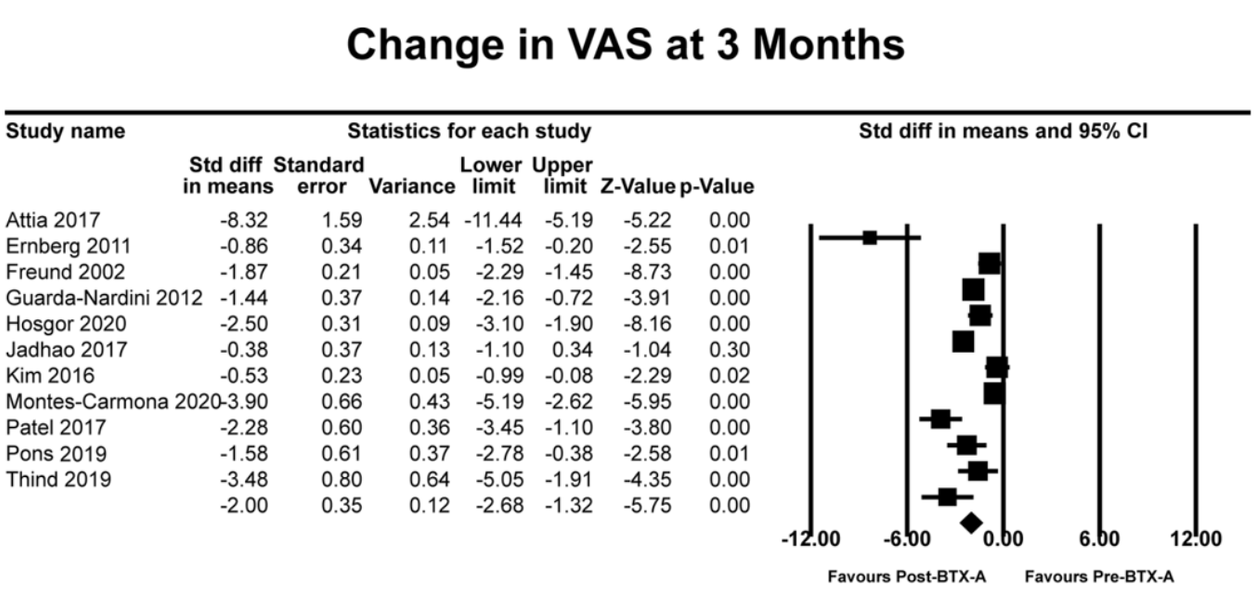

Fig. 4: Forest plot for the change in VAS associated with BTX-A (pre and post-treatment) at 3 months. The decrease in VAS is statistically significant. Standardized mean difference = -2.00, 95% CI = -2.68 to -1.32, *p-value < 0.01*. There is considerable heterogeneity across studies (I-squared = 88.0%, Cochran Q = 83.17, df = 10, *p-value < 0.01*).

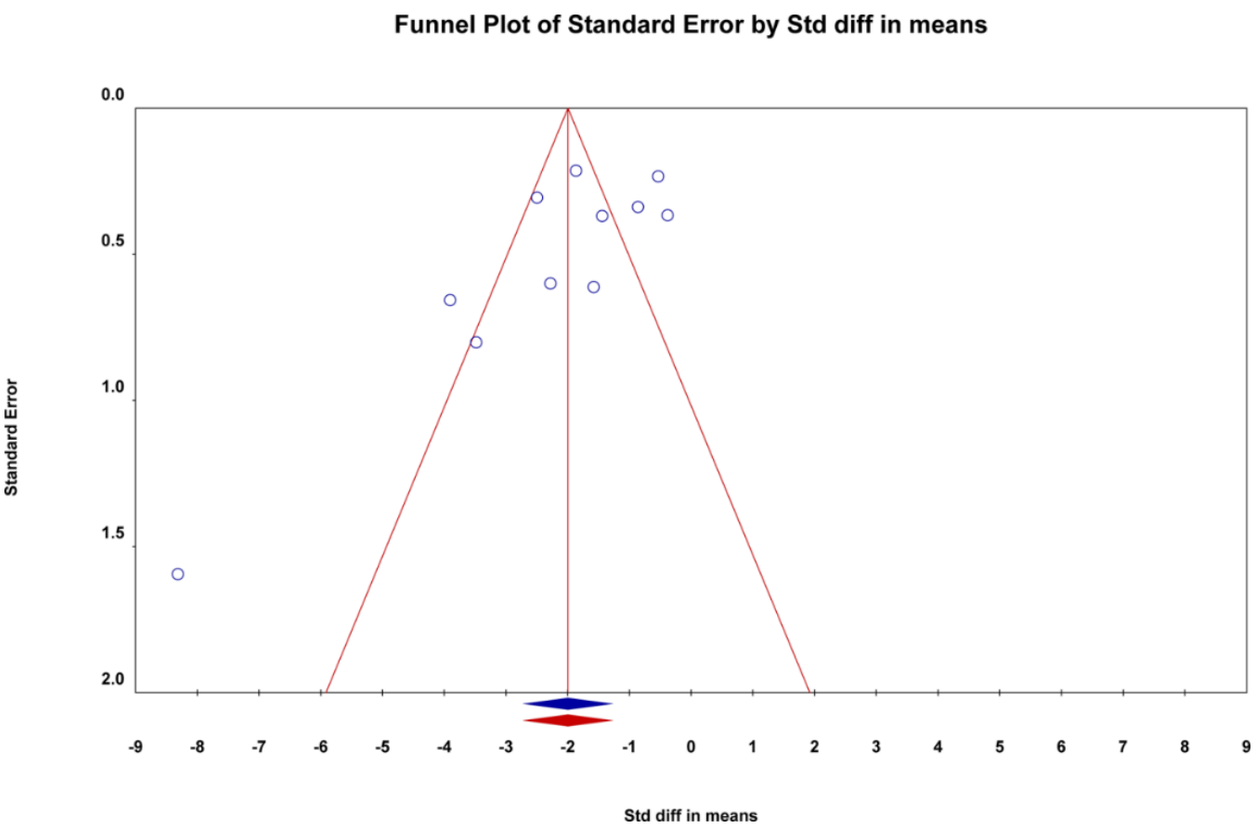

Fig. 5: Funnel plot for the change in VAS associated with BTX-A (pre- and post-treatment) at 3 months. There is no evidence of publication bias. Both the rank correlation test and regression test for funnel plot asymmetry are not statistically significant (*p-value = 0.06* & 0.07, respectively). Under the random effects model the point estimate and 95% confidence interval for the combined studies is -2.00 (-2.68, -1.32). Using Trim and Fill these values are unchanged.

