Chapter 18
Future Perspectives of Botulinum Toxin Application in Dentistry

Shahroo Etemad-Moghadam

Abstract In recent years, the therapeutic application of botulinum neurotoxin (BoNT) has expanded to encompass a variety of issues beyond its well-known usage for hyperkinetic movement disorders, autonomic hyperactivity, and facial rejuvenation. Dentistry is one of the fields that has benefited greatly from botulinum toxin therapy, as evidenced by multiple clinical trials which provided evidence for usefulness of this mode of therapy in common issues encountered in the field of dentistry (described in Chap. 16). In this chapter, the future potentials for BoNT therapy in the field of dentistry and its use in oral and maxillofacial region with its rich network of nerves and muscles are described. In addition, this chapter focuses on preclinical and preliminary studies on the effect of intramuscular injections of BoNT on craniofacial growth and proposes the possibility of using this toxin to influence the dentofacial complex during growth. Existing data or suggestions on the use of BoNT in implant dentistry, tongue thrust, temporomandibular joint dislocation, bone/plate fractures, herpes simplex virus, angular cheilitis, and burning mouth syndrome are also presented.

Keywords Botulinum neurotoxin · Dentistry · Orthodontics · Gummy smile · Bone fracture

Introduction

The head and neck constitute a complex arrangement of structures composed of a variety of tissues, including muscles and nerves, which work in harmony to provide the normal functions inherent to this area. As meticulously discussed in Chap. 16, there are multiple well-documented uses of botulinum toxin (BoNT) in this region for which considerable studies, some with high levels of evidence, have been performed and are being used as reference by oral surgeons and dentists. However,

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there are several other applications for this toxin which still lack a high level of scientific evidence and would benefit from further research based on randomized controlled trials, when possible. In this chapter, we present potential applications of BoNT for the treatment of less investigated issues in the orofacial complex and explore other ways to take advantage of this safe and accessible substance in different areas and specialties of dentistry. Whether BoNT will gain widespread acceptance for use in these areas would depend on future research to confirm or reject its application. The cases presented herein are intended to familiarize practitioners with additional approaches to applying BoNT in clinical situations, where there is a need to avoid invasive procedures or to supplement an existing treatment.

Orthodontics

Orthodontics is the art and science of providing the patient with an esthetically pleasing oral and facial appearance through correction of the teeth and jaws. It is sometimes paired with orthognathic surgery to treat dentofacial problems. Certain circumstances such as age, negative attitude towards orthodontic appliances, hesitance to undergo orthognathic surgery, and a number of medical conditions limit the use of orthodontic therapy [1], and therefore, patients need to be presented with alternatives that offer acceptable results. Additionally, a number of factors including muscular activity can compromise the outcome of orthognathic surgery leading to its instability and relapse [2]; the potential impact of these factors needs to be reduced as much as possible with simple techniques. Finally, if feasible, access to uncomplicated methods to manipulate growth and development of the dentofacial complex in a desirable direction could help avoid going through subsequent more intricate treatments.

Within this context, BoNT injection can be a valuable tool in orthodontic treatments and it may be used in different aspects of this specialty. A selection of applications ranging from treatment of existing issues to prevention of relapse and the possibility of manipulating growth is presented below:

Treating Existing Issues

Gummy Smile or Excessive Gingival Display

Definition Maxillary gingival display of more than 3 mm upon smiling is known as "gummy smile" and is regarded as unattractive by most people. Various etiologic factors have been identified for this condition, one of which is hyperactivity of the muscles responsible for lip elevation. Accordingly, different treatment methods ranging from orthodontic therapy to surgical procedures have been used to improve the esthetic appearance of these patients [3–5]. In many cases, patients and/or clini-

cians decide on nonaggressive methods that cause the least posttreatment morbidity, regardless of the specific etiologic factor. Therefore, BoNT injections would be a perfect choice, even in cases other than those caused by muscular hyperactivity that could be camouflaged with labial modification.

Treatment of Cases with Muscular Etiology Excessive gingival display due to lip muscle hyperfunction includes individuals who demonstrate normal maxillary dimensions on cephalometric analysis, but display 2 mm of the upper incisors while their lips are at rest [3]. Gummy smilers have been shown to possess more powerful lip-elevating muscles compared to individuals with normal lip lines [3, 6]. To eliminate this problem, numerous surgical methods have been employed through the years [4] including muscle detachment from the underlying bone to lower the lip [7], partial amputation of the levator labii superioris muscle (with or without the addition of a spacer) [8, 9], subperiosteal cutting of the labial elevators through the exterior aspect of the nasal septum [10], and surgical remodeling of the gingiva and alveolar bone [11]. In addition to being complex, time-consuming and expensive surgical procedures carry the risk of complications such as formation and contraction of scar tissues [3, 12]. BoNT has been used to treat gummy smile for nearly a decade; however, a uniform and standardized application method is still lacking.

Muscles Involved in Gummy Smile Appearance In order to achieve optimal treatment results with BoNT injections, the muscles responsible for lip activity and their best access points should be identified. Different studies have proposed different muscles as targets for injection, with the levator labii superioris alaeque nasi being the most commonly proposed target [13].

Mazzuco and Hexsel [12] analyzed muscle function and localized each of the muscle groups responsible for moving a specific part of the lip and used it to classify gummy smile into anterior, posterior, mixed, and asymmetric subtypes. They reported levator labii superioris alaeque nasi, levator labii superioris, zygomaticus minor, zygomaticus major, and risorius to be the major muscles associated with gingival exposure, providing a guide for patient-based injections (Fig. 18.1) [12].

Number of Injections Different studies have reported between 1 and 3 injections per side, some with the additional use of electromyography [3, 4, 12, 13]. In order to minimize the number of injections, the Yonsei point was introduced as a single spot situated at the intersection of the levator labii superioris alaeque nasi, levator labii superioris, and zygomaticus minor muscles. This point could be easily located in both males and females, at the crossing of a horizontal line drawn 1 cm lateral from the ala and a vertical line drawn 3 cm above the lip line, when the lips are at rest (Fig. 18.2) [3]. Initially, the Yonsei point was established based on information gathered from Asian subjects [3], but further studies in other populations reported significant improvement of gummy smiles following single injections into this point [13–15].

