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Application of Botulinum Toxin in Dental Therapeutics: A Systematic Review

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KEYWORDS

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Facial Palsy, Efficacy,

Adverse Effects.

ABSTRACT:

Introduction: Botulinum toxin (BoNT) is extensively used as a therapeutic adjunct in management of several orofacial ailments, as it offers temporary relief from pain and has a relaxing ability on the muscles.

Objectives: In this systematic review various applications of BoNT in head and neck region for therapeutic purpose is discussed..

Methods: A systematic electronic database search was conducted in Six scientific literature databases for relevant studies published between January 2000 to July 2024. The included articles were evaluated for recording therapeutic benefits, efficacy, dosage, adverse effects and complications.

Results: The evidence based conclusion of this systematic review is BoNT administration into the musculature is beneficial, but efficacy was for limited period that called for repeated administration.

Conclusion: However when injected in smaller doses BoNT was much efficient and caused minimal adverse effects, serving as a non-invasive and conservative medicament.

1. Introduction

Botulinum Neurotoxin (BoNT) is produced by gram positive anaerobic, spore forming bacterium namely *Clostridium botulinum* under low-oxygen conditions. They are extremely toxic, yet its promising therapeutic benefits were discovered in the middle of the previous century. Administration of small doses of BoNT intramuscularly exhibited prolonged inhibitory effect on the release of neurotransmitter acetylcholine, thereby reducing the transmission of signals from nervous system to the skeletal muscles and glands[1, 2]. It also has inhibitory effect on intafusal muscle fibers, so to reduce afferent input from muscle spindles to central nervous system offering therapeutic benefits temporarily for several months. The efficient paralytic effect on the muscle occurs in 4-7 days after injection and was dose dependent. The dosage is expressed in terms of units of biologic activity. One unit of botulinum toxin corresponds to the calculated median intraperitoneal lethal dose (LD50) in female Swiss-Webster mice[3]

The blockage of neurotransmitter release from BoNT is irreversible and the affected nerve terminals do not undergo any degeneration process. The functioning would be recovered by the sprouting of nerve terminals and formation of new synaptic contacts, usually in around 2-3 months. The toxin requires 24-72 hours to take effect and this reflects the time necessary to disrupt the synaptosomal process. In very rare circumstances it may take around 5-10 days for the full effect of BoNT to be observed.

Initially, the use of BoNT was used to alleviate strabismus and blepharospasm. But then it was much sought after when it showed significant results for wrinkles and to ameliorate several autonomic disorders, by injecting into the skeletal muscles. Its notable benefit in pain management in ailments like migraines, headaches, neuropathic pains has made BoNT unique choice to the medical professionals[4, 5].

Since its approval by FDA in 2002, it became cosmetically important. Of the eight antigenically distinguishable exotoxins (A, B, C1, C2, D, E, F and G) of BoNT, type A is the most potent, followed by types B and F toxin [6.] However, it is contraindicated for its known allergic reactions, active inflammation or infection at the proposed injection site, during pregnancy or breast-feeding and in cases of chronic degenerative neuromuscular disorders[7].

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2. Rationale:

Over the last two decades, the use of BoNT in the field of dentistry has widened and is greatly accepted by the patient population. However, the evidence based data is a requisite for its judicial use to overweight its benefits over risks. This study was conducted to assess various dental applications, efficacy and adverse effects of BoNT when used as dental therapeutic agent.

3. Objective:

This systematic review summaries the available literature in the main scientific databases to address the following research questions, that were based on the PRISMA 2020 checklist[8]. **(Table 1)**

Table 1: PICO framework for the focused Clinical Question

Population	Human adults above the age of 18 years
Intervention/ Exposure	BoNT Injection used in adult subjects for any of the dental therapeutic purpose.
Comparison	Therapeutic effect before and after the administraton of BoNT injection.
Outcome of Interest	The efficacy and adverse effects were evaluated in the articles available in database

4. Review questions.

RQ1. What are the research / publication trends and intellectual structure of botulinum toxin for therapeutic purpose in dentistry?