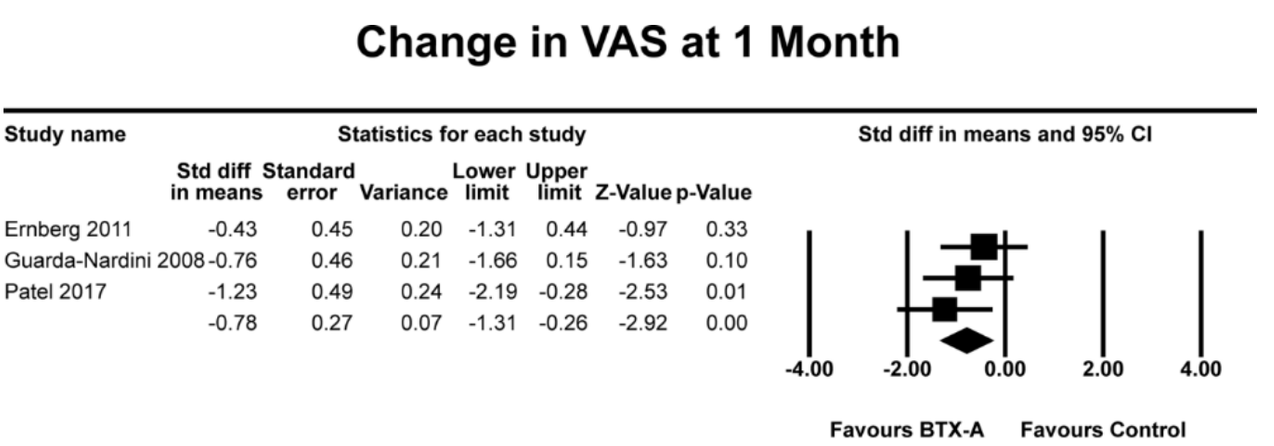

Fig. 6: Forest plot for the change in VAS associated with BTX-A versus Control at 1 month. The difference between BTX-A and Control is statistically significant. Standardized mean difference = -0.78, 95% CI = -1.31 to -0.26, *p-value < 0.01*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 1.48, df = 2, *p-value = 0.48*).

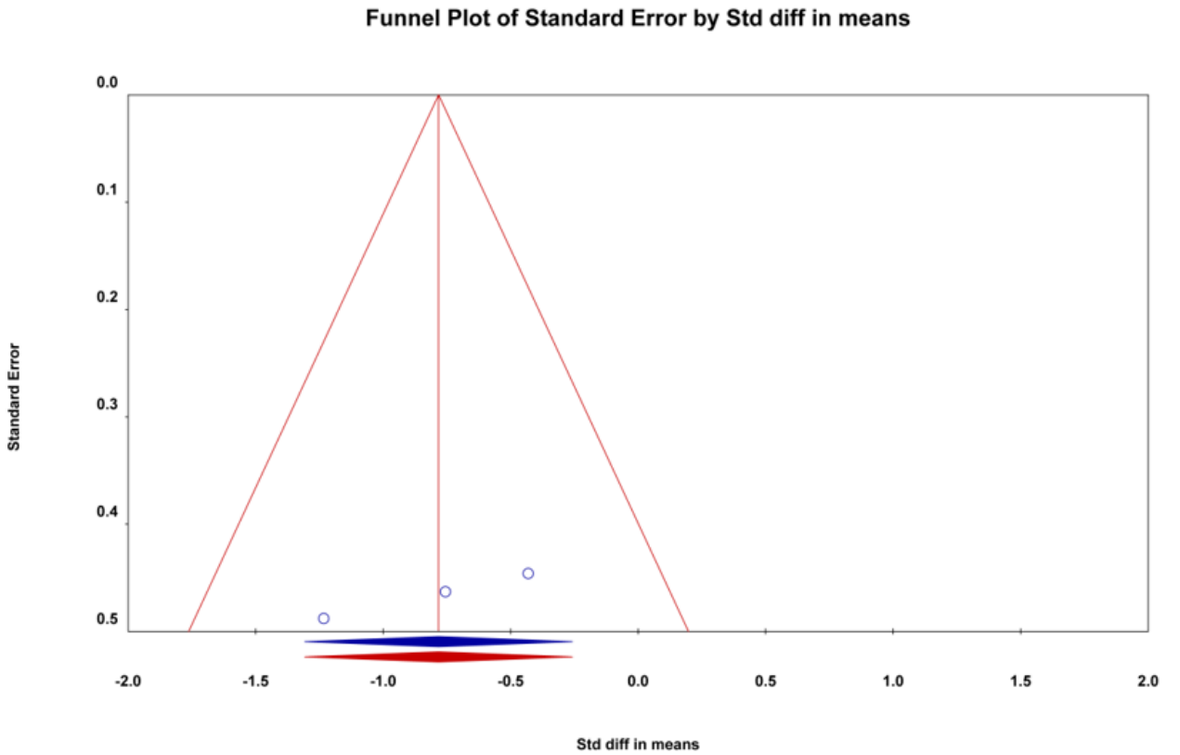

Fig. 7: Funnel plot for the change in VAS associated with BTX-A versus Control at 1 month. There is no evidence of publication bias. The rank correlation test is not statistically significant (*p-value = 0.30*) but the regression test for funnel plot asymmetry is statistically significant (*p-value < 0.01*). Under the random effects model the point estimate and 95% confidence interval for the combined studies is -0.786 (-1.31, -0.26). However, using Trim and Fill these values are unchanged.