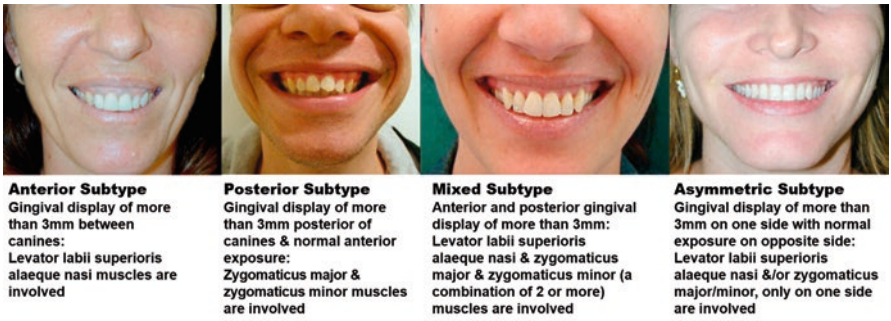


Fig. 18.1 Subtypes of gummy smile and the major muscles involved in each type. (Adapted from Ref. [12] and reproduced with permission from Publisher: Elsevier)

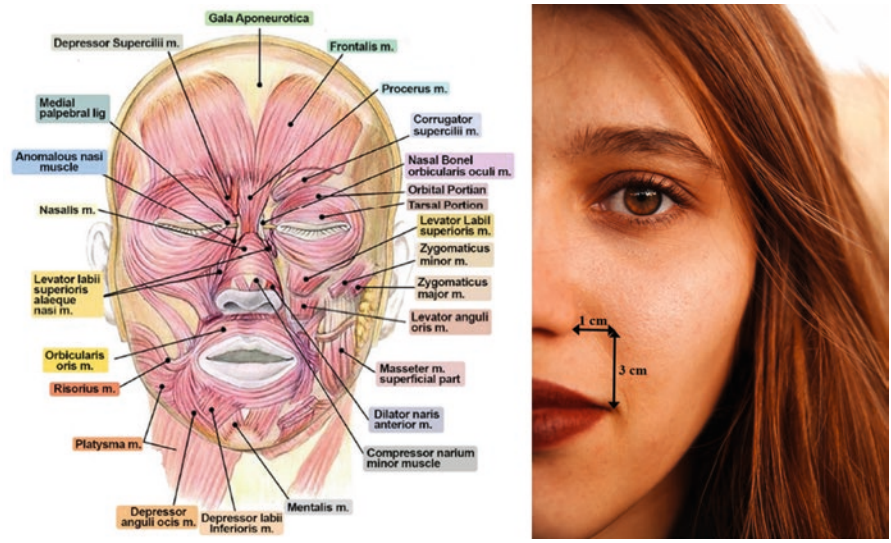


Fig. 18.2 The Yonsei point at the convergence of three muscles involved in lip function including levator labii superioris alaeque nasi, levator labii superioris, and zygomaticus minor muscles. (The schematic image (left) is reprinted from Kwon KH, Shin KS, Yeon SH, Kwon DG. Application of botulinum toxin in maxillofacial field: part I. Bruxism and square jaw. Maxillofac Plast Reconstr Surg. 2019 Oct 1;41(1):38 which has been made available under http://creativecommons.org/licenses/by/4.0/, the right image is obtained and modified from https://unsplash.com/ "internet's source of freely usable images")

Evidence for Effectiveness of BoNT A considerable number of reports, with the number of patients ranging from 1 to 52 [3, 4, 12–20], have indicated BoNT to be an effective method for the treatment of gummy smile. Nevertheless, there is a lack of randomized controlled trials on this subject. A total of 3 clinical trials specific to gummy smile and BoNT are listed in the Clinical Trials Registry (https://clinicaltri-

als.gov/). However, their status is "not yet recruiting" (NCT03717987), "withdrawn" (NCT03284047), and "unknown" (NCT03186547).

Three systematic reviews have evaluated BoNT in the treatment of gummy smile [21] and assessed its ideal dose [15] and duration of effectiveness [22]. According to their results, when administered by an experienced clinician, BoNT is a safe, reversible, and effective method to treat excessive gingival exposure, either as a separate treatment or as accompanying other techniques.

The levator labii superioris alaeque nasi was reported to be the most important muscle when using this protocol [21]. BoNT dosage generally depends on its formulation, potency, or the practitioner's experience and preference. A total dose of 5 IU onabotulinum toxin per side was reported to be effective, with subsequent follow-up administrations, as necessary. The Yonsei point was considered a convenient target for injection in all types of gummy smile [15]. There is a gradual reduction of the paralyzing effect of this toxin, which continues up to week 12 and, even then, may not completely return to baseline levels. Gummy smile patients remain free of excessive gingival exposure for at least 8 weeks, postinjection [22].

All three systematic reviews highlighted a lack of randomized controlled trials and high-quality studies for the use of BoNT in the treatment of gummy smile [15, 21, 22].

Considerations and Adverse Effects Certain facts should be contemplated when selecting BoNT for the treatment of gummy smile:

- Gingival display is more pronounced in females compared to males and it becomes less conspicuous with age due to an increase in upper lip length following loss of soft tissue volume and support [23, 24]. Therefore, spontaneous correction is expected up to a certain level, particularly when dealing with male patients [23].
- Most adverse effects of BoNT are temporary and treatable in follow-up sessions; nonetheless, they should be considered when deciding to use it in clinical practice. Unwanted consequences of injection for the treatment of gummy smile reported in the literature include but may not be limited to asymmetric smile, difficulty in smiling, "sad smile" [12], pain and twitching at injection site, headache, vertigo [15, 21], "joker smile," protrusion of the lower lip, drooling [25], and in one case appearance of a horizontal depressed line when smiling [26].

Before administering BoNT, we have to make sure that the toxin is injected only into the muscle and does not enter the bloodstream; for this purpose, aspiration is suggested before completing the injection [23, 24].

Concluding Remarks In conclusion, there is a need for further research and well-designed trials that can lead to the establishment of a set of universally accepted guidelines for the proper use of BoNT in the treatment of gummy smile. Researchers are currently working on this important task [27] and one of the pioneers in this field has suggested an injection protocol based on the amount of gingival display (Table 18.1) [28].

Preventing Issues Following Orthognathic Surgery

Treatment Relapse

One of the most common options for the treatment of dentoskeletal discrepancies is the combination of orthodontics and orthognathic surgery. A major consideration after achievement of the desired dentofacial appearance is to maintain the stability of hard and soft tissues, or in other words to prevent relapse. Treatment relapse is dependent upon a number of factors, one of which is the activity of facial muscles [2].

Following orthognathic surgery, the original relationship of the jaws is altered, and as a consequence, the muscular system tries to adapt by making modifications in the size and/or function of the involved musculature [29]. Masticatory muscles tend to return to their original state, which is due to the activation of stretch receptors. Therefore, BoNT would be a good option to consider when trying to sustain postoperative stability and prevent muscular tension [30]. This is especially true when comparing simple injections to the use of more invasive methods such as myotomy [31]. Additionally, considering that the majority of relapse following orthognathic surgery occurs within the first 6 months, the transient nature of BoNT would not be a problem in these cases [32].

