International Journal of Community Medicine and Public Health
Khounganian RM et al. Int J Community Med Public Health. 2024 Dec;11(12):4974-4983
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20243448

Review Article

Botulinum toxin type A for pain control in temporomandibular joint disorder patients

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Received: 29 October 2024
Accepted: 14 November 2024

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ABSTRACT

Temporomandibular disorders (TMDs) include different conditions, such as: myofascial pain that involves discomfort or pain in the muscles that control jaw function, also internal derangement of the jaw involves a displaced disc, or injury to the condyle, and arthritis that refers to a group of degenerative/inflammatory joint disorders, the causes of TMDs is multifactorial; it includes occlusal factors such as bruxism, stress and psychological status, hormonal factors, and systemic diseases, treatment encompasses simple treatment for example physiotherapy, intra-oral appliance, certain medications, as well as complex treatment such as intra-articular injection and surgery. Botox is considered a peripheral muscle relaxant and a very effective option to reduce pain with TMD patients. Consequently, the present review article was undertaken to shed some light on the different treatment modalities of TMDs and specifically the relevance of botulinum toxin type A (BTX-A) for pain relief in TMD patients. Searches were conducted in Medline (via PubMed, Scopus, The Cochrane library), all original relevant studies that discussed the effectiveness of BTX-A in managing temporomandibular disorders were included. BTX-A injection in masticatory muscles of patients with TMD can be a useful supportive therapy to control pain and improve quality of life.

Keywords: Temporomandibular joint disorders, Botox, Fillers, Hyaluronic acid, BTX-A

INTRODUCTION

The temporomandibular joint (TMJ) is a bilateral synovial joint located on both sides of the craniomandibular complex, which is involved in chewing, swallowing, speech, and other automatic movements such as yawning, grinding, or clenching, TMJ pathophysiology significantly impacts individuals.[1]

The glenoid fossa of the temporal bone and the mandibular condyle come together to form the TMJ, which is a ginglymoarthrodial joint.[2] A range of musculoskeletal or neuromuscular problems that affect the temporomandibular joint, the muscles of mastication, and the surrounding tissues are referred to as temporomandibular disorders (TMDs).[3]

TMD comprises a cluster of conditions that causes pain and discomfort in the masticatory muscles, TMJ, and surrounding structures, TMDs include a range of painful symptoms, such as ear and facial pain, headache in the temporal region, and tooth sensitivity, as well as non-painful symptoms such as clicking, popping, or crepitus of the TMJ, limited jaw-movements, and muscle fatigue or stiffness.[4] The most common TMD conditions are illustrated in Figure 1.

The goal of treatment for TMDs is elimination or reduction of pain and joint sounds, also return to normal function. Upon pharmacotherapy for TMDs, the utmost used medications are, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, tricyclic antidepressants, and corticosteroids.[6] Occlusal appliances may also be used for occlusal stabilization, for the treatment of temporomandibular disorders, or for the prevention of

dentition wear.[7] The possibility of applying botulinum toxin type A (BTX-A) for the treatment of disc displacements is also carried out using injections in the lateral pterygoid muscles. BTX-A decreases myofascial pain and symptoms in the bruxers by reducing muscle tension.[8]

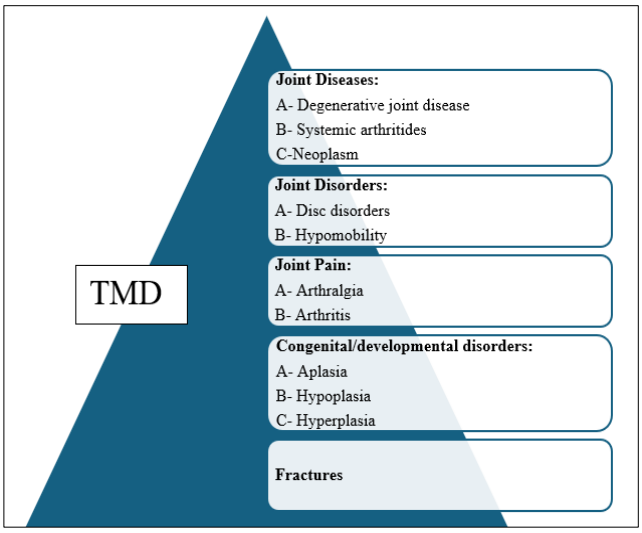

Figure 1: Temporomandibular joint disorders.[5]