RQ2. What are the various applications of Botulinum Toxin in dental ailments?

RQ3. What is the efficacy and adverse outcomes of BoNT when used as a therapeutic agent for dental / oral and maxillofacial ailments?

5. Methodology

This systematic review was built on fair depiction of current research trends on this topic. Quantitative evaluation of the research topic was done to analyses the vast information extracted from database[9, 10].

Literature search strategy:

An electronic database search was conducted on PubMed, Cochrane, AMED, CINAHL, LILACS, Clinical Trials.gov, search engines using 'publish or perish' and endnote software for the articles dating back from 1st Jan 2000 till 30th July 2024, using all Mesh Terms, text words, combination key terms and search strings taken from the review questions. The following key terms were used: "Botox", "botulinum toxin", "botulinum toxin type A", "Dentistry", "treatment", "therapy", "Oral and maxillofacial", "bruxism", "gummy smile", "trigeminal neuralgia", "clenching", "sialorrhea", "myofascial pain", "application ", "usage", "TMJ disorder/pain", "orolingual dystonia", "mandibular dystonia","Mandibular spasm", "Hemifacial Spasm/ Bell's palsy","implant","masseteric hypertrophy", "migraine", "Facial nerve palsy", "para functional habits", "Salivary gland secretory disorder", "Maxillofacial trauma and fractures", "adverse effects", "side-effects". After identifying the relevant key articles, their ancestral references and descendant references and search strategy were also checked upon.

Inclusion and Exclusion Criteria:

Retrieved publications based on the preliminary search were cleaned for suitability based on the following criteria:

Inclusion Criteria:

i. Any published studies that were comparative, experimental, case-control, Cohort, Clinical Trials, Cross-Sectional and RCT's were included to assess the effects of the intervention.
ii. Only the English articles with fully downloadable texts were selected.
iii. Studies done on human adults above the age of 18 years with no other systemic diseases.
iv. Articles pertaining to BoNT injection in Head and Neck region for therapeutic purpose, where there was mentioning of dosage of BoNT, site and/or number of injection points were selected.

Exclusion Criteria:

i. Review articles, case series, case reports, unpublished articles, grey literature, conference proceedings, pilot studies, duplicate records, incomplete reports or data that could not be reliably extracted, abstract only articles, theses, books and conference papers were excluded.
i. Animal studies, human subjects under age of 18 years.
ii. Studies using BoNT for cosmetic/aesthetic reasons in other parts of the body.
iii. Application of BoNT for other reasons in head and neck region i.e., skin texture, scar, androgenic alopecia, neck wrinkles, and trapezius.

Data Extraction and Analysis

The quantitative evaluation of research topic from the available database was independently done by the two reviewers and was cleaned to extract the included studies. Any disagreements were resolved by discussion and further reevaluation by the third reviewer.

RQ1: The research/ publication trends and study objectives were clustered based on countries that published the highest

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literature on BoNT usage for orofacial ailments, their site of administration, efficacy assessment method and its therapeutic purpose in dentistry.

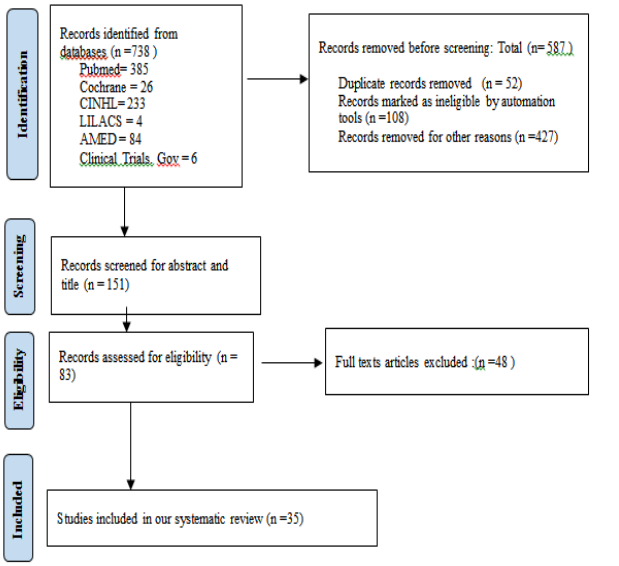
RQ2, RQ3: All the articles in the database were scrutinized using the title, abstract and keywords by two reviewers independently. Then the included articles were screened to elicit answers for the research question.