Supporting Studies

- Patients with skeletal class II malocclusions have mandibular deficiency. When this condition is accompanied by anterior open bite, their treatment can involve counterclockwise rotation of the mandible and a high rate of posttreatment relapse is expected. A 21-year-old woman with this type of facial deformity was treated with presurgical orthodontic therapy, orthognathic surgery, and double genioplasty. This was immediately followed by injection of a total dose of 20 U BoNT (Meditoxin, Type A) into 4 points of the anterior belly of the digastric muscle (Fig. 18.3). A 15-month follow-up of this patient showed complete retention and no relapse [32].

The same injection has been suggested to treat open-bite patients who do not respond to comprehensive rubber traction [33].

Table 18.1 Injection guide based on the amount of gingival exposure as proposed by Polo. Adapted from reference 28, with permission from Publisher: Oxford University Press

Gingival exposure (mm)	Injection sites Number (location)	Dosage per side (U/site)	Total units (U)
4–5	1 (overlapping area of LLSAN/LLS)	2	4
5–7	1 (overlapping area of LLSAN/LLS)	2.5	5
7–8.5	2 (overlapping area of LLSAN/LLS; overlapping area of LLS/Zmi)	2	8
>8.5	2 (overlapping area of LLSAN/LLS; overlapping area of LLS/Zmi)	2.5	10

LLSAN levator labii superioris alaeque nasi, *LLS* levator labii superioris, *Zmi* zygomaticus minor

- Deep bite occurs when maxillary incisors cover more than the normal percentage of the mandibular incisors, and in some cases, the lower anterior teeth come into contact with the palatal surface of their opposing antagonists or the palatal mucosa. Along with retroclination of the maxillary incisors, deep bite is a major finding in class II division II individuals. Relapse has been reported in one-third of patients treated for this malocclusion. Twenty units of BoNT (Botox®, Allergan) was administered bilaterally into the mylohyoid muscles of 8 deep-bite class II division II adult patients treated with orthognathic surgery and compared to 24 controls with the same malocclusion and treatment method, except for the injections. According to the results, none of the BoNT-treated patients exhibited relapse, while more than half the controls showed signs of relapse after a maximum of 1-year follow-up. The backward pull of the mylohyoid muscles in response to advancement of the mandible during surgery was considered to be a responsible factor for relapse, which was relieved by BoNT injection in this study, hence, the decreased occurrence of relapse [34].

Concluding Remarks The mechanisms and likelihood of posttreatment relapse vary among different types of surgical procedures. Also, depending on the type and direction of surgery, muscles would be affected differently (traction versus pressure), resulting in distinct impacts on the bone and different amounts and forms of relapse [31, 32, 34, 35]. Therefore, targeting the specific muscles known to be affected by the particular type of surgery and reducing its negative impact on the supporting bone, would be extremely helpful in clinical practice. Consequently,

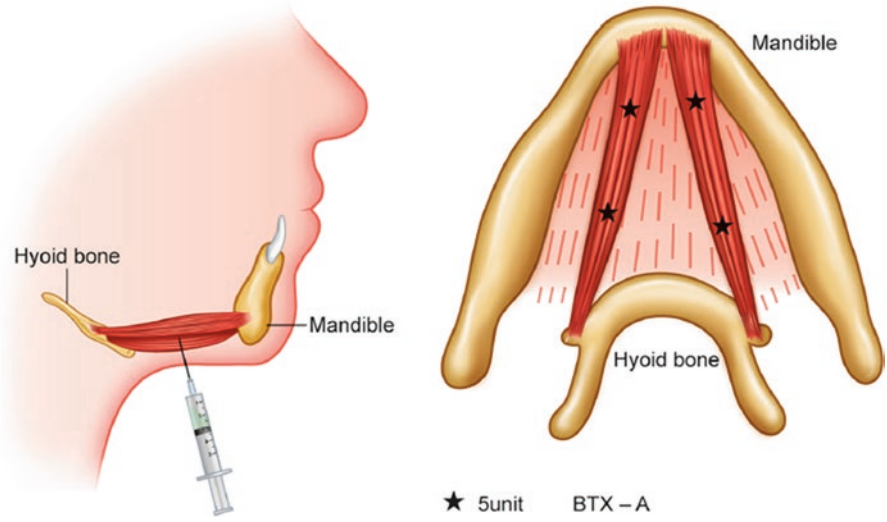


Fig. 18.3 Injection of BoNT (Meditoxin Type A) into four points (stars) of the anterior belly of the digastric muscle. Five units were administered into each point. (Original figure is reprinted from Ref. [32] with minor changes to the legend, which has been made available under http://creativecommons.org/licenses/by/4.0/)

where ethically permissible, there is a need for well-designed, controlled clinical trials developed separately for the different surgical protocols and malocclusions in order to gain access to an acceptable approach to help reduce relapse.

Sculpturing Facial Bones During Growth

Premise As long as an individual is still growing, the position and growth direction of the teeth and jaws could be altered by noninvasive measures. However, after skeletal maturation, the clinician usually resorts to more aggressive procedures, such as surgery [36]. If skeletal development could be controlled through manipulation of soft tissues during growth, future orthognathic surgery might be avoided or less complicated.

Definition Growth and development of facial structures is an extremely complex process, as evidenced by the multiple theories intended to provide an explanation of the mechanisms responsible for its occurrence and progression [37]. One of the most important hypotheses was the functional matrix theory by Moss (1968), which strongly supported the role of extrinsic and epigenetic factors in cephalic development. While recognizing the contribution of genetics, emphasis was placed on external stimuli which induced a response in the supporting bone, ultimately leading to the promotion of bone growth [37, 38]. One of the major external stimuli in the dentofacial complex is that elicited by the masticatory muscles, which have been widely exploited in orthodontic treatments with devices such as the Frankel appliance and lip bumper.

Such myofunctional appliances are activated through muscle function, which in turn transmit (or prevent) force to dental and osseous hard tissues causing change [39]. Using shields in the buccal and labial vestibules, these devices theoretically permit the targeted bone and teeth to grow laterally and anteriorly [40, 41]. Similarly, tongue cribs are suggested to help overcome tongue thrust and infantile swallowing habits, which are occasionally associated with open-bite and flared incisors, leading to stability of treatments aimed at correcting these issues [42].

The same concept could be applied to the use of BoNT. This toxin could reduce the function and force of overactive muscles to allow hard-tissue growth or repositioning, where needed. An in-depth comprehension of the muscular anatomy and the direction of muscle movement is essential for more precise prediction of the effect of injections. Different amounts of pressure generated by the lip, buccinator, and tongue muscles can induce changes in both dental inclination [43, 44] and facial growth pattern [45], according to some investigators.

Initial Evidence Several animal studies have been conducted to investigate the effect of BoNT injection on facial bones during growth, which have shown the capability of BoNT to impact these structures [46–54] (Table 18.2). BoNT injection into the masseter of adult humans has resulted in modification of the alveolar bone,

digastric fossa [55], condyle [55, 56], and mandibular angle [57] in some studies, but not others [58].

