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Review Article

Efficacy of botulinum toxin in masseteric muscle hypertrophy: A Systematic Review

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ABSTRACT:

Background: Masseter hypertrophy is uncommon and can occur unilaterally or bilaterally. Pain may be a symptom or asymptom, but most frequently, a clinician is consulted for cosmetic reasons. **Aim**: To assess the use of botulinum toxin in masseteric muscle hypotrophy **Methodology**: A literature review was performed using Pubmed, Science Direct and Cochrane using the MeSH term"botulinum toxin and masseter muscle hypertrophy". According to Prisma guidelines, the mesh terms were altered in search engines. **Result and conclusion**: In the available literature, botulinum toxin was proven effective in masseter muscle hypertrophy.

Keywords: Botulinum toxin, masseter muscle hypertrophy.

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INTRODUCTION

Legg first described masseteric muscle hypertrophy in 1880; it is more probably a congenital, genetically acquired anomaly. The masseter muscle is essential for adequate mastication, which is located laterally to the mandible ramus and plays an important role in esthetics. In addition, the masseteric muscle hypertrophy will alter the facial line, generating discomfort and negative cosmetic impacts for some patients. It can occur unilaterally or bilaterally. This symptom is benign and asymptomatic (1). Masseteric muscle hypertrophy is an asymptomatic persistent enlargement of one or both masseter muscles resulting in hypertrophy(2).The aetiology of this condition remains unknown, but some authors correlate it to bruxism or heavy gum chewing, temporomandibular joint disorder or emotional disorder. Clinically, the patient has a rectangular or square face configuration(3).Diagnosis can be clinical examination, directed interview, panoramic x-ray, and muscle palpation. The last diagnostic test consists of palpating the muscle with fingers while the patient clenches the teeth so the muscle is more prominent during contraction. With the muscle relaxed and the patient's mouth slightly open, extra oral palpation with both hands will pinpoint the intramuscular location of the hypertrophy. Under relaxation, the jaw angle may reveal irregularities that, on the x-ray image, may appear to be a bone increase. Differential diagnoses must include muscle tumours, Salivary gland diseases, parotid tumours, parotid inflammatory diseases and intrinsic masseter muscle myopathy(2).Treatment can be done by surgical treatment and injecting botulinum toxin or excision of the masseter muscle(2).Now heading, botulinum toxin was the first toxin used in the history of human medicine. Botulism is known as food poisoning caused by the ingestion of rotten meat. Justinus Kerner reported this toxin in 1817.Botulinum toxin is a neurotoxic protein produced by bacteria clostridium botulinum and their species(4). Its mechanism blocks the release of the neurotransmitter acetylcholine at the neuromuscular junction with reversible chemical denervation of the muscle fibre, thereby inducing partial paralysis and atrophy. The released toxin was used for medical and cosmetic purposes. The most commercially used type of

botulinum toxin in humans is type-A and type- B(5).It is employed in the medical field as well as in dentistry for temporalis and masseter muscle hypertrophy, dentofacial esthetics and gummy smile dropping of corners of the mouth, Temporomandibular joint disorder, bruxism, myofascial pain, trismus, sialorrhea and salivary secretory disorder, facial nerve palsy, trigeminal neuralgia, implantology, oral and maxillofacial trauma, adjunct to orthodontic to prevent relapse and mainly in masseteric muscle hypertrophy(7).At the injection site, there may be discomfort or oedema, bruising, headache, flu-like syndrome, crooked smile, and drooling are side effects(6).Contraindications of BT is any allergy to btx a and btx b, pregnancy and lactation, drugs like anticholinergic, aminoglycosides and other agent related to neuromuscular transmission(7).

OBJECTIVE

To assess botulinum toxin's effectiveness in the treatment of masseteric muscle hypotrophy.

MATERIALS AND METHOD USED

Study design: A systematic review of randomised controlled trials with interventions.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

i. Original article
ii. Full-text article
iii. Studies which take botulinum toxin as a measure for masseter muscle hypertrophy.

EXCLUSION CRITERIA

i. Articles without full text
ii. The studies do not take botulinum toxin in masseter muscle hypertrophy
iii. Studies written in other languages were disqualified.