6. Results

We identified 738 studies that fulfilled inclusion criteria from all six databases listed as follows: PubMed= 385; Cochrane = 26; CINAHL= 233; LILACS = 4; AMED = 84 and Clinical Trials. Gov. = 6. Each paper was screened manually and evaluated based on the PRISMA 2020 Expanded Guidelines Checklist[8].

The study selection process followed the flow chart diagram and presented in accordance with the PRISMA statement **(Figure 1**). Only 35 identified article/paper were rechecked to confirm its potential relevance to the research question with regards to their title and abstract were completely read (including the objective, methodology, results, body of the article and conclusion references) to reconfirm its eligibility. The reason for exclusion was documented for the excluded articles. After the final selection, the data that was extracted/ imported onto Microsoft Excel Spreadsheet for evaluation.

Figure 1: Flowchart consisting of preferred reporting items for systematic review (PRISMA) Statement.



7. Discussion

RQ1. What are the research / publication trends and intellectual structure of botulinum toxin for therapeutic purpose in dentistry?

The top 7 countries that published majority number of original scientific literature/clinical trials on the therapeutic efficacy of BoNT for oro-facial aliments were from Canada (5), Korea and Brazil (4), Turkey (3) and US, Egypt, Sweden (2). (**Table 2**)

Table 2: Top nations contributing towards BoNT literature for orofacial ailments.

Country	No of articles
Canada	5
Korea	4
Brazil	4
Turkey	3
US, Egypt,Sweden	2
India, Iran, Netherland, Iraq, Finland ,Norway	1

RQ2: What are the various applications of Botulinum Toxin in dental ailments?

The therapeutic usage of BoNT on different anatomical structures for various treatments is shown in **Table 3.**

Table 3. Number of articles summaries the various applications of BoNT for dental therapies.

Head & Neck Muscles (n)		Oro- facial Treatments	(n)	Bite force & Occlusual Therapy (n)		Lip Positioning (n)		Salivary Gland Treatment (n)	
Masseter Alone	10	Gummy Smile	5	Pain relief + Muscle Relaxation	1	Occlusual Therapy + Implant	1	Mandibular Duct Injection	2
Masseter & Temporalis	7	Bruxism	5	Myogenic	1	Extra -Oral Injections	1	Intraparotid Injections	1
Masseter & Anterios Temporalis	3	Myo-Facial Pain (MFP)	5	Articulation associated Headache	1				
All Masticatory Muscles	1	TMJ + MFP	3						
Levator Labi Superioris Alae & Lateral Labi Superioris	1	Sialorrhea	2						
Levator Labi Superioris Alq. Naris & Orbicularis Oris	1	MAsseter Hypertrophy	2						
Lateral Pterygoid	2	Gingival Dysplasia	2						
Angularis Oris & Lobular Article	1	Bruxism + MFP	1						
		Bruxism + Cerebral Palsy	1						
		TMJ Clicking	1						
		Masticatory Muscle Disorder	1						
		TMJ + Joint Displacement Reduction	1						
		Drooling	1						

Temperomandibular joint Disorders (TMD)