Application in Children The effect of BoNT on bones may be even more conspicuous in growing children who have not reached full development. In the head and neck regions, this toxin has been used for treating sialorrhea in 4- to 18-year-old individuals [59, 60], as off-label treatment in pediatric otolaryngology/laryngology patients older than 2 years [61], strabismus [62], conservative management of displaced condylar fracture in a 3-year-old child [63], and chronic migraine in adolescents [64].

We found one study in a growing child (an 8-year-old girl) who was injected with a total dose of 10 U BoNT into two points of her masseter muscle following orthodontic therapy to correct a masticatory movement disorder, facial asymmetry, and unilateral masseter hypertrophy. After this combined treatment, ramus height notably increased on the opposite (non-injected) side, correcting the transverse deviation of the upper jaw. It was concluded that mandibular growth could be modified by reduction of masseteric hypertrophy [65].

Concluding Remarks Clearly, there is a lack of strong evidence regarding the effect of muscle injections of BoNT on the growth and development of facial hard tissues, especially in children and adolescents. Considering that this age group, especially those with skeletal and dental malocclusions, may benefit most from this safe and simple approach, prospective studies and randomized controlled trials are necessary, when possible. The importance of BoNT treatment becomes more evident when considering the difficulties encountered in current routine treatments such as lack of compliance of young patients to use myofunctional devices [66], inability to manage the growth potential of soft tissues, unexpected complications in the rotation of the mandible, and relapse of more invasive methods such as distraction osteogenesis [47]. However, as mentioned in Chap. 16, the effect of muscle force on bone quantity/quality and mechanical properties of the temporomandibular joint should be given focused attention, when considering the use of BoNT. There is a long way to go before information from various studies can be incorporated into clinical treatments for this age group, especially considering that they are ethically regarded as a vulnerable population for use as subjects in clinical trials.

Treatment of Parafunctional Habits

Definition Habits are described as actions that are performed repeatedly and automatically. Parafunctional habits are behaviors that are enacted by a body organ in a manner beyond the original purpose/function of that organ. In the oral cavity, it includes actions other than mastication, swallowing, and talking which could appear in a wide array of behaviors such as bruxism, clenching, lip- or nail-biting, digit/object sucking, or chewing and tongue thrust. Muscular hyperactivity is a common

Table 18.2 Studies using muscular BoNT injections to evaluate craniofacial skeletal changes in growing rats

Authors	No. (groups)	Age	Study period	BoNT	Dose	Injection site	Assessment methods	Significant effects	Conclusions
Kim et al. 2008 [50]	80 (4)	4w	4w	BTXA®, Lanzhou Institute of Biological Products, Lanzhou, China	2.5 U, 0.05 ml	Bilateral Mst.	Histology, TUNEL, measurements on computer images from photographs of dry Mand.	Smaller lengths of the mandibular body, condyle, and coronoid process in addition to diminished heights of the anterior mandibular region, condyle, and coronoid process	Mandibular growth is affected by BoNT through its apoptotic impact on the condylar cartilage The influence of BoNT on growth should be considered before prescription to developing children
Tsai et al. 2009 [52]	11 (2)	30d	45d	BoNT/A, Botox, Allergan, Irvine, Calif.	1 U, 0.04 ml: (0.02 ml in each point)	2 points of the superficial and deep layers of the Mst.	Measurements on dry skulls by an electronic digital caliper	Reduced muscle weight after injection Some craniofacial and mandibular, but not maxillary measurements decrease when comparing between sides and groups	Mst. atrophy due to BoNT can change osseous growth and development, confirming the functional matrix theory indicating regulation of bone development by soft tissues

Authors	No. (groups)	Age	Study period	BoNT	Dose	Injection site	Assessment methods	Significant effects	Conclusions
Babuccu et al. 2009 [46]	49 (4)	15d	4 m	Botulinum toxin A; Botox, Allergan Pharmaceuticals, Ireland	0.4 IU, 0.05 ml	Unilateral Mst. or Temp.	Histology, direct cephalometric measurements	Atrophy in both injected muscles Decrease in all craniofacial/ mandibular dimensions after Temp. injection Decrease in most measurements after Mst. injection	Muscle paralysis due to BoNT, negatively impacts bone structures, during growth Further considerations should be given to the use of BoNT in pediatrics to control craniofacial deformities
Tsai et al. 2011 [49]	60 (4)	30d	45d	Botox®, Allergan Pharmaceuticals, Dublin, Ireland	1 U, 2.5 ml	Bilateral Mst. ± Temp.	DEXA, graphic software to analyze digital photographs of decalcified bone under an optical microscope	Lower muscle volume, cortical thickness, and BMD (skull and Mand., adjacent to muscle insertion areas) after injection	Reduced masticatory function has an impact on bone structure during growth
Park et al. 2015 [51]	60 (3)	4w	4w	Botox®, Allergan Inc., Irvine, CA,USA	3 U, 0.05 ml	Unilateral or bilateral Mst.	Measurements on computer images from photographs of dry Mand.	Smaller mandibular measurements in the BoNT-injected side compared to the saline side[a]	Unilateral BoNT injection induces unilateral changes in craniofacial development, regardless of the fact that the Mand. functions as a single unit

(continued)

Table 18.2 (continued)

Authors	No. (groups)	Age	Study period	BoNT	Dose	Injection site	Assessment methods	Significant effects	Conclusions
Seok et al. 2018 [53]	11 (2)	13d	47d	BoNT-A, Botulax® 50, HUGEL, Chuncheon, Korea)	0.5 U, 0.5 ml	Unilateral Mass	Measurements on micro-CT images	Reduction in some aspects of ramus height and mandibular plane angle and decreased bigonial mandibular width Mandibular midline deviation to BoNT side	Mst. BoNT administration decreases the development of the lower jaw
Ahn et al. 2019 [47]	10 (2)	13d	47d	Botulax® 50, BoNT type A, HUGEL, Chuncheon, Korea	0.5 U, 0.5 ml	Anterior belly of the DM	Micro-CT analysis	Decrease in the zygomatic arch and mandibular bicondylar width Increase in maxillary posterior arch width	Maxillofacial transverse bony width was affected by BoNT during growth possibly because of functional change of masticatory muscles in reaction to the decreased function of the DM

Authors	No. (groups)	Age	Study period	BoNT	Dose	Injection site	Assessment methods	Significant effects	Conclusions
Tsai et al. 2019 [48]	48 (4)	4w	42d	25 U/mL, Allergan Pharmaceuticals, Ireland	1 U, 0.04 ml	Bilateral Mst. ± Temp.	Electronic caliper, fluorescing line marking for calculation of bone apposition rate by fluorescence microscopy, micro-CT for sutural bone mineral density measurement	Weight reduction in injected muscles Diminished maxillary arch size only after injections into both muscles Decreased suture density dependent upon the muscle and muscle-suture position Reduced sutural apposition rate, most prevalent in paralysis of both muscles	Maxillofacial suture bone growth in developing rats can be influenced by masticatory muscle action