SEARCH STRATEGY

The study used results from original publications and research papers that have been published on the use of botulinum toxin for masseteric muscle hypertrophy in databases including Pubmed Central, Science Direct, and Cochrane Central Register of Controlled Trials(CENTRAL). The MeSH phrase "Botulinum toxin "was used to conduct a literature search to find pertinent information. The mesh phrases modified in each search engine in accordance with the prisma recommendations

Figure1: flow diagram showing the number of studies observed, screened, assessed, for eligibility, excluded and included in the systematic review.

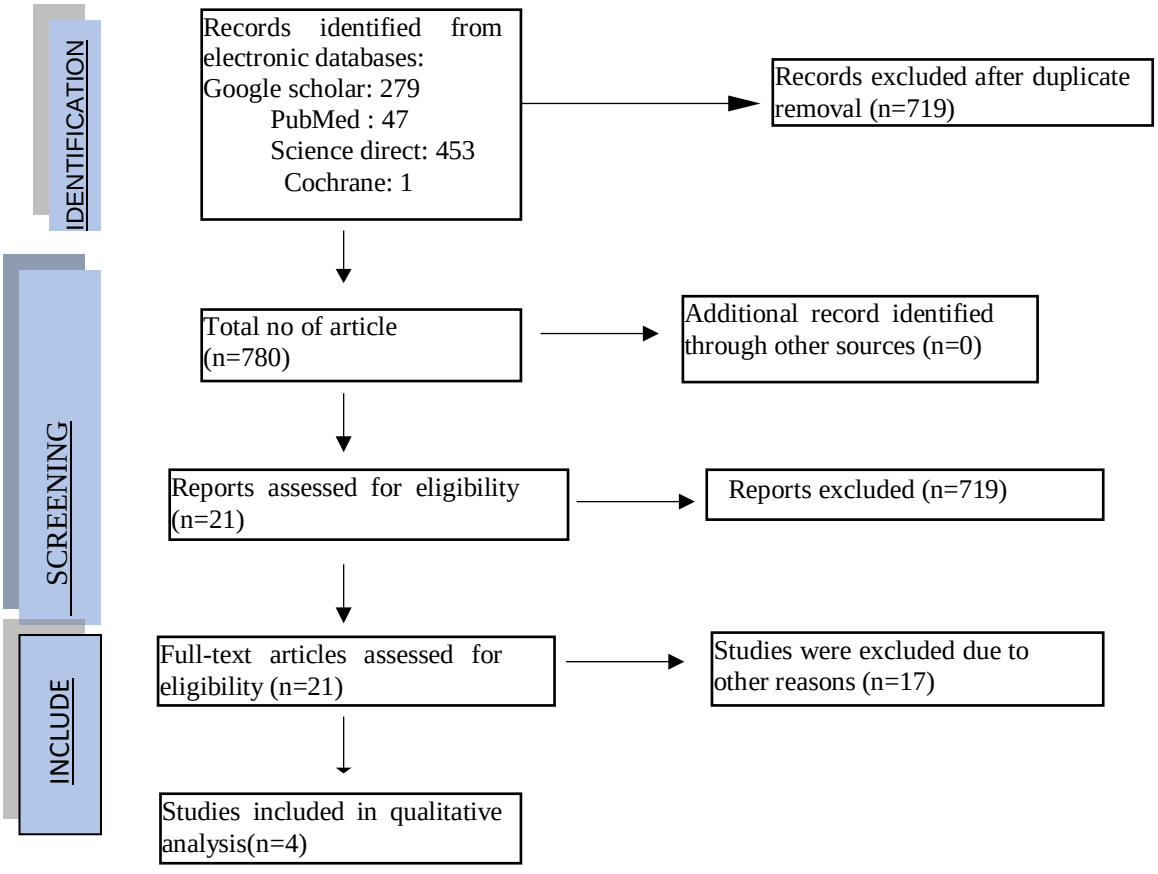

Table 1:Showing the number of data included and studies taken for qualitative analysis