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BoNT is extensively used in management of TMD because of its analgesic effects. TMD is a group of musculoskeletal or neuromuscular condition related to the true pathology of temporomandibular joint along with dysfunction of muscles of mastication and the surrounding tissues[11].Though TMD is the commonest pain causing ailment (next only to headaches and back pains) only few patients seek medical attention. Recent increase in the prevalence of TMD by 10-30% has raised concern, as very few individuals seek medical treatment for TMD[12]. TMD has a conventional treatment approach including physiotherapy and exercise, anti-inflammatory and analgesic drugs, muscle relaxants, oral appliances (mostly stabilization splints), and / or combination of these modalities. In 2002, Schwartz et al. were the first to report beneficial properties of BoNT for TMD patients after applying it topically to the affected structure. Many subsequent studies reported similar findings, but with different dosages and BoNT application techniques.

The TMD varies among individuals and may include signs of neck pain, orofacial pain involving jaws, periorbital pain, ear pain or headaches. Underlying psychological / inherited / para functional habits (bruxism, trauma due to occlusion, malocclusion) can also be an additive factor in contributing for TMD[13, 14]. Bruxism or unconscious clenching of jaw is one of the main contributing factors for TMD. BoNT as an adjunct treatment, while the main treatment approach being pharmacological and surgical methods[15, 16]. However, treating TMD with BoNT has viable benefits in managing of associated symptoms like bruxism, clenching, trims, myofascial pain, hypermobility, masseter and temporalis hypertrophy and headaches[17.] BoNT is injected intramuscularly, which blocks acetylcholine release from presynaptic nerve endings causing muscle relaxation and analgesia from neurogenic pain[18]. Additionally it reduces the release of inflammatory mediators, so decrease the sensitization for chronic pain[19, 20]. It has relaxing ability when injected into the masticatory muscle by relieving pain gradually, without any noticeable complications in the patient. Aside from reducing the release of chemical transmitters at the nerve endings, BoNT also has a direct analgesic effect on nociceptors via inhibition of substance P, calcitonin, glutamine and gene regulated peptide, which decreases pain in the neighboring groups of muscles within four days of injection[17, 19, 21].

The site of injection and the masticatory muscles of target were different for BoNT injection to alleviate TMD pain. In majority of the studies masseter muscle was the target, followed by masseter and temporalis. However, the site will be chosen based on the muscle that exhibited tenderness. One study even mentioned about injecting into the intra- articular area[22]. Additionally, Slight to significant improvement in the dimension of mouth opening and reduction in TMJ clicking were observed in patient with BoNT injections ranging when treated with BoNT for TMD treatment[22].

Upon reviewing the articles it's conclusive that there is no set standard dose of BoNT injection. However lowest effective dose is recommended to be administered to prevent the antibodies formation, as excess dosage would lead to poisoning. 25-150 U into the muscles of mastication can be administered. However its adverse effects like headaches, weakness, increased pain, flu-like symptoms, chewing discomfort and unilateral paralysis of the zygomaticus major muscle were noticed. BoNT on TMD has significant result on temporomandibular system without severe side-effects[23, 24, and 25].

Gummy Smile:

Excessive display of gingival tissue in the maxilla due to uncontrolled contraction of upper lip muscles is called Gummy Smile. This is primarily due to levator labii superioris alaeque nasi, which is displayed upon smiling. To correct hyperfunctioning of these lip elevator muscles, several surgical techniques including Le Fort I maxillary osteotomies and gingivectomies are performed. However, titrated administration of BoNT injections of around 3U at the center point in the triangle formed by the levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor displayed considerable result[26].

Masseter Muscle Hypertrophy:

It is a clinical phenomenon with uncertain etiology, characterized by swelling of the masseter near the angle of the mandible and is associated with para functional clenching, emotional stress, bruxism, micro trauma and facial pain[27, 28]. Masseter hypertrophy would result in prominent facial disfiguration appealing surgical resection. The hyperactivity associated with chronic pain can be adjunctively treated by injecting 12U of BoNT into the thickest part of the masseter muscle, that is palpable upon clenched and the beneficial effect can last up to 18 months[29].