(continued)

Table 18.2 (continued)

Authors	No. (groups)	Age	Study period	BoNT	Dose	Injection site	Assessment methods	Significant effects	Conclusions
Choi et al. 2019 [54]	11 (2)	6w	12w	BoNT type A, Botulax®, Hugel, Inc., Korea	2 IU (2.5 IU per 0.1 ml): 0.91 IU in Mst., 0.73 IU in Temp., and 0.36 IU in Med.Ptr	Unilateral Mst. + Temp. + Med.Ptr followed by boosters, 6w later	3D analysis of micro-CT images, histochemical analysis (H&E and Masson trichrome)	Reduction in size + lateral tilting of Mand. causing asymmetry Supraeruption of U/ & /L molars and downward canting of occlusal plane on BoNT side Decreased density of alveolar bone, smaller PDL space, and disorganized periodontal collagen fibers	The dentoalveolar complex responds to diminished occlusal forces by causing increased occlusal canting and pronounced skeletal asymmetry Diminished occlusal forces can be the result of BoNT injection, inducing depletion of masticatory functional loading

Mst. masseter, *Temp.* temporalis, *TUNEL* terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling, *DEXA* dual-energy X-ray absorptiometry, *BMD* bone mineral density, *DM* digastric muscle, *Med.Ptr.* medial pterygoid, *U/ & /L* upper and lower, *PDL* periodontal ligament, *w* week, *d* day

[a]Mandibular body, condylar, and coronoid process lengths and anterior region, condylar, and coronoid process heights

finding among these habits. Additionally, they can be destructive to the gnathic and dentoalveolar complex and/or any type of restoration placed within this system including fillings, crowns, bridges, and implants [67, 68]. Therefore, the use of BoNT to reduce the excessive force of these behaviors in order to minimize their negative effects could be an acceptable choice.

Here, we discuss the available literature on the use of BoNT in eliminating the effects of parafunctional habits on implants, and also, we hypothesize the impact that treating these habits could have on preventing dentoskeletal problems.

BoNT in Implant Dentistry

Definition Bruxism, clenching, and tongue thrust are the main parafunctional habits noted to be associated with implant failure [68]. Study results on the effect of bruxism on different aspects of implants are conflicting, with some regarding it as an important cause of biological and mechanical failure [68, 69] and others maintaining that its role is mainly mechanical, only resulting in issues such as screw loosening and porcelain/implant fractures as opposed to problems such as impaired osseointegration [70] (discussed in Chap. 16).

Clinical Evidence In a study by Mijiritsky et al. [71], the efficacy of preoperative administration of BoNT-A was evaluated in 13 bruxism patients receiving immediately loaded implants set in fresh extraction sockets for full-arch restorations and compared with 13 controls with the same characteristics. Injections of BoNT (Dysport) were delivered 3 weeks before surgery in the test group. For the temporal muscles on each side, a total dose of 70 U was injected into 4 points in an area located on the zygomatic arch and temporal region. For each masseter, a total dose of 90 U was administered into 3–4 points in proximity to the mandibular angle. Follow-up (18–51 months) revealed no implant failure in the test group. Of the 103 implants placed in this group, only 4 implants in one patient showed 1- to 2-mm bone loss. In contrast, among the 102 implants placed in the control subjects, 2 implants were lost in 1 individual and 3 implants in another patient demonstrated 2-mm bone loss.

Another recent study on bruxism patients receiving delayed loaded implants for full-arch restoration of the upper jaw showed less prosthetic complications in 5 patients injected with BoNT (masseter and temporal muscles) compared to the same number of controls without BoNT treatment at the end of a 2-year follow-up [72].

There are also case reports using Botox (Allergan) [73], 200 U Dysport [74], and 400 U Dysport [75] to inject masseter muscles before or during implant treatment in patients with bruxism and hypertrophic masseters with successful results.

Concluding Remarks It is noteworthy that despite promising findings reported in the literature, randomized controlled studies on this subject are still lacking. The

need for trials on the efficacy of BoNT in implant dentistry has been noted since 2007 [76]. Randomized controlled trials for the possible use of BoNT during the "stability dip phase of integration" or periodic injections in patients with bruxism receiving full-arch immediately loaded implant-supported prosthetic rehabilitations are underway [77].

Theoretic Prevention of Dentoskeletal Issues

Tongue Thrust Parafunctional tongue thrust is defined as either an abnormal pressure of the tongue against the teeth in the course of swallowing or its passive anterior positioning during rest. The former is also known as an "atypical swallow" and its relation to malocclusion is controversial, while the latter has been more commonly associated with problems such as open bite, proclination of incisors, and lisping [78]. In any case, reduction of tongue pressure during orthodontic therapy and retaining it after treatment could help preserve the stability of the corrected dentoalveolar relation [79]. Some clinical studies have suggested that after orthodontic treatments, the tongue adapts to the new position of the teeth. The reduced tongue pressure following tongue crib utilization was shown to remain in a diminished state, even after removal of the tongue crib [80]. Therefore, considering that appliances such as tongue crib could be displeasing for the patient, BoNT may be a potential substitute and its transient nature would not be a problem due to the adaptive behavior of the tongue.

Tongue Injections Complications involving swallowing, speech, and chewing have been reported following administration of BoNT into the lingual muscles. To overcome these issues, injection into the extrinsic muscles of the tongue has been suggested while avoiding intrinsic muscles [81]. On the other hand, for an unrelated problem (dystonia) [82], lingual muscle injections by BoNT were reported to be safe when the clinician had a thorough knowledge of muscle anatomy.

Concluding Remarks BoNT could be considered as a treatment or an adjunct to other procedures that help resolve the symptoms caused by tongue thrust. Well-designed studies and randomized controlled trials, when possible, can help elucidate the effectiveness and safety of BoNT for the treatment of those tongue thrusts that lead to clinical problems.

Oral and Maxillofacial Surgery

As discussed in Chap. 16, popular uses of BoNT by oral surgeons include treatment of temporomandibular disorders, sialorrhea, orofacial pain [83, 84], and promotion of facial wound/scar healing [85–87]. Other areas where application of this toxin

could be considered as a therapeutic option but requires further investigation are listed below:

Temporomandibular Joint Dislocation

Definition and Existing Treatment Options Temporomandibular joint dislocation occurs when the condyle moves anteriorly to a location in front of the articular eminence during jaw movement and causes a lock in an open position. Subsequently, the masticatory muscles react by going into spasm and prevent the condyle from relocating to its normal position. When there are recurrent episodes of dislocation, a number of treatment modalities based on the responsible etiologic factor are used. These include occlusal adjustment and parafunctional habit therapy, autologous blood injection, surgical intervention and administration of BoNT as an adjunct to – or independent of – intermaxillary fixation and surgery [88–90].