One thing must be remembered that pharmacotherapy has its goal in decreasing pain and inflammation within the joint and/or surrounding muscles. This therapy improves function and inhibits the progression of the disease.[9] In order to prevent the target muscle from contracting too much, the neurotoxin botulinum toxin type A have been recently introduced in the treatment of TMDs since it has the capacity of blocking the release of the neurotransmitter acetylcholine at the neuromuscular junction, alleviating pain and tenderness.[10] The history of botulinum toxin in dentistry began in 1999 when Howard Katz created the original protocols for the use of Botox in dentistry as a treatment for TMJ disorders resulting from excessive bruxism.[11]

As a consequence, the present review article was undertaken to shed some light on the different treatment modalities of TMDs and specifically the relevance of BTX-A for pain relief in TMD patients.

METHODS

The present review was carried out following "The Cochrane Handbook for Systematic Reviews of Interventions" and reported as suggested using preferred reporting items for systematic reviews (PRISMA) guidelines.

Search strategy and study selection

The search for related studies were carried out regardless of the language or year of publication in the following electronic databases: Medline (via PubMed, Scopus, The Cochrane Library).

Inclusion criteria

All original relevant studies that discussed the effectiveness of BTX in managing temporomandibular disorders.

Exclusion criteria

If it was a pilot study, duplicate records, incomplete reports, or data that could not be reliably extracted, abstract-only articles, theses, books, and conference papers. The title and abstract screening were undertaken independently by four reviewers.

LITERATURE REVIEW

Causes of TMJ disorders (TMDs)

The cause of the most common types of temporomandibular disorders is complex and is still largely unresolved, Psychogenic factors have also been implicated, but, like trauma and malocclusion, these are often considered as exacerbating factors rather than the primary cause of temporomandibular disorders, causes include biologic, environmental, social, emotional, and cognitive triggers.[12,13] Some investigators related TMD with bruxism but to date there is no clear association between bruxism and TMDs.[7] Other investigators related TMD to hormonal factors, where they reported that low levels of estrogen during menopause predisposes the TMJ to degeneration and increase the risk of alveolar bone loss.[14]

Recently, Mustafa et al, in 2022, stated that 70% of rheumatoid arthritis patients suffer from some degree of temporomandibular joint disorder.[15] Smoking is associated with an increased risk of TMD in females younger than 30 years, TMD can also be associated with disk dysfunction, with or without reduction.[16,17] A systematic review and meta-analysis done in 2023 about association between obesity and TMD, the results showed that obesity is not a risk factor for TMD, and maybe a protective factor for TMD, of which patients with larger BMI are less likely to suffer from TMD pain.[18]

Clinical manifestations

Most patients experience collective decrease in clinical manifestations of TMD including pain relief and improved masticatory functions after treatment.[19] Regarding the fact that pain is the main manifestation and complaint of patients with TMD, it is not surprising that most related review studies have focused on the effects of botulinum toxin in reducing pain in these patients.[20]

Calis et al in 2019 reported that to improve clinical success in the practice use of BTX-A in temporomandibular joint

diseases; "there are some conditions that should be encountered prior to treatment such as correct identification of the painful chewing muscles, absence of generalized hyperactivity in the masticatory muscles, any possibility of arthrogenic causes must be eliminated, the patient exhibits resistance to conservative treatments for a period of at least 3 months, with no apparent contraindications for BTX-A treatment".[21]

Management and treatment modalities of TMD

The treatment of TMD is complicated and requires specific knowledge and exercises to strengthen some groups of muscles and weaken others, occlusal splint therapy, massage, and pharmacotherapy. Although the treatment seems difficult, most of the patients searching for help due to TMD assess that the treatment is successful, although an accurate diagnosis needs to be made to start the proper protocol of treatment.[22]

Different modalities have been implied for the treatment of TMJ disorders including surgical and non-surgical interventions. Surgical intervention is needed in 5-10% of TMD patients, however surgery is considered the last option.[12] Nevertheless, the more localized the symptoms of the TMD are, the more likely surgery will have a favorable outcome.[23] It is noteworthy that not all oral and maxillofacial surgeons are trained to perform surgery on the TMJ region since it is a highly specialized area of surgical practice.[24]