Author	Year	Sample size	Group characteristic	Intervention
Si-Yeok Park1 , Young-Wook Park2 , Young-Jun Ji3 , Sung-Wook Park4 and Seong-Gon Kim	2015	Ten male adult white rabbits	GROUP 1: Five units of BTX-A were diluted with normal saline as five units/ 0.1 Ml were administered into the middle of the masseter muscle. GROUP 2: Twenty units of BTX- A were diluted with normal saline as five units/ 0.1 mL were administrated into the middle of the masseter muscle.	DURATION:12 HOURS General anaesthesia was administrated by an intramuscular injection of 0.5 tiletamine, zolpidem and 0.5 ml of xylazine. In addition, the rabbits were implanted with electrodes for telemetrical recording of EMG of the masseter muscle. The activity of the muscle was recorded continuously for 4 hrs, 8 hrs and 12 hrs after surgery and was divided into mentioned groups. Muscle activity was recorded immediately after 12 hours. The variation between the groups were assessed with independent t samples. The significance level for all the tests was $p<0.05$.
Fedorowicz Z, van Zuuren EJ, Schoones J	2013	Individuals of any age who have bilateral benign masseter hypertrophy	Transcutaneous intramasseteric injection of botulinum toxin vs placebo or no treatment.	DURATION: 2 YEARS Improvement in facial appearance, pain or discomfort associated with tempero-mandibular joint or jaw muscles using a validated pain scale.

Chanyoungpark, kitaepark, jiyeon Kim	2014	A total of 63 four-week-old male Sprague-Dawley rats	GROUP 1: Animals served as control and were injected with saline. GROUP 2: Animals were injected unilaterally with BTX-A GROUP 3: Animals were injected bilaterally with BTX –A	DURATION:4 WEEKS Animals were sacrificed, dry skulls were prepared, and mandibles were measured. In the unilateral group, the experimental side was reduced dimensions for all mandible measurements compared with the control side, suggesting a local effect of BTX-A on mandible growth, likely due to muscle reduction.
Gunwoopark, young-chan Choi, Jung-hee bae, Seong-taek Kim	2017	20 patients	Of the 20 volunteer patients, ten were assigned to an experimental study (injected with each side 25 U of botulinum toxin into both masseter muscle) and 10 to a control group. The thickness was measured before and after the injection.	DURATION: 4,8 and 12 weeks The thickness of the masseter muscle was measured at 4,8 and 12 weeks after the injection. The subcutaneous tissue does not differ significantly at rest or during maximal contraction.

Table 1 shows the characteristics of interventions in included studies. All four studies reveal the effectiveness of botulinum toxin in masseteric muscle hypotrophy. But the studies are different individually regarding the sample size, age of population and duration of intervention. In addition, two of the studies were among animals, and two were among patient.

Table 2: Outcome data as reported in the included studies

Author	Year	Outcome	Result
Si-Yeok Park1 , Young-Wook Park2, Young-Jun Ji3 , Sung-Wook Park4 and Seong-Gon Kim	2015	Effect of botulinum toxin type A (BTX-A) in masseter muscle using electromyography in an animal model(rabbit).	In group 1, The peak voltage before injection was 6.42±0.50mV and 4.73±1.25mV after injection.The difference was significantly noted(P=0.044). The RMS before injection 0.28±0.07mV and

			0.12±0.05mV after infection. The difference was significantly noted(P=0.002). In group 2, The peak voltage was 6.49±0.63mV and 2.70±0.98mV before and after infection, and the difference was p=0.001. When group 1 was compared with group2, the relative peak voltage was 73.93±18.88% and 41.14±12.96%, and the difference was p=0.013. Additionally, the relative RMS activity in groups 1 and 2 were 41.68±11.06% and 30.38±11.84%, but the difference was insignificant, p>0.05.
Zbys Fedorowicz , Esther van Zuuren, Jan Schoones	2013	Randomised controlled trials (RCT) and controlled clinical trials (CCT) comparing intra-masseteric injection of botulinum toxin versus placebo in individuals of any with bilateral benign masseter hypertrophy.	This review highlights the need for well-designed, adequately powered, randomised controlled trials to evaluate the efficacy and safety of botulinum toxin for reducing the size and volume of the masseter muscle in people diagnosed with bilateral benign masseter hypertrophy.
Chanyoung park, kitae park, jiyeon Kim	2014	Botulinum toxin on mandible skeletal development in developing rats by inducing muscle hypofunction.	The study was randomly divided into three groups. Average body weight was highest in the control group (9.19±5.72 g), with the lowest weight in the unilateral BTX-A group (83.19±1.65 g). The Rate was significantly higher in group 1(273.48±22.14%) and group 2(270.26±21.67%) than in group 3 (249.97±24.37%), but there was no significant difference between group1 and 2.
Gunwoopark,young-chan Choi,, Jung-hee bae, Seong-taek Kim	2017	Twenty volunteer patients were assigned to an experimental study injected with botulinum toxin into both the masseter muscle, and the subcutaneous thickness was measured at rest and during maximum and minimum contraction.	The masseter muscle thickness was constantly decreased at rest (14.19±2.13mm at preinjection, 12.51±3.23mm at four weeks, 11.76±2.67mm at eight weeks.11.27±2.85mm at 12 weeks, and a total decrease was 2.92mm) and during contraction(16.58±2.17 mm at preinjection,14.04±3.48 mm at four weeks,13.72±2.87 mm at eight weeks,13.24±2.97 mm at 12 weeks and the total decrease was 3.34mm) in the experimental group.