Clinical Application of BoNT Despite the fact that BoNT treatment for temporomandibular dislocation is off-label, its application has been suggested to be included as a new indication [91]. BoNT injection with or without the use of electromyography to treat temporomandibular dislocation has mostly been presented as case reports and case series of patients with or without other underlying diseases [92–100]. The largest number of patients (32) was studied by Yoshida et al. [92], who also reported the longest follow-up among these studies (75 months). In general, favorable outcomes, with minimal and usually transient side effects, have been reported for BoNT treatment of dislocations [91–93, 95–100].

A study compared intraoral pterygoid injection of 35 U Botox® (Allergan) with intermaxillary fixation in 20 patients and followed them for 6 months. The BoNT group, in contrast to the intermaxillary fixation patients, showed significant improvement in pain levels based on the visual analogue scale [101].

According to a recent review by Renapurkar and Laskin [102], as well as other investigations [88, 90, 91], level 1 evidence studies for the treatment of temporomandibular dislocation have not been published and most investigations have provided level 4 evidence.

Dosage Single-muscle injections of Botox® (Allergan) [92, 93, 96, 101], Dysport [93, 95], and BoNT-A (Lanzhou) [99] were used with doses ranging from 20 U to 50 U, 50 M U (mouse unit) to 150 MU, and 25 U to 50 U, respectively. According to Daelen et al. [95], "In terms of quoted MU, the toxin preparation Botox is apparently 3-5 times more potent than Dysport."

Muscle(s) The lateral (external) pterygoid was accessed either intraorally [92, 96, 101] or extraorally [93–95, 99, 100] for unilateral or bilateral injections, depending on the patient and study. The superficial masseter and lateral pterygoid were both injected extraorally in one patient, with the masseter receiving injections at 4 points

on the mandibular angle [95]. In another case, injections were administered in the lateral pterygoid and the anterior bellies of both digastric muscles [94].

Access Intraorally, the pterygoid was located at the mucobuccal fold of the distal root of the upper second molar. For injection, a posterior-superior angle of 30° to the occlusal plane and 20° medially was used to insert the needle to a depth of 20–30 mm [92]. In another study [96], the needle insertion point was located halfway on the anterior ramus border and was entered superiorly and medially while the patient was requested to open the mouth.

For extraoral injection, the insertion point was located 1 cm anterior to the condyle, directly under the anterior zygomatic process while the mouth was open with a distance of 1.5 cm between the incisors. The needle was entered transversely pointing towards the contralateral temporomandibular joint [95]. In another investigation, two injections were administered: one was 1 cm inferior to the central zygomatic arch and the other, 0.5–1 cm in back of the first injection site, immediately anterior to the mandibular condyle. The mouth was closed and the insertion was made at 90° angle to a depth of 3–4 cm [99].

A comparison between intra- and extraoral injections for the treatment of anterior disc displacement with reduction was made; there was no significant difference in joint click, pain reduction, and joint tenderness between the techniques. However, the patients were more comfortable with the intraoral approach and it took a shorter amount of time [103].

Duration of Effect The temporary effect of BoNT has been a concern for some clinicians; however, a number of patients receiving a single injection have been reported to be symptom-free after 6–7 months [92, 94, 99, 100]. Others have used prophylactic injections before reappearance of symptoms [95, 96] or additional injections, when necessary [92–96]. A 2- to 4-month wait period has been suggested between injections [95]. It has been postulated that, at first, patients might need repeated administrations of BoNT, but after a minimum of 4 injections, a decrease or cessation of relapse may be expected, at least during the following 6 months. The reason for this experience was proposed to be related to the pterygoid not fully recovering its initial level of hyperactivity, or in other terms, the pterygoid may have sustained "involution" [93]. Another explanation was that in addition to permanent muscle weakening, perhaps there is a formation of fibrotic tissue around the temporomandibular joint following limitation of movement [96].

It should be noted that the effect of BoNT injection is not immediate and it may require 4–5 days [104], 3–10 days [96], or 2–14 days [92] to demonstrate effectiveness, which has led to reoccurrence of dislocation early after administration in some patients [99]. This is why some authors have recommended close observation [92], limiting movement of the jaws or mandibular fixation for the first few days after injection [99].

Concluding Remarks Due to ethical and logistical issues, inclusion of a control group may not be feasible and large numbers of double-blind randomized controlled

trials may not become available in the near future [92, 93, 102]. Regardless, the need for level 1 evidence has been highlighted in the literature. Until such information becomes available, treatment doses and intervals should be selected according to existing evidence, preferably starting from the lowest dose and highest intervals possible and adjusting them as required [92, 93, 96].

The number of injections has been reported to increase in dislocations due to neurological dysfunction compared to those with habitual dislocations and no hyperactivity [92].

Trauma and Bone/Plate Fractures

Bone Fracture

Premise The attachment of muscle and bone promotes movement and loading and, in the orofacial complex, controls maxillofacial growth and dental occlusion. The masticatory and facial muscles work in concert to support these functions. Therefore, any disruption in the balance of this system, as in the case of fractures, could lead to undesirable outcomes, with various complications depending on factors such as the severity of the dissociation, direction of the fracture line, and age of the patient, among others [30, 55, 105]. BoNT could be used to relax the components that have been forced to exert unwanted pressure as a consequence of the injury.

Example Following an angle fracture of the mandible, the body and ramus are no longer connected and, therefore, each segment is controlled by its attached muscles. Generally speaking, the jaw-closing muscles are mostly attached to the ramus, while the ones connected to the body assist in jaw opening [33]. When the fracture has an unfavorable horizontal pattern (Fig. 18.4), ramal and body muscles pull in different directions and can complicate surgical procedures and their outcomes [105]. Relaxing the undesirable pulls of muscles by BoNT injection can be an effective approach to be used as an adjunct to surgery. The strength of muscles inhibiting reduction of fractures could be decreased with BoNT and used as a promising method in conservative treatment procedures. Confirming the "unfavorable" pattern as opposed to the "favorable" pattern of fracture is important when considering treatment (Fig. 18.4).

Preliminary Evidence Two animal studies on femoral bone presented opposing results regarding the effectiveness of BoNT in fracture reduction management. One reported reduced callus diameter and improved histological and biomechanical healing parameters [106], while the other demonstrated an absence of callus and woven bone formation and reduced biomechanical characteristics [107]. The shape and mechanism of the fractures differed between these investigations: the standard closed fracture used in the former study protected the vasculature and periosteum which might have contributed to the superior results by increasing the blood supply.