On the other hand, 40% of patients who exhibit TMD signs and symptoms may undergo spontaneous resolution without any intervention, while 50% to 90% of patients' experience pain relief with conservative therapy.[25,26]

TMD management include different treatment modalities

Muscular training is the primary mode to achieve muscle restoration, especially after traumas and injuries. It is thought to be the most conservative treatment as well as the most non-invasive method of TMD treatment. The exercises can require stretching, relaxation movements that should be performed routinely to eventually lead to a shortening of the excessively expanded muscles or to a restoration of the full length of the shortened muscles.[27]

Occlusal appliance therapy is considered the most common form of treatment provided by dentists for TMJ disorders. Short term studies have shown that the use of an appliance has been effective in reducing signs and symptoms of TMD disorders.[28] Removable devices such as a bite raising appliance, occlusal splint, or a bite guard, is usually fabricated from hard acrylic, that is custom made to fit over the occlusal surfaces of patient`s teeth, although occlusal appliance therapy has been shown clinically to alleviate symptoms of temporomandibular disorders in over 70% of patients, the physiological basis of the response to treatment has never been well understood.[12]

Occlusal splints therapy is used in a vast majority of patients with TMDs to restore the static and dynamic symmetry of the stomatognathic system. Most commonly, they are used in cases with disc displacement.[27,29,30] The splints are fabricated individually for each patient by the dentist with the help of the technician.

Massage therapy can be used to relieve myofascial pain, which is a common symptom of TMD that is often associated with the clenching of teeth, grinding and stress.[31,32] Massage can lead to re-establishing the proper flexibility and muscular length of the jaw muscles and relieving pain.[33]

Physiotherapy massage was found to be a suitable method for pain relief in TMD, however there is not enough evidence that support long term success of physiotherapy in relieving pain, nevertheless, can be used in short term for pain relief due to its safety.[34,35]

Pharmacotherapy is used when somatic symptoms, such as sleep disorders, chronic pain, arthralgias, inflammatory diseases, myalgias or neuropathies are associated with TMD.[6] As TMD may manifest from different systemic diseases (e.g., arthritis, inflammatory bowel diseases, Parkinson disease), it is important to properly diagnose the patient and implement treatment for the underlying disease, especially when depression is a suspected diagnosis.[36,37]

Different types of medications were reported to be effective in the treatment of TMD; anticonvulsants like gabapentin, clonazepam, and diazepam were proven effective in reducing pain of TMD patients.[38] It has been proposed that anticonvulsants should be used as adjuvant analgesics in TMD, particularly for patients who have a history of failed TMJ surgeries or those who have long-standing unremitting pain.[39]

Although non-steroidal anti-inflammatory drugs (NSAID) may affect the efficiency of antihypertensive drugs, the decreased ability of blood clot may increase the probability of bleeding and gastric erosion that in turn may lead to peptic ulcer and drug-to-drug interactions that cause unwanted effect, nevertheless NSAID shows great effect as pain reliever for TMJ disorders for example: naproxen showed a significant reduction of the symptoms displayed by the painful TMJ disc displacement, celecoxib showed mild pain reduction in comparison with placebo, but was not significantly effective for TMD pain control.[40] Another commonly used drug meloxicam was suggested which is considered a COX-2 inhibitor.[41]

Antidepressants have been utilized for more than thirty years to treat chronic TMD pain as a primary analgesic for the management of headaches and neuropathic pain, reducing the feeling of depression caused by pain and improving sleep quality.[9] Among these medications, tricyclic antidepressants (TCAs) appear to be the most effective, however, selective serotonin reuptake inhibitors

(SSRIs) have also been reported to reduce orofacial pain as well, however, they have adverse effects including dry mouth, constipation, dizziness, drowsiness, and impaired vision.[42] Epinephrin dosage for patients taking TCAs should be kept at 0.04 mg to avoid potentially harmful cardiovascular events.[40] SSRIs have been associated with fewer unwanted effects compared with the TCAs, nonetheless, SSTIs drugs cause GI disturbances, such as nausea and vomiting, headache, sexual dysfunction, dry mouth, and sweating.[43]

Henceforth, pharmacotherapy can be considered as a complementary therapy rather than a treatment itself. The exceptions are systemic diseases with TMJ involvement.[44] In myositis and other inflammatory disorders, the most appropriate strategy is the administration of one intramuscular dose of corticosteroid. Another approach is the injection of an analgesic or anti-inflammatory agent.[45]