Bruxism*:*

Multifactorial etiological factors for bruxism namely emotional stress, neurological disorders, certain drugs and occlusal interference were suggested[30, 31]. Yet, bruxism is mediated by central and autonomous nervous systems; and has its effects on other anatomical structures that need relief[32]. Its management includes use of occlusal splints, drugs namely benzodiazepine or L-dopa and cognitive-behavioral therapy[33, 34]. Adjunct therapy with BoNT Injections (25-100U) was found to be efficient with response for 19 weeks period[35] .However, the effect remained transient and is largely limited to the injection area. A review has indicated that the most common adverse effects of BoNT local, such as sensitivity and mild cutaneous reaction at the site of injection; systemic effects such as headache and nervous atrophy, which are reversible; and specific effects including dysphonia, dysphagia and dry mouth were noticed, especially in patients

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who received large dosage (> 100 IU) or had a condition that was further complicated by BoNT[36, 37].

***Oromandibular Dystonia*:**

It is focal involuntary contraction of the muscles of the face, jaw, and/or tongue causing difficulty in opening and closing the mouth[38]. The strong spasm of the muscles cause muscle pain and general fatigue, leading to trauma to the lips, cheek, tongue and alveolar processes. This also cause involuntary movements of the mouth and jaws typically resulting in severe attrition and damage to the dentition, denture adaptation problems, alveolar atrophy, affecting chewing and speech[39].

Injecting BoNT into the masseters and/or to the submentalis complex has reported to improve functioning of chewing and speaking in 67.9% of the patients with mean duration of clinical improvement in 16.4 ± 7.1 wk[40]. It is stated that from the point of injection, BoNT diffused around 1-1.5 cm, therefore varying from 1-5 injection sites per muscle[41]. Best and safest mode of injecting was by injecting with ElecroMyoGraphy (EMG) guided annulated electrode at rest position, so to reconfirm on dystonic activity[42, 43]. Percutaneous injection for masseter at the lower half of its superficial part; for temporalis muscle at its anterior voluminous part; for the medial pterygoid muscle on its medial side of the ramus just above its fusion with the sling with the masseter; and for the digastric muscle the anterior belly resulted in best activity. With regard to the orbicularis oris muscles, the injection at the protruding parts, but just above (upper lip) and below (lower lip) the carmine red margin of the lip and for the lateral (external) pterygoid intraoral approach was best, due its direct access for palpation and injection. Unintentional deposition of BoNT into masseters would lead to dryness of the mouth because of its close proximity to the parotid gland.

Sialorrhea:

Sialorrhea is excessive salivation/drooling/uncontrolled salivation into the oropharynx or to the mouth in neurological patients, who are socially/clinically handicap, as in infantile cerebral palsy, the disease of Parkinson's and amyotrophic lateral sclerosis. It is described as 'anterior' if salivary overflow from the mouth is due to inadequate lip closure; and as 'posterior' if it is due to coughing, aspiration and it may have the risk of lung infection. Sialorrhea can be socially embarrassing, discomfort and patient may experience reduced quality of life[44, 45, 46, 47, 48] .

Intraglandular injection of BoNT in each parotid (25–40 IU) and each submandibular (15–30 IU) exhibited inhibitory action at the cholinergic receptors of the salivary gland cells, by blocking the neurogenic (parasympathetic) control of salivary secretion[48]. It was noticed that both drooling and salivary flow was reduced by 2 weeks after treatment with maximal reductions of 30–40% [49]. However, injecting at the right site using ultrasonography guidance is safe and helps in preventing ill effects like hyperactivity of depressor anguli oris. Yet, side effects of 3–5% dry mouth, 0–3% dysphagia and difficulty to chew were reported in studies.