BoNT Application in Studies

Angle Fractures

Treatment of angle fractures through open reduction leads to attachment loss between the ramus and masseter, tilting the balance in favor of muscles connected to the mandibular body, promoting postsurgical open bite.

A 21-year-old man with a prior history of 2 surgeries and rubber traction for bilateral angle fracture presented with malocclusion and wound dehiscence. His third surgery did not resolve the open bite and it persisted, even after 1 week of rubber traction. A total dose of 20 units BoNT-A (Meditoxin) was injected into 4 points of the anterior belly of the digastric muscles (5 units each) on the 10th day after surgery, leading to complete resolution of the open bite, 3 days postinjection. Elastic traction was removed after observation of stable occlusion and a 6-month follow-up did not show recurrence of the open bite and additional injections were not considered necessary [33].

Symphysis Fracture

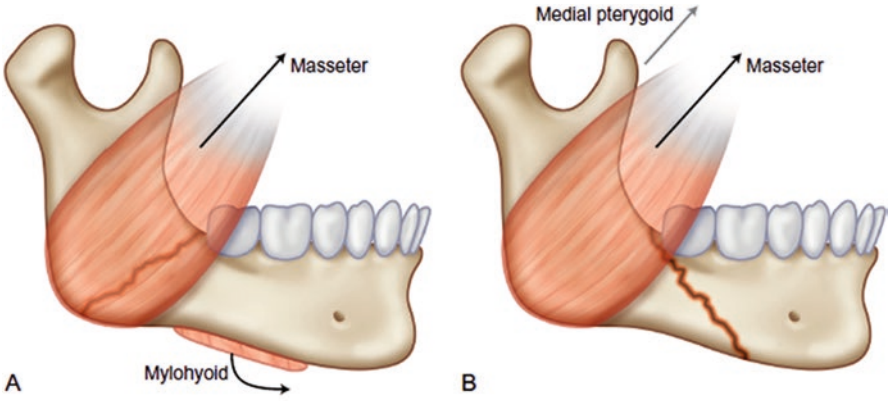
An incomplete fracture of the symphysis associated with a displaced condylar fracture of a 3-year-old boy was treated with intermaxillary fixation and an asymmetrical occlusal splint. This resulted in failure, demonstrated by 90° angulation between the condyle and ramus, due to caudal traction of the mandible by the masseter and temporalis muscles and medial traction of the condyle by the medial pterygoid. Therefore, a total dose of 20 IU BoNT was extraorally injected into 6 points along the temporalis, 15 IU extraorally into 5 linear points on the masseter, and 6 IU transorally into 2 points of the medial pterygoid, with an additional transoral injection of 6 IU into the masseter muscle. BoNT administration led to full recovery and fusion of the condyle with no adverse side effects [63].

Condylar Fracture

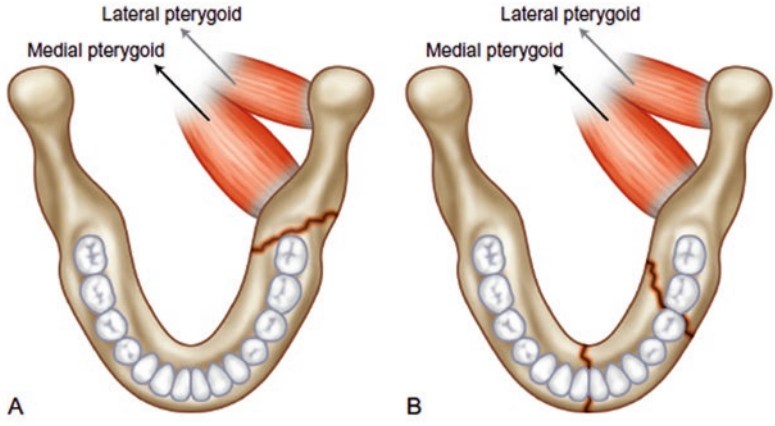
Bilateral condylar fractures lead to anterior open bite due to premature molar contacts caused by the horizontal traction of the lateral pterygoids and upward pull of the masseter causing the ramus to override the condyle. Ten patients with unilateral subcondylar or condylar neck fractures with no considerable angulation or dislocation were treated by closed reduction through injection of 100 units of BoNT (Botox, Allergan) into the muscles of the injured side, after which maxillomandibular fixation was performed with an asymmetric occlusal splint for 10 days, followed by application of intermaxillary guiding elastics for 2 months. A concentration of 20 IU/ml was used to deliver 30 IU into the masseter and anterior fibers of the temporalis muscles extraorally. Medial and lateral pterygoid muscles were accessed intraorally to receive a total of 40 IU toxin around the fractured bone fragments. Healings were uneventful and there was no complaint of complications such as malocclusion, deviation, or temporomandibular issues. Normal muscle functions were reestablished after 3–6 months [108].

Zygomatic Fractures

Displaced zygomatic fractures are usually treated by rigid fixation to prevent muscle traction, especially by the masseter which is regarded as a main reason for displacement of the zygoma after reduction. BoNT has been used presurgically, to decrease the number of fixation sites and surgical procedures. Five men with zygomatic fractures (with or without fractures of other bones) were extraorally injected with 100 IU BoNT (Botox, Allergan) into 5 points of the ipsilateral masseter, 12 to 24 hours before rigid fixation with mini- and/or microplates and screws. During a 5- to 12-month follow-up, no esthetic or functional complications were seen and muscle contractions returned after 3 to 6 months. It was concluded that masseter



(A) Horizontally unfavorable fracture; (B) horizontally favorable fracture.



(A) Vertically unfavorable fracture; (B) vertically favorable fracture.

Fig. 18.4 Different directions of fracture lines relative to muscle insertion sites predict whether a fracture is favorable or unfavorable. (Reprinted from Ref. [105], with permission from publisher: Elsevier)

paralysis of individuals with zygomatic fractures could reduce the number of fixation sites and make the use of weaker plate systems possible. However, the study lacked control patients for comparisons [109].

Plate Fracture

Plates are utilized for fixation of bone segments. In a study using bilateral sagittal split ramus osteotomy for orthognathic surgery on 16 skeletal class III patients, immobilization of rami was achieved through single four-hole extended titanium miniplates. A total of 25 units BoNT-A was administered into 5 points of each masseter muscle of 8 patients immediately after surgery, while the rest received no injections. After a maximum of 6 months of follow-up, the number of plate fractures was significantly lower in the group who underwent BoNT treatment compared to those without BoNT administration [31].

Titanium plates and screws are regarded as the gold standard for orthognathic immobilization. However, several issues related to these materials have prompted the need for their removal after treatment, leading to the introduction of bioresorbable fixation systems. Despite the favorable features of bioresorbable substances, they have been reported to be weaker and possess inferior skeletal stability compared to their titanium counterparts in some types of orthognathic surgeries such as mandibular setback [31, 35]. By reducing muscular pressure, it seems that BoNT may help overcome this weak point, making the use of the bioresorbable fixation systems more feasible.