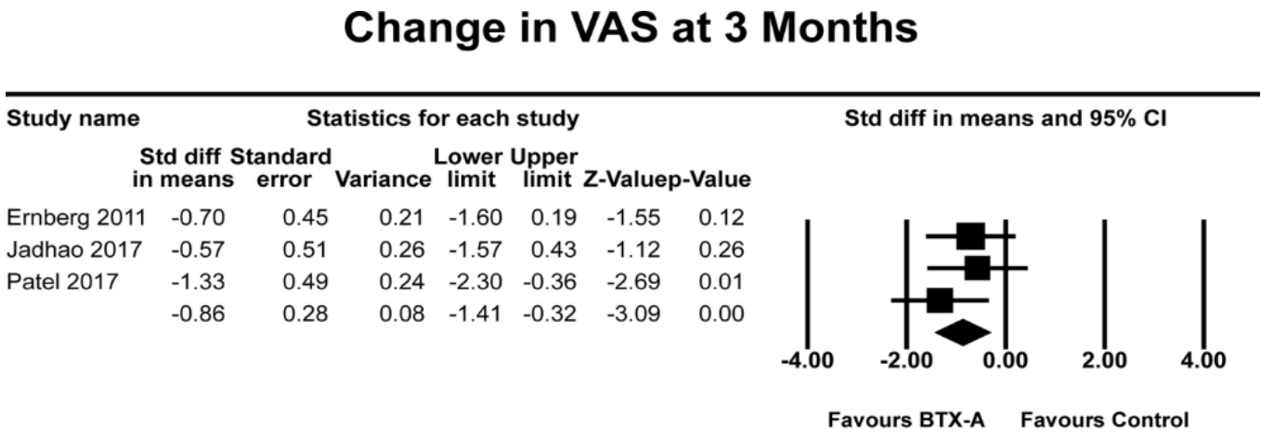

Fig. 8: Forest plot for the change in VAS associated with BTX-A versus Control at 3 months. The difference between BTX-A and Control is statistically significant. Standardized mean difference = -0.86, 95% CI = -1.41 to -0.32, *p-value < 0.01*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 1.34, df = 2, *p-value = 0.51*).

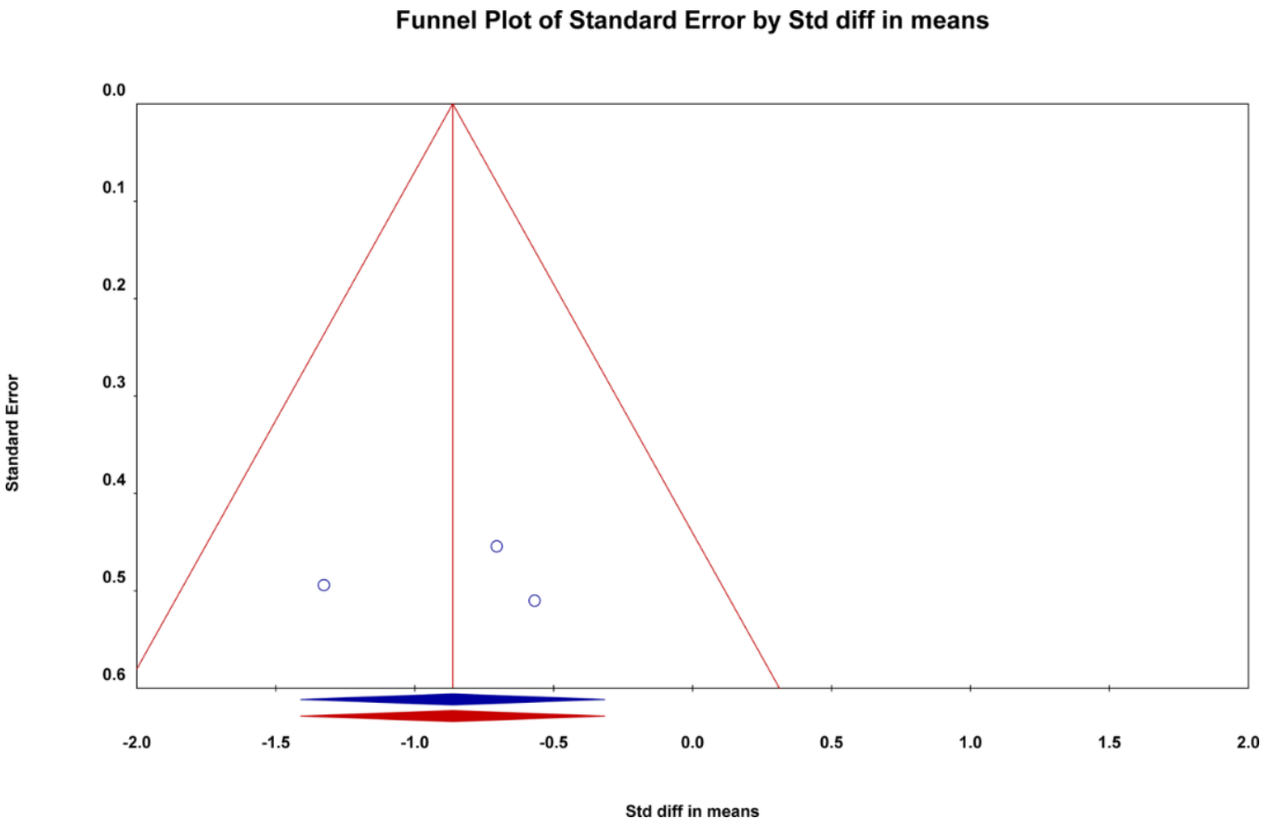

Fig. 9: Funnel plot for the change in VAS associated with BTX-A versus Control at 3 months. There is no evidence of publication bias. Both the rank correlation test and regression test for funnel plot asymmetry are not statistically significant *(p-value = 1.00* & 0.92, respectively). Under the random effects model the point estimate and 95% confidence interval for the combined studies is -0.86 (-1.41, -0.32). Using Trim and Fill these values are unchanged.

B) Maximum mouth opening (MMO):

Five of the twelve RCTs assessed the jaw function through measurement of the maximum mouth opening in mm, we pooled the results of them (studies 4, 7, 8, 12 & 19) in the meta-analysis at two time points: 4 studies at one month and 3 studies at three months post-treatment as shown in (figures 10, 11, 12 & 13).