Table 2: shows the outcome data of botulinum toxin in masseter hypertrophy in the included studies. There were progressive reduction in the masseter muscle.

Table 3: BIAS ASSESSMENT OF INCLUDED STUDIES

Author name, year	Random sequence generation	Allocation concealment	Blinding of outcome	Incomplete outcome data	Blinding of participant and personnel	Selective reporting	Judgemental bias
Siyoek park et al [8]	+	+	?	+	-	+	+
ZbysFedorowicz et al [9]	_	_	?	_	?	+	+
Chanyoung park et al [10]	+	-	?	-	?	?	?
Gunwoo park et al [11]	+	+	?	+	?	+	?

Table 3 shows the biased analysis of the included studies, and all the studies had a positive outcome
+=low risk of bias, - = high risk of bias,?=unclear risk of bias

DISCUSSION

Botulinum toxin has been widely used in the medical field for cosmetic and therapeutic purposes. Botulinum toxin produces paralysis by blocking presynaptic release of neurotransmitters, i.e. acetylcholine at the neuromuscular junction, with reversible chemical denervation of muscle fibre. The systemic review found conflicting results of botulinum toxin in masseter muscle hypertrophy. Among the four included studies, three reported a reduction in scores of the conditions measured from the baseline. However, four of these studies reported a reduction in masseter muscle hypertrophy, the subject as botulinum toxin. Si-yoek park et al. reported a significant reduction of rabbit's masseter muscle hypertrophy by injecting botulinum toxin. The masseter muscle activity was measured using electromyography. Ten male adult rabbit was taken into the studies and divided into two groups. In each group, rabbits received botulinum toxin and were recorded continuously for 8 hours, starting 12 hours after surgery. Both groups significantly reduced masseter muscle activity after BTX-A injection ($p<0.005$). Zbys Fedorowicz et al. reported the efficacy and safety of botulinum toxin in masseter muscle through randomised controlled trials. Individuals of any age with bilateral masseter hypertrophy received botulinum toxin for several periods and followed for two years. This review highlights the need for well-designed, randomised controlled trials to evaluate the efficacy and safety of botulinum toxin for reducing the size and volume of the masseter muscle in people diagnosed with bilateral benign masseter hypertrophy. Chanyoung park et al. reported the effects of botulinum toxin on mandible skeletal development by inducing muscle hypofunction.63 four-week rats were taken and divided into three groups. Each group received botulinum toxin and waited for four weeks.Finally, the animals are sacrificed, measured and concluded with the reduction in the dimension of mandible measurement. Gunwoo park et al. aimed to use ultrasonography to measure not only changes in muscle thickness but also changes in subcutaneous thickness. This study enrolled 20 patients injected with botulinum toxin. A large decrease in the masseter muscle thickness was seen in the experimental group compared to the control group. Hence, these studies could show the efficacy of botulinum toxin in masseteric muscle hypertrophy.

CONCLUSION

All the articles taken for this systemic review proved the efficacy of botulinum toxin in masseter muscle hypertrophy. Botulinum toxin is widely used for medical and therapeutic purposes. However, further must be conducted to prove its effectiveness on masseter muscle hypertrophy.

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