Intra-articular injection of morphine showed a significant increase in the pain threshold in the diseased joint, however chronic use may lead to tolerance or physical dependence.[46] Addiction may occur in patients predisposed to chemical dependency.[47]

Intra-articular injection of corticosteroids is effective in TMJ synovitis if inflammation is confirmed, even though steroids have many advantages, there are still unwanted side effects such as acute adrenal crisis, hypertension, and electrolyte anomalies, as well as damage to the TMJ fibrous layer and bone resorption.[40,48]

TMJ replacement may be an alternative modality in patients where the TMJ is too severely damaged by the inflammatory process to be cured in a conservative way, implants are used to replace the TMJ.[49] The main indication for TMJ replacement is pain relief and functional improvement in arthritis cases including osteoarthritis, psoriatic, rheumatoid arthritis, and ankylosing spondylitis.[50,51]

Surgical procedures combined with orthodontic treatment should be considered in cases of severe malocclusion, unilateral condylar hyperplasia or hypoplasia complicated by TMJ dysfunction.[52,53]

Dermal fillers and botulinum toxin have made their way into dentistry in recent years for both cosmetic and medicinal purposes. Dermal fillers and botox have been acknowledged by dentists and brought into clinical dentistry due to the encouraging outcomes acquired in facial esthetics and restoring a beauteous smile. The combination of a complete aggregate of teeth and good facial esthetics creates a radiant smile.

Dermal fillers (hyaluronic acid)

When arthrocentesis is not performed, the intraarticular injection of hyaluronic acid (HA) is more effective in pain reduction in comparison to injections of either corticosteroids or physiologic saline solution. HA is a non-sulfated glycosaminoglycan, a polysaccharide composed of repeated units of D-glucuronic acid and N-acetylglucosamine with alternating beta glucuronide and beta linkages, hyaluronic acid naturally exists in the synovial fluid and articular cartilage, and secreted by the synoviocytes type B cells, which resemble fibroblasts.[54] Higher molecular weight and less sensitivity of stretch-activated channels to mechanical stresses were shown to be the cause of HA. Because HA lessens the mechanical sensitivity of these channels, it may be possible to effectively suppress the pain response.[55] The outcomes of five intraarticular injections of HA either or physiologic saline solution were compared. The scientists discovered that the only individuals who showed a discernible improvement in TMJ pain were those who had HA injections. When combined, the results of this comprehensive analysis demonstrated the fascinating benefits of intra-articular HA injections for TMD patients, including decreased pain intensity and enhanced functioning.[56] Recently several studies were carried out discussing the effectiveness of HA in TMD management as shown in Table 1.[57-63]

Botox (botulinum toxin A)

TMD is known to be closely associated with pain of the masticatory muscles adjacent to the TMJ, applying BTX-A for the treatment of disc displacements using injections in the lateral pterygoid muscles, BTX-A decreases myofascial pain and symptoms in the bruxers by reducing muscle tension.[8]

BTX is the exotoxin of a gram-positive aerobic bacterium called *Clostridium botulinum* with eight different types. BTX-A is a biologic variant that temporarily inhibits the skeletal muscle through hindering the production of acetylcholine and inactivation of calcium channels in the nerve endings.[64] Injections of botulinum toxin for patients with articular disc displacement resulted in pain relief and return of the normal movements of the mandible. The treatment was effective and stable up to 6 weeks.[65]

A randomized clinical trial was recently conducted in 2022, where they reported that BTX-A and low-level laser therapy could be considered as effective alternative treatment modalities to anterior repositioning appliances regarding reducing joint pain, clicking, and improving disc position in patients with symptomatic disc displacement with reduction.[66]

Another recent randomized clinical trial was also carried out to measure the effect of BTX-A injection on the lateral pterygoid muscle in patients with a painful temporomandibular joint click, the study concluded that BTX injection can make the click sound disappear, however their study revealed that click and pain severity decreased, but the difference was not statistically significant.[67]

Table 1: Published studies between 2021-2024 in PubMed discussing the effectiveness of hyaluronic acid in the management of temporomandibular disorders arranged according to publication dates.[57-63]