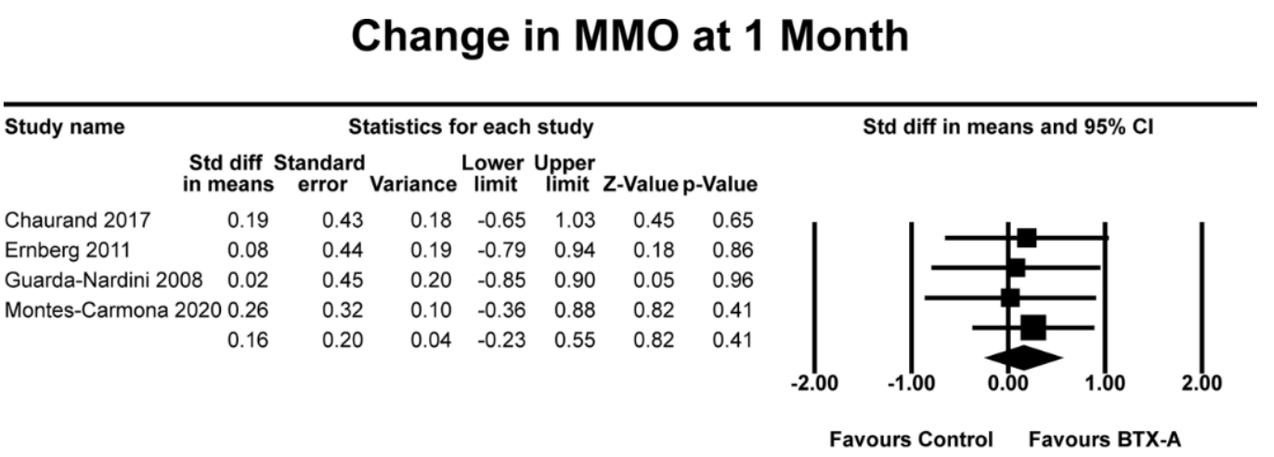

Fig. 10: Forest plot for the change in the maximum mouth opening (MMO) associated with BTX-A versus Control at 1 month. The difference between BTX-A and Control is not statistically significant. Standardized mean difference = 0.16, 95% CI = -0.23 to 0.55, *p-value = 0.41*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 0.23, df = 3, *p-value = 0.97*).

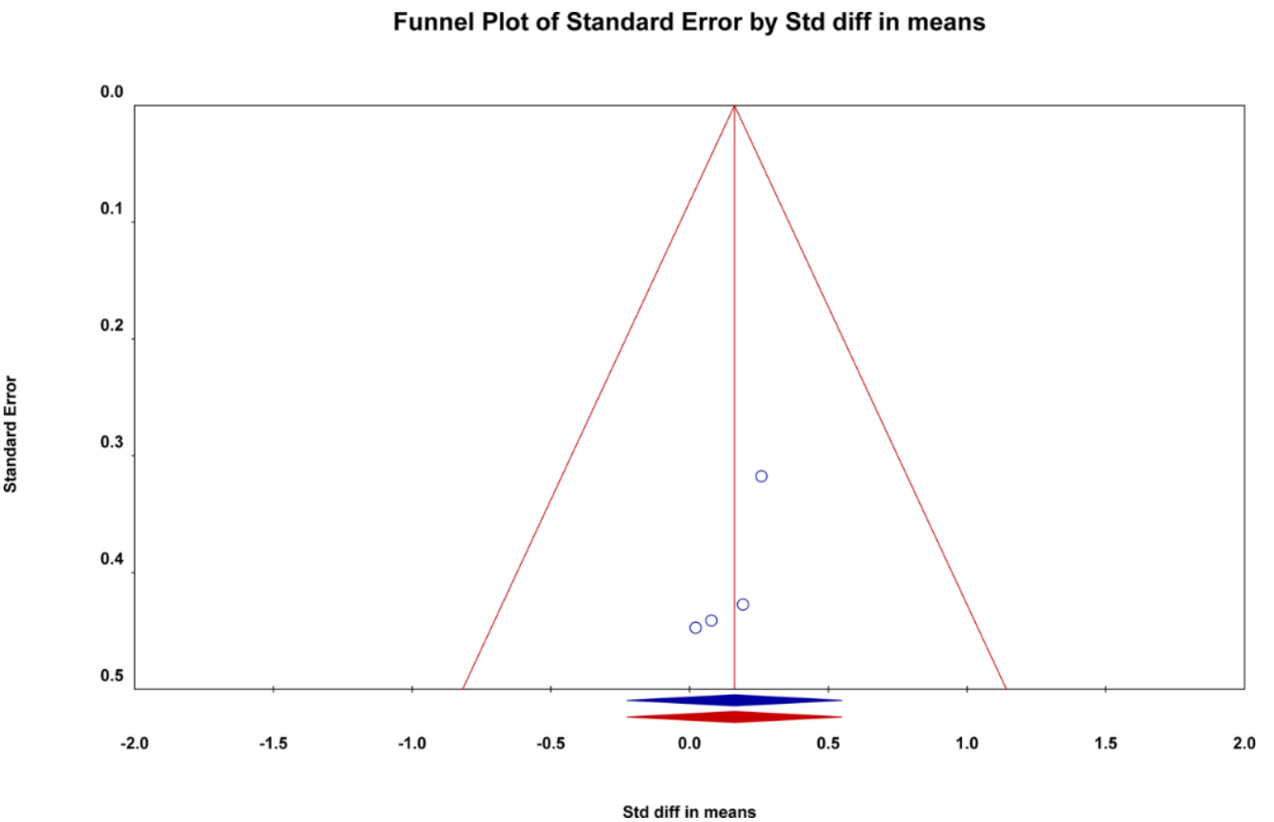

Fig. 11: Funnel plot for the change in MMO associated with BTX-A versus Control at 1 month. There is no evidence of publication bias. Both the rank correlation test and regression test for funnel plot asymmetry are not statistically significant (p-value = 0.09 & 0.13, respectively). Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.16 (-0.23, 0.55). Using Trim and Fill these values are unchanged.

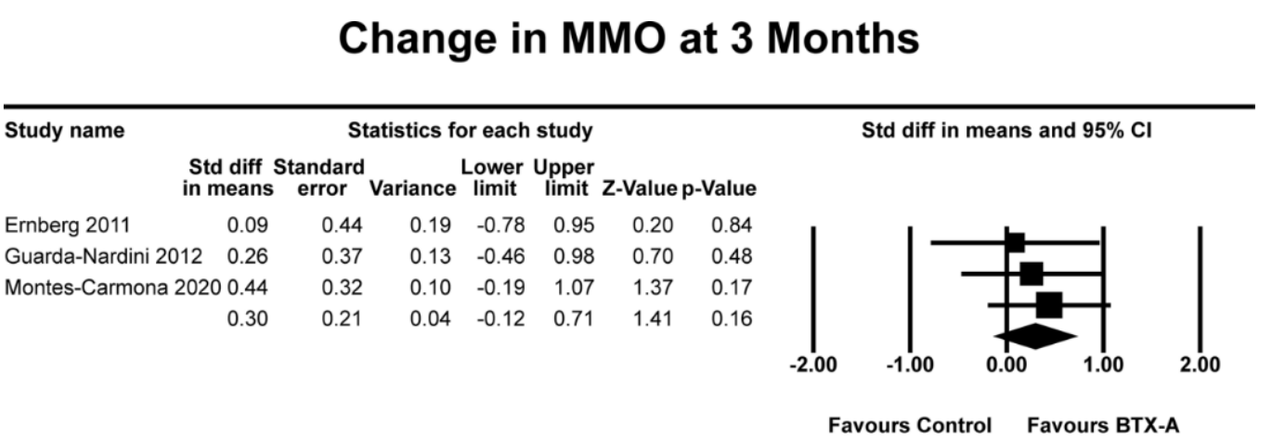

Fig. 12: Forest plot for the change in MMO associated with BTX-A versus Control at 3 months. The difference between BTX-A and Control is not statistically significant. Standardized mean difference = 0.30, 95% CI = -0.12 to 0.71, *p-value = 0.16*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 0.44, df = 2, *p-value = 0.80)*.