Trigeminal Neuralgia and Facial Palsy:

BoNT can be used as an adjunct in cases of trigeminal neuralgia, as it reduces the acute severity of pain by acting upon the nerve endings. The excruciating pain associated with inflammation of the trigeminal nerve is relieved along with the relaxation of over activity of muscle in the pericranium that is inhibited due to BoNT activity on the nerve impulse of the pericranial muscles[50, 51]. Untoward muscle movement in the normal side of the face and tautness of the facial area due to muscle hyperactivity is improved in patients with facial nerve palsy when they were administered with BoNT injections[52].

Fracture:

Traumatic injuries in the maxillofacial region i.e., maxilla, mandible, nasal bone, orbital bone or zygomatic bone could be adjunctively treated with BoNT, as it slows the concerned muscle activity.[58] Anterior open bite caused due to trauma was reported to be successfully treated by injecting BoNT into the anterior belly of digastric[53,54].

***Orthodontic Treatment*:**

BoNT can reduce the intensity of muscle activity by contracting the musculature and reducing its effects on the dentition, especially in case of strong muscles like mentalis. Post the orthodontic treatment, the muscles can be gradually trained to adapt to the physiological movement [55, 56].

Palliative Therapy:

Resection of the oral anatomical structures in oral cancer patients may cause dystonia, spasticity and degree of functional disorder. Palliative therapy through BoNT will improve the quality of life in patients with head and neck cancer. It is also reported in the literature that BoNT would open up tumor vessels and provide an opportunity for better efficiency of chemotherapy and radiotherapy[57].

Denture Stability:

Reduced vertical dimension in completely edentulous patients who have remained without denture would reduce the vertical dimension and they have concerns on denture instability. Injecting BoNT into the jaw muscles ease the adaptation by relaxing the muscles and stabilize the physiological vertical dimension[55].

Implantology:

BoNT into the masticatory muscles relaxes them, so to facilitate Osseo integration as it can prevent excessive

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exertion of muscular forces on the implants site due to para functional habits, which might cause implant failure[58].

RQ3: How is the efficacy and adverse outcomes when Botulinum Toxin was used as a therapeutic agent for dental / oral and maxillofacial ailments?

Various assessment methods were used to report the efficacy of BoNT in orofacial region as mentioned in **Table 4.**

Table 4 : Assessment methods used in literature to know the efficacy of BoNT

BoNT Efficacy Assessment Methods	No.Of Articles
ElecroMyoGraphy	9
Combined (Visual + Clinical)	8
Visual Scale Analysis	6
Clinical Assessment	4
Bite Force Analysis	2
Self Description	3
MRI	1
CT	1
CBCT	1

Reduced therapeutic efficacy was noticed due to antibody formation, due to the production of neutralizing antibodies when high doses, incremental dose and short frequencies of BoNT were administered[59, 60].

However, the reported local adverse effects include immunogenicity, allergy, and pain at the injection site, erythema, edema, ecchymosis, and hypoesthesia[61, 62]. Drooping of mouth, dry eyes, asymmetry of facial expression during dynamic facial movement, ptosis, eye lid edema, facial muscle weakness were noticed when BoNT was injected too close to the salivary glands. Transient dysphagia, difficulty in chewing, breathing risk aspiration, recurrent jaw dislocation, salivary duct calculi, xerostomia, nasal speech, nasal regurgitation were reported. Headaches in the first 24 hours, blepharoptosis and peripheral muscular palsy were noticed in few individuals, mainly for non-adhering to the post-operative instructions given after BoNT injections[63, 64]. Blurred vision, dizziness, gastrointestinal upset, weakness, voice changes and local injuries of carotid arteries or branches of facial nerves were reported [61]. Pterygoid hematoma, dysarthria, and dysphagia were reported when BoNT was injected for management of myofascial pain.

Systemic side effects like infections, transient weakness, fatigue, nausea, pruritus and flu - like symptoms was also reported in a rare case [63].

Conclusion

The review concludes that BoNT has significant positive effect when used as a medicament in dentistry. The positive effect is however for short span and repeated administration of BoNT is required. Yet, BoNT remains a promising palliative adjunct to treat several orofacial ailments temporarily.

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