Author, year	Country	Design	Title	Conclusion
Xu et al, 2023	China	Systematic review and network meta-analysis	Comparative effectiveness of hyaluronic acid, platelet-rich plasma, and platelet-rich fibrin in treating temporomandibular disorders	PRP and PRF exhibited similar short-term efficacy in treating TMD, while PRF was more advantaged terms of long-term efficacy. Therefore, PRF was recommended for treating TMD.
Miglani et al, 2023	India	Review article	Hyaluronic acid: exploring its versatile applications in dentistry	Various temporomandibular disorders can be treated by injecting HA into the joint space. It assists decreasing inflammation, enhances joint lubrication, and stimulates tissue regeneration.
Lippi et al, 2023	Italy	Review	Multidisciplinary rehabilitation after hyaluronic acid injections for elderly with knee, hip, shoulder, and temporomandibular joint osteoarthritis	TMJ injections with HA can represent a possible alternative in the complex management of TMD patients suffering from chronic pain and/or not responding to conservative approaches, considering that TMJ injection procedure is minimally invasive with a low number of complications.
Akshita et al, 2023	India	Review	Enhancing pain relief in temporomandibular joint arthrocentesis: platelet-rich plasma and hyaluronic acid synergy	The synergistic interplay between PRP regenerative properties and HA's lubrication and anti-inflammatory effects presents a comprehensive solution to the multi-faceted nature of TMJ disorders. While our analysis of existing evidence is encouraging, it is imperative to acknowledge that more extensive randomized controlled trials and mechanistic studies are essential to validate the long-term efficacy and safety of this therapeutic option.
Checinski et al, 2022	Poland	Systematic review and meta-analysis	The administration of hyaluronic acid into the temporomandibular joints' cavities increases the mandible's mobility	The increase in the amplitude of mandibular abduction was expressed as the quotient of the mean value during the observation periods, and the initial value was achieved in all study groups, and in the line regression model, it was 0.5 mm on average per month. Multiple administrations of the drug may reduce the analgesic effectiveness of the treatment.
Cardoneanu et al, 2022	Romania	Review	Temporomandibular joint osteoarthritis: pathogenic mechanisms involving the cartilage and subchondral bone, and potential therapeutic strategies for joint regeneration	The regenerative potential of such therapies as PRP, MSCs, and HA regarding the cartilage and subchondral bone (alone or in various combinations) in TMJ OA remains a matter of further research, with studies sometimes obtaining discrepant results.
Derwich et al, 2021	Poland	Systematic review	Mechanisms of action and efficacy of hyaluronic acid, corticosteroids and platelet-rich plasma in the treatment of temporomandibular joint osteoarthritis	The intraarticular injection of HA is more effective in pain reduction compared to injections of either CS physiologic saline solution.

PRP: Platelet-rich plasma, PRF: platelet-rich fibrin, HA: hyaluronic acid, OA: osteoarthritis, CS: corticosteroids, MSCs: mesenchymal stem cell-based treatment.

Patients with TMD sometimes experience mouth-opening limitation, and botulinum toxin A therapy can relax the adjacent masticatory muscles, BTX-A thereby may improve muscle inflammation, which in turn lead to improved mouth opening.[68] Multiple injections of BTX are effective (at least temporarily) in relieving TMJ pain, clicking and noises, with less adverse effects.[69] Myofascial pain and spasm can additionally be relieved by Botulinum toxin injection of the temporalis muscle.[70]

Regarding BTX injections to the masticatory muscles, a systematic review revealed controversial results for BTX therapy. Among the included five studies, two obtained a significant reduction in pain, one showed equal effects compared with masticatory manual therapy, and two showed no significant differences for BTX compared with placebo.[71]

Several studies were found investigating the long-lasting pain-reducing effect of BTX-A on pain intensity in patients with TMD of muscular origin. BTX-A has been shown to be more effective than placebo in reducing local pain of muscular origin in bruxers and patients with TMD of muscular origin.[72]

The local injection of BTX-A constitutes an innovative and adequately efficient treatment method for chronic facial pain associated with hyperactivity of the masticatory muscles. An improvement in the painful symptoms can be expected in up to 90% of patients who do not respond to conservative treatment methods.[73] The injection of BTX-A was shown to decrease the muscle action potential in 14 days. The patients also showed improvement in pain and psychological status.[74]

Patel and his colleagues demonstrated the utility of Inco BTX-A in treating patients with TMD with pain, despite pain medication usage and other conventional treatments.[75]