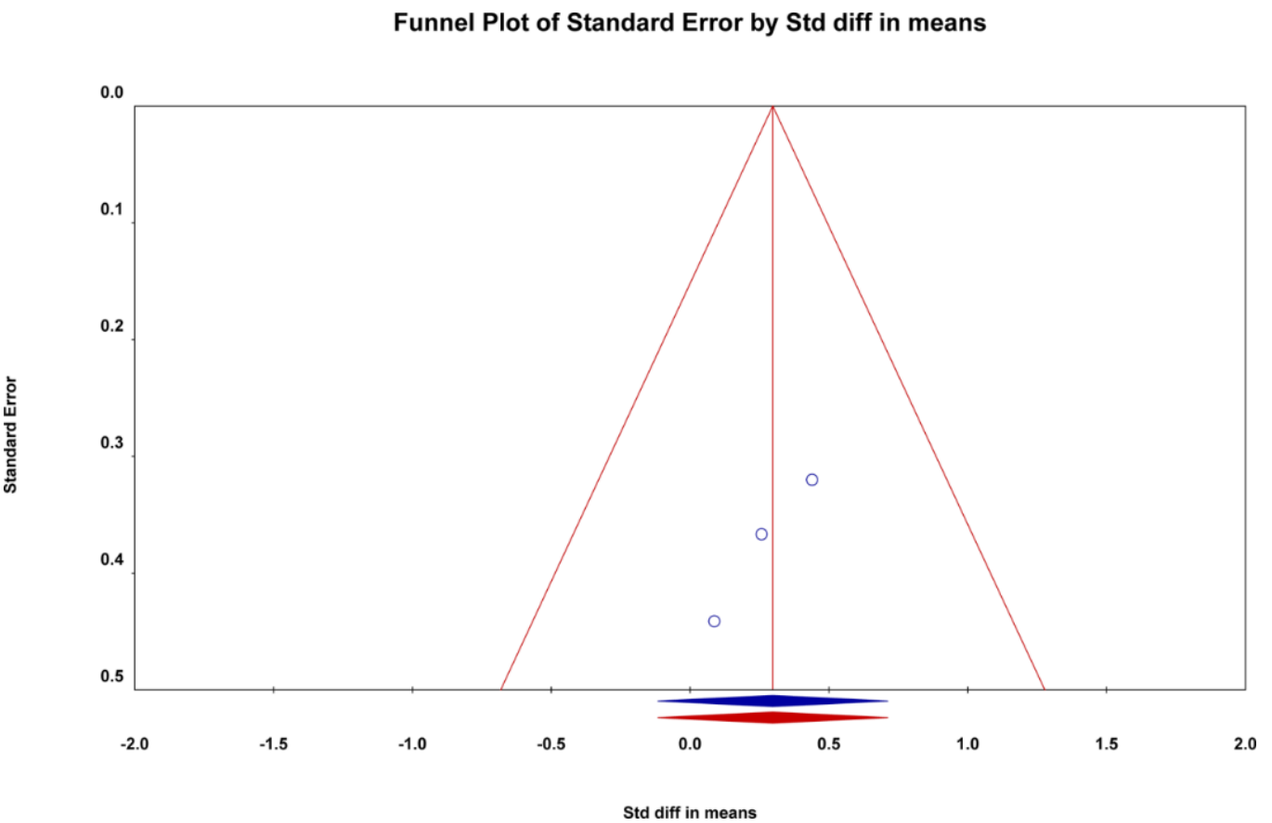

Fig. 13: Funnel plot for the change in MMO associated with BTX-A versus Control at 3 months. There is no evidence of publication bias. Both the rank correlation test and regression test for funnel plot asymmetry are not statistically significant (*p-value = 0.30* & 0.10, respectively). Under the random effects model the point estimate and 95% confidence interval for the combined studies is 0.30 (-0.12, 0.71). Using Trim and Fill these values are unchanged.

C) Change in electromyogram amplitude (EMG):

Three RCTs assessed the change in the masseter muscle electromyogram amplitude (EMG), we pooled the results of these RCTs (studies 5, 6 & 20) in meta-analysis at two time points: 3 studies at one month and 2 studies at three months post-treatment (Figures 14, 15 & 16).

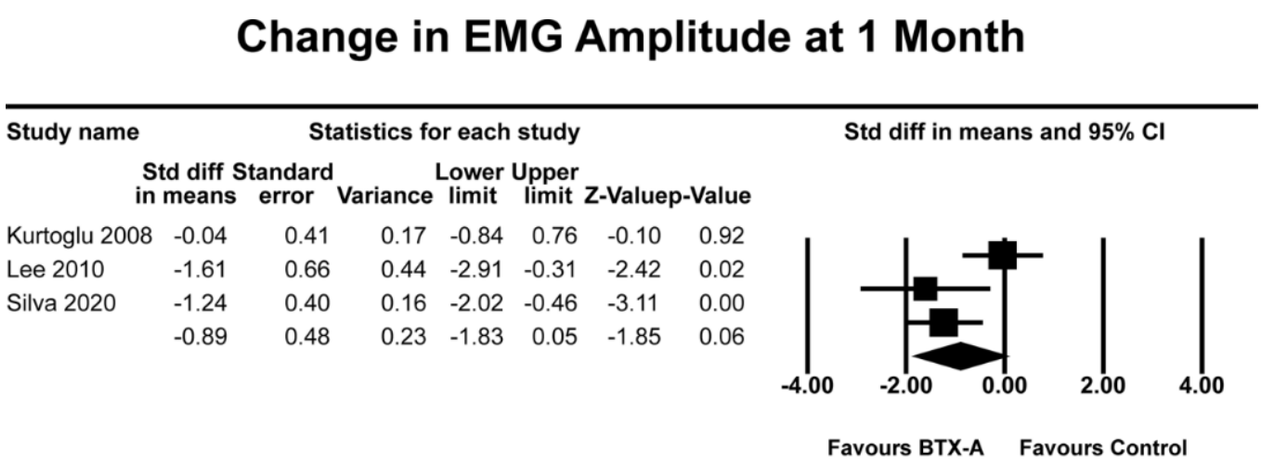

Fig. 14: Forest plot for the change in EMG amplitude associated with BTX-A versus Control at 1 month. The difference between Botulinum toxin –A and Control is not statistically significant. Standardized mean difference = -0.89, 95% CI = -1.83 to 0.05, *p-value = 0.06*. There is substantial heterogeneity across studies (I-squared = 67.5%, Cochran Q = 6.14, df = 2, *p-value = 0.05*).