Intra-articular injection of BTX is a safe and effective alternative treatment for severe, refractory TMJ pain, to avoid surgery.[76] No significant immediate or delayed complications were reported by other investigators. Thus, intramuscular injection of BTX into the lateral pterygoid muscle is an effective and safe treatment for habitual temporomandibular joint dislocation. More injections are required in cases of neurogenic temporomandibular joint dislocation than in those of habitual dislocation without muscle hyperactivity.[77] de-la-Hoz et al added that the BTX-A injection for the treatment of muscular temporomandibular joint disorder is a viable treatment option in the case of patients who do not respond to conservative treatment methods.[78]

Clinical application of BTX-A in dentistry and oral and maxillofacial surgery

BTX-A has recently been widely used for cosmetics. For diminishing facial wrinkles most commonly seen along the glabella lines and platysma bands, and for perioral cosmetic therapies such as gummy and asymmetrical smile treatment. BTX-A has been additionally used for the correction of prominent mandibular angle and facial asymmetry due to masseter muscle hypertrophy.[68]

BTX-A has therapeutic uses in TMD, as it appears to be as effective in controlling myofascial pain related to TMDs as conventional treatments.[79] BTX-A injection in masticatory muscles of patients with TMD can be a useful supportive therapy to control pain and improve quality of life, likewise it can be used in patients with facial nerve palsy.[80] Because BTX-A has local effects on extrafusal and intrafusal motor fibres, it is an excellent treatment for spasticity and dystonia when injected into overactive muscles.[81] In conditions with salivary gland secretory disorders, injections of botulinum toxin A into the parotid and submandibular glands have effectively improved sialorrhea without compromising dysphagia in patients with Parkinson's disease (PD).[82] BTX-A offers a highly effective, safe, and noninvasive method of treatment as an adjuvant for wound healing after oral and maxillofacial surgery particularly in post parotidectomy sialocele surgical interventions.[83]

BTX-A has been used for management of sleep bruxism, BTX-A were injected bilaterally into the masseter or temporalis muscles (50–100 units overall), they showed the efficacy of BTX-A in reducing the sleep bruxism number of events.[84] While in another research, the treatment with botulinum toxin, oral appliances and biofeedback did not demonstrate short-term efficacy in reducing sleep bruxism.[85]

BTX-A showed success in terms of improvement and reduction of 3.22 mm of gummy smile in the short term up to three months.[86]

Furthermore, BTX-A has demonstrated its clinical efficacy in trigeminal neuralgia, with patients reporting improvement in their pain frequency and intensity, However, several factors limit the clinical use of BTX-A: due to a lack of specific guidelines about optimal dose and injection techniques.[87] BTX-A injection could be additionally considered as the primary option for the prevention of postsurgical relapse in class II malocclusion patients.[88]

Side effects and complications of BTX-A

Overdose of BTX-A may cause systemic complications including nausea, fatigue, malaise, flu-like symptoms such as fever and chills, elevation of blood pressure, diarrhea, abdominal pain, and anaphylaxis shock in case of true allergic reactions.[89] Various local complications may additionally arise based on the injection site, including headache, pain at the injection site, edema, ecchymosis, ptosis, dry eye syndrome, lagophthalmos, orofacial edema, dysphonia, and sensory abnormality. Headache is the most common adverse effect reported by patients, although BTX-induced headaches have been known to develop within 24 hours after the injection, they tend to reduce with increasing the injection frequency, bruises or ecchymosis may develop in any area, whereas ptosis usually develops as the neurotoxin diffuses to adjacent areas when it is injected into the corrugator supercilia. Bruises or ecchymosis are considered local complications that can be prevented by avoiding superficial vessels through using the thinnest needles as possible in bright light for adequate illumination during the procedure. Ptosis can be prevented

by inhibiting toxin diffusion by pressing on the orbital rim with the finger.[74]

CONCLUSION

BTX-A injection in masticatory muscles of patients with TMD can be a useful supportive means of therapy to control pain and improve quality of life.

Further research is required to determine the therapeutic effects of varying BTX-A injectable dosage, locations, and durations with various TMDs.

ACKNOWLEDGEMENTS

The authors would like to thank the College of Dentistry Research Centre and Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia for supporting and approving this research project (CDRC # IR 0504).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Khounganian RM, Mahdi AA, Aloshaywi AK, Almanqur AI. Botulinum toxin (A) for pain control in temporomandibular joint disorder patients. Int J Community Med Public Health 2024;11:4974-83.