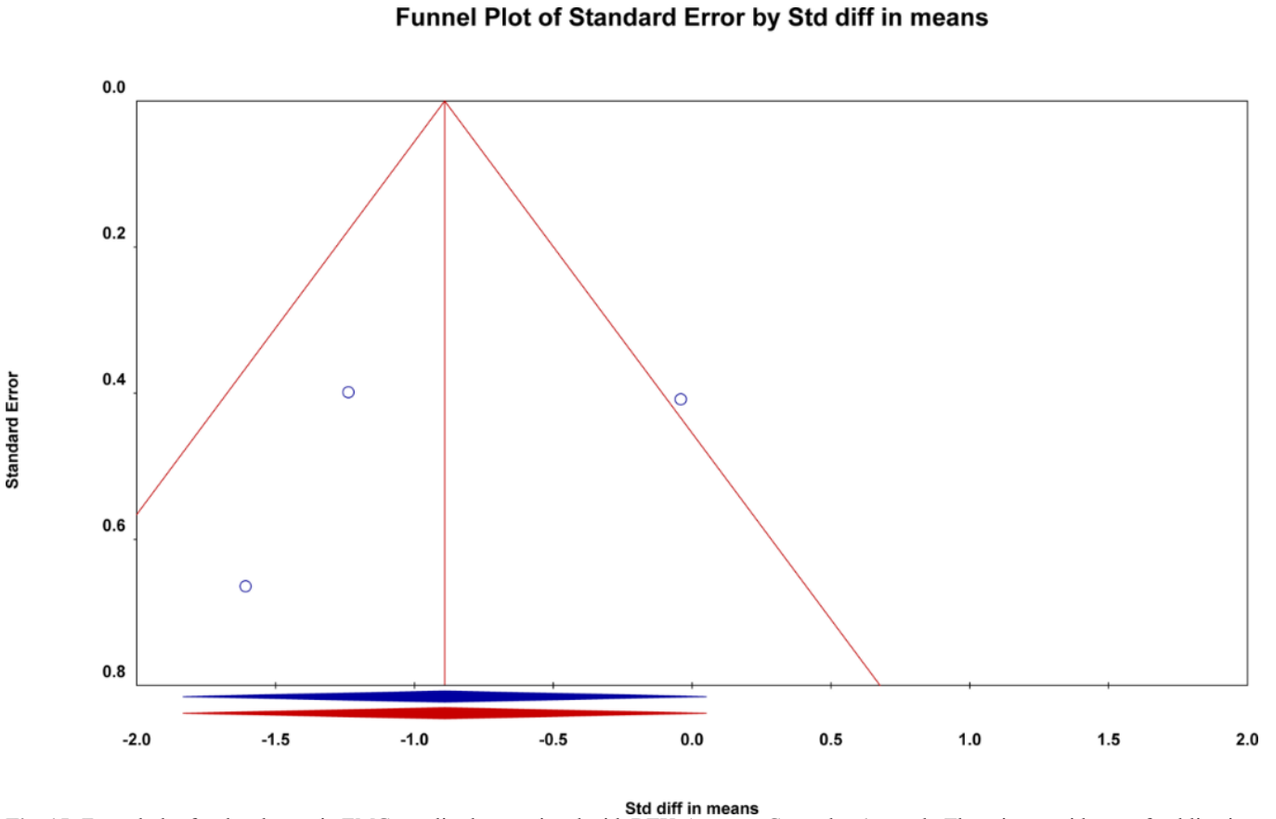

Fig. 15: Funnel plot for the change in EMG amplitude associated with BTX-A versus Control at 1 month. There is no evidence of publication bias. Both the rank correlation test and regression test for funnel plot asymmetry are not statistically significant (*p-value = 1.00* & 0.67, respectively). Under the random effects model the point estimate and 95% confidence interval for the combined studies is -0.89 (-1.83, 0.05). Using Trim and Fill these values are unchanged.

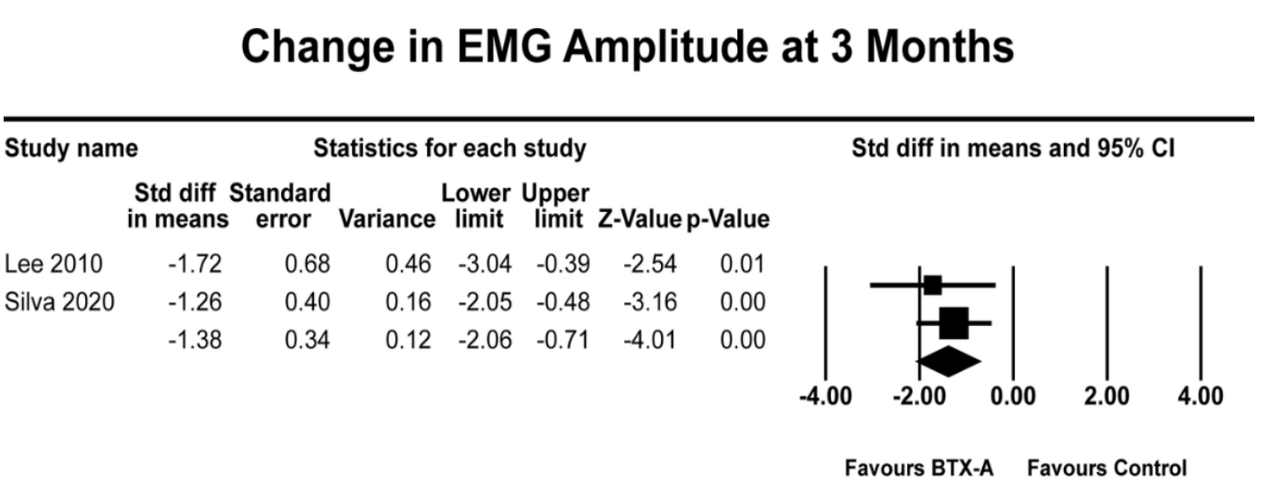

Fig. 16: Forest plot for the change in EMG amplitude associated with BTX-A versus Control at 3 months. The difference between BTX-A and Control is statistically significant. Standardized mean difference = -1.38, 95% CI = -2.06 to -0.71, *p-value < 0.01*. There unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 0.33, df = 1, *p-value = 0.57*).

D) Change in the maximum bite force:

Two trials (studies 10 & 13) assessed the change in maximum bite force that we pooled their results in meta-analysis at three and six months post-treatment (Figures 17 & 18).

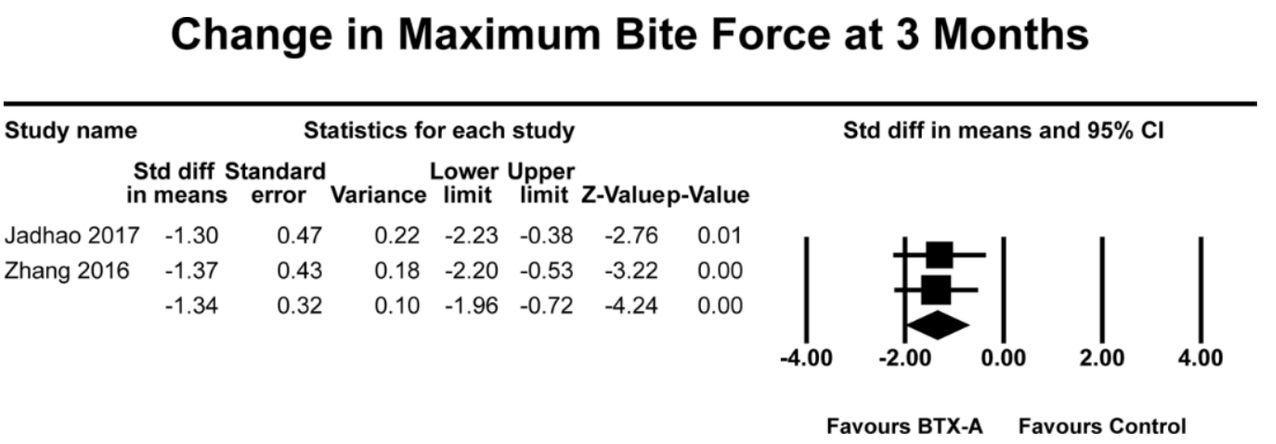

Fig. 17: Forest plot for the change in maximum bite force associated with BTX-A versus Control at 3 months. The difference between BTX-A and Control is statistically significant. Standardized mean difference = -1.34, 95% CI = -1.96 to -0.72, *p-value < 0.01*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 0.01, df = 1, *p-value = 0.92*).

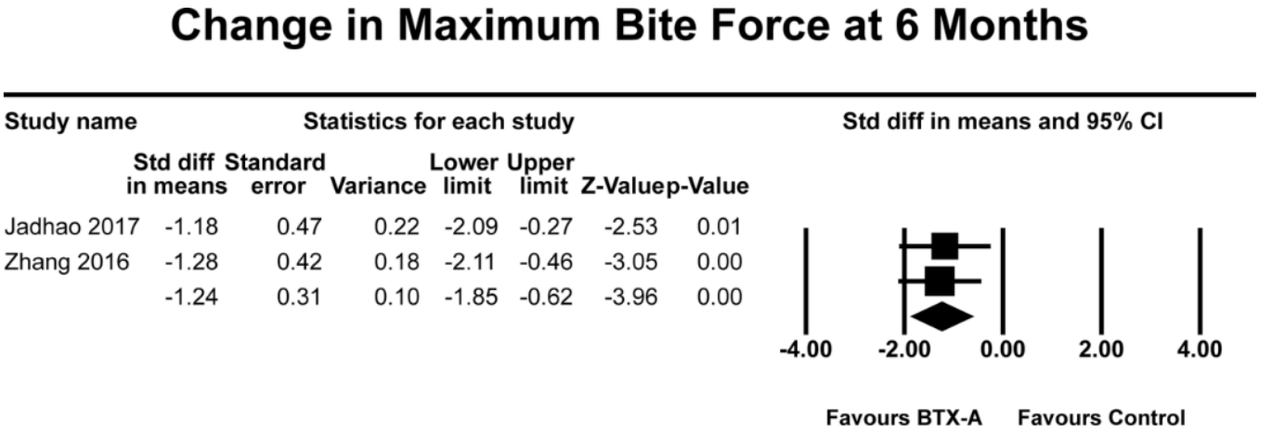

Fig. 18: Forest plot for the change in maximum bite force associated with BTX-A versus Control at 6 months. The difference between BTX-A and Control is statistically significant. Standardized mean difference = -1.24, 95% CI = -1.85 to -0.62, *p-value < 0.01*. There is unimportant heterogeneity across studies (I-squared = 0.0%, Cochran Q = 0.03, df = 1, *p-value = 0.86*).

DISCUSSION

Temporomandibular joint disorders (TMDs) are a group of non-specific disabling disorders that affect the temporomandibular joint (TMJ). TMDs are classified into myogenic TMD that is caused by muscle disorders and arthrogenic TMD which is related to the TMJ itself. Patients may complain of one or more of the following symptoms that may be worsen during jaw motion; pain around the TMJ area, headache, joint locking, limited jaw opening and tinnitus.

Different lines are described in the management of TMD. These lines of treatment are divided into invasive and non-invasive treatment. Reassurance of the patient, psychological therapy, non-pharmacological treatments (diet control, physiotherapy, warm compress and occlusal splints) and pharmacological drugs are the non-invasive lines of treatment. The invasive treatments include dry needling, acupuncture, different modalities of surgeries and injection of drugs like botulinum toxin.

Botulinum toxin is a neurotoxin produced by a gram-positive, anaerobic spore-forming bacterium called Clostridium botulinum. There are seven serotypes ordered from A to G, with serotypes A (BTX-A) and B (BTX-B) being the most commonly used. BTX action is mediated through inhibition of acetylcholine release at the neuromuscular junction that leads to muscle weakness. It also has a direct effect on peripheral nociceptors and can be used to treat neuropathic pain as it regulates the release of inflammatory mediators.

The results of the current study showed that there is a statistically significant decrease in VAS score associated with intramuscular BTX-A injection (pre- and post-treatment) at 1 and 3 months post-treatment (favors post-treatment; *p-value < 0.01*). Also a statistically significant decrease in VAS score associated with BTX-A versus control at 1 and 3 months (favors BTX-A; *p-value < 0.01*). While the change in the maximum mouth opening (MMO) associated with BTX-A compared with control at 1 and 3 months isn't statistically significant (*p-value = 0.41* & 0.16 respectively).

The results of the meta-analysis done by Machado *et al*., (2020)[32] matched our results according to the change in VAS at 1 month post-treatment, in contrast to the result at 3 months as it reported no significant change in VAS score at this time-point but the authors postulated their results based on only 2 studies for each outcome (VAS and MMO). As regard the maximum mouth opening (MMO), Machado *et al*.[32] reported no significant differences between BTX-A versus control at 1, 3 and 6 months that corresponded to the result of the current study.

Patel *et al*., (2019)[33] conducted a systematic review of eleven studies with different outcomes. Like the current study, the results of this study support the use of BTX-A in the treatment of TMD of myogenous origin. It agreed with the current study results as regard the decrease in pain after BTX-A and the non-significant improvement of MMO after BTX-A. But because of the diversity of the studies outcomes, the authors of that review didn't conduct any meta-analysis.

In contrast to the current study results, the systematic review done by Thambar *et al*., (2020)[34] didn't support the use of intramuscular injection of

BTX-A in cases of TMD as regard change in VAS score and the maximum mouth opening. They hypothesized their results based on a review of a small number of studies (7 studies) that also lacked of statistical data to perform a meta-analysis.

The current study also reported that the change in EMG amplitude associated with BTX-A versus control at 1 month is not statistically significant (favors control; *p-value = 0.06*), but it is statistically significant (favors BTX-A; *p-value < 0.01*) at 3 months post-treatment. This result disagreed with those of Gupta *et al*. (2016)[35] that reported a statistically significant decrease in the muscles activity at 1 month post-treatment (*P < 0.05*). But the number of patient in this study was only 12 patients.

The results of Fernández-Núñez *et al*., (2019)[36] corresponded to the results of the current study that BTX-A is a safe and effective treatment for patients with bruxism but they depended on a subjective tool in the assessment of the bruxism events (subjective questionnaire) in contrast to the current study, an objective accurate method (masseter muscle EMG amplitude) was used for assessment.

As regard the change in the maximum bite force, the results of the current study showed that there is a statistically significant change associated with BTX-A versus control at 3 and 6 months (favors BTX-A; *p-value < 0.01*). There was neither meta-analysis nor systematic review assessed the effect of intramuscular injection on the patients bite force.

Diffusion of BTX-A into adjacent or deeper musculature may result in both local and systemic side effects which need no treatment or only conservative measures. Systemic side effects of botulinum toxin include transient flu-like symptoms, fatigue, nausea and pruritus. Local side effects are generally mild and transient including facial muscle weakness, transient dysphagia, restricted mouth opening pain, edema, erythema, ecchymosis and transient hypoesthesia at the site of injection.

No adverse effects were reported as a result of intramuscular BTX-A injection apart from four studies; Ondo *et al*. (2018)[37], Von Lindern *et al*. (2003)[38], Gupta *et al*. (2016)[35] and Zhang *et al*. (2016)[19] that showed that a small number of patients experienced some side effects. These side effects were transient and completely reversible without treatment as a cosmetic change in the patient smile, swallowing difficulty, facial paralysis, pain and numbness at the site of injection.

Awan *et al*., (2019)[39] performed a systematic review composed of seven studies. The results of this study reported that the therapeutic efficacy of BTX-A was unclear due to heterogeneity in the methodology and outcome assessment used in the systematic review.

Shehata *et al*. (2015)[40] performed a comparison between the intramuscular BTX-A injection and intermaxillary fixation (IMF). The study results showed that the BTX-A group showed obvious improvement in VAS score, as well as, the mouth opening after one week of treatment till 6 months after injection while the IMF group shows improvement in the 1st week after fixation release but the pain and mouth opening started to worsen again from the 3rd month.

Yilmaz *et al*. (2021)[41] compared the intramuscular BTX-A with local anesthesia and platelet rich plasma (PRP). BTX-A and Local anesthesia groups showed superior improvement in pain score (VAS) compared with the PRP group at 3 months. Improvement in VAS values were significantly better in BTX group than local anesthesia group at 3 months. At 6 months, significant improvement in pain scores was recorded only in BTX group.

Venancio *et al*. (2009)[42] compared the effect of dry needling with intramuscular BTX-A and lidocaine injection. The authors reported that all groups showed favorable results, so considering its reduced cost, lidocaine could be adopted as a substance of choice and botulinum toxin should be reserved for refractory cases. These results disagreed with Kütük *et al*. (2019) [43] that compared the intramuscular BTX-A injection with dry needling. The results of this study showed that the pain as well as mouth opening were relieved more effectively in the dry needling group at the end of 6th months.

DE LA Torre Canales *et al*. (2021)[44] performed a unique comparison between BTX-A, acupuncture and placebo. The results of this study showed that pain score showed a significant decrease in all groups after one-month of therapy. Improvement in pain levels didn't significantly differ between the acupuncture and BTX-A groups (*P > 0.05*), but both groups presented a significant reduction on pain compared to the control group.

A three armed comparison between BTX-A injection, placebo and occlusal splint was performed by DE la Torre Canales *et al*. (2020)[45]. The results revealed that BTX-A injection reduced pain intensity (*P < 0.0001*) for up to 24 weeks compared to the placebo; however, compared with oral appliance, no statistical differences were found up to the end of

the study ($P > 0.05$). These results agreed with the results of Kaya and Ataoğlu (2021)[46] and Miotto *et al*. (2021)[31] that revealed that both groups' (BTX-A and occlusal splint) outcomes are almost the same ($P < 0.05$).

Ivask *et al*. (2016)[47] performed a prospective study comparing the effect of intramuscular injection of BTX-A as an adjunct to arthrocentesis and BTX-A injection only. VAS score decreased significantly ($P = 0.005$) and MMO improved significantly ($P < 0.005$) in the group treated with arthrocentesis with BTX-A when compared with BTX-A only. So arthrocentesis is more superior to BTX-A injection on moderate to severe cases of TMD.

De Carli *et al*. (2016)[48] compared the effect of intramuscular BTX-A injection with low level laser therapy (LLLT). Seven patients received 60 U of BTX-A in each masseter and 20 U in each temporalis muscle and after 15 days, 30 U in each masseter and 15 U in each temporalis muscle. Eight patients received low level laser therapy (LLLT) (Gallium Arsenide and Aluminum) in each side. Both therapies were effective in reducing pain, but the effect of LLLT was faster than the BTX-A; the pain was improved after 12 days and 30 days respectively. Both treatments showed no statistically significant improve in mouth opening ($P = 0.272$).

CONCLUSION

The available data showed that BTX-A is a safe, effective and minimally invasive alternative line of treatment in the management of myogenous type of temporomandibular joint disorders compared with placebo and other active treatments (occlusal splints, behavioral interventions and medication), low-level laser, dry needling, acupuncture and surgery.

CONFLICT OF INTEREST

There are no conflicts of interest.

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