Oral Medicine

Herpes Simplex Virus Type-1 (HSV-1) Treatment with BoNT

Definitions HSV-1 is a DNA virus and belongs to the herpesviridae family with other members including herpes zoster. The virion is composed of a core with a double-stranded DNA, covered by a capsid and encompassed by the tegument and finally a lipid envelope. After entry through skin breaks or mucosa, HSV-1 replicates in the epithelial cells and causes lysis and destruction followed by inflammation which increases the permeability of the blood-nerve barrier. Viral particles then enter through the free endings of the neurons in contact with the infected epithelial cells and travel through axons to neuronal cell bodies where they become latent for life.

The oral region is innervated by the trigeminal nerve, and therefore, the trigeminal ganglion is the primary site for latency subsequent to oral infections. Reactivation occurs following diminished immune response and exogenous stimuli which ultimately leads to increased replication. HSV-1 is then transported from the cell body,

through the axon to the nerve terminals, resulting in reinfection of the epithelial cells [110, 111].

The association between BoNT and herpesviridae (if any) is complex, and conflicting findings have been reported.

Positive Effect of BoNT on HSV-1 Reactivation It has been suggested that BoNT may have an inhibitory effect on the reactivation of HSV. A 33-year-old woman with simultaneously occurring impetigo and eczema herpeticum on the face and hands along with an extended history of atopic dermatitis and 5- to 6-year involvement with labial HSV recurrence was injected intradermally with BoNT after receiving treatment for her eczema and impetigo. Four points were selected on the skin of the upper lip and each were injected with 1 U onabotulinumtoxinA. New lesions erupted on another site away from the injection area after 4 weeks, followed by an outbreak of the eczema and a new HSV lesion on yet another site. A further treatment round was administered using 15 units of abobotulinumtoxinA (Dysport) resulting in prevention of outbreaks at the original areas, but 2 other recurrences took place within the next 3 months, again at a non-treated region. Ultimately, the authors reported complete resolution of the treated areas with repeated BoNT injections every 4 months for 19 months [112].

A double-blind, randomized, placebo-controlled, crossover study titled "Botulinum Toxin A for Herpes Labialis" has been registered at ClinicalTrials.gov (NCT01225341) with the aim of determining the effectiveness/safety of BoNT (onabotulinumtoxinA) for the prevention of herpes labialis. Injection of BoNT or bacteriostatic normal saline was considered to be administered into the orbicularis oris muscle at the site of re-eruption in 20 participants. Recurrence and duration of herpes labialis lesions, lesion size, and pain were to be assessed. Recruitment was completed but no results have been posted.

Negative Effect of BoNT on Herpesviridae Reactivation In contrast to the above-mentioned study, others have found a negative effect of BoNT on re-eruption of HSV or herpes zoster lesions. Narang et al. [113] reported HSV-1 stromal keratitis recurrence, 3 weeks after treating refractory epiphora with BoNT. The patient was a 59-year-old female, with a history of bilateral stromal keratitis, which had remained quiescent for the past 2 years. Stimulating factors such as psychogenic and surgical stress were considered as possible explanations for the HSV-1 recurrence; however, the authors suggested a possible association between viral reactivation and BoNT injection and recommended that clinicians exercise caution when considering BoNT for treatment in previously HSV-infected patients.

Similarly, another study also observed viral keratitis recurrence 1 week after BoNT administration for treatment of spastic entropion in a 55-year-old man who was infected with HSV-1, 6 years ago, and had not experienced recurrences for the past 1 year. The authors stated that despite involvement of other elements in the reactivation of HSV, the role of BoNT injection could not be entirely ruled out and suggested caution in patients receiving ocular BoNT with a history of herpes simplex viral keratitis [114].

A third study reported development of herpes zoster in the face of two (55- and 48-year-old) female patients approximately 1 week after BoNT injection into the glabella, forehead, and lateral periorbital regions for cosmetic purposes. The authors recommended considering re-eruption of herpes zoster if a patient reports prodromal symptoms or skin eruptions following BoNT therapy. However, they did not regard the incidents of these occurrences high enough to warrant prophylactic antiviral therapy for all patients before BoNT injection [115].

The exact effect (if any) of BoNT on infections caused by herpesviridae is unpredictable, unless supported by future well-designed studies.

Other Uses for BoNT in the Oral and Maxillofacial Region

Angular Cheilitis

Angular cheilitis or inflammation of the corner(s) of the mouth is clinically manifested as redness, cracks/fissures, crusting, and ulceration of the oral commissure(s). Various situations could lead to this condition, but the most common is infection. When deep creases develop at the corners of the mouth for any reason (age, malocclusion, shortening of vertical dimension, etc.), they collect saliva and skin maceration occurs, which is usually further complicated by colonizing of candida and infectious agents [116]. BoNT has been proposed either independently or in conjunction with other modalities such as dermal fillers, to physically eliminate the deep commissure lines leading to prevention of saliva collection and the ability to obtain a dry environment free from contamination [117, 118]. Its recommended use involves the injection of a total of 20 U BotoxCE with 5 U in 2 different points of the depressor muscles on both sides and results are expected within 2 weeks. The muscles suggested for injections included depressor anguli oris, mentalis and orbicularis oris [117]. A 60-year-old patient with a 2-year history of bilateral angular cheilitis refractory to pharmacotherapy has been reported to have been successfully treated with BoNT [119].

Burning Mouth Syndrome

Burning mouth syndrome presents as a burning sensation of the mouth accompanied by symptoms such as oral mucosal dryness, salivary gland functional issues, and taste problems. Its diagnosis is based on exclusion of other clinical and laboratory abnormalities [120]. Restivo et al. [121], relying on the focal analgesic effect of BoNT, bilaterally injected a total dose of 16 U incobotulinumtoxinA into the lip and anterior tongue (4 U each) of 4 patients (3 with diabetes) who had burning mouth syndrome involving the lower lip and anterior two-thirds of the tongue.

Simultaneously, 2 patients with similar pain scores and symptoms received the same volume of saline into the same injection sites. All 4 BoNT-treated patients were free of symptoms within 48 hours, which lasted up to 16–20 weeks, while in the 2 control patients, the burning sensation did not resolve. BoNT was suggested as an efficacious treatment for burning mouth syndrome, especially when other less invasive treatment options fail to provide comfort.

Summation

BoNT injections are generally safe, uncomplicated, reversible, and relatively inexpensive and comfortable for the patient. Standardization of injection sites, methods, numbers, and dosage of this toxin is required for many dentistry-related issues. There are still several conditions in the head and neck which could potentially benefit from BoNT therapy, but require accumulation of additional data for clinical application. A thorough and detailed knowledge of the facial muscles and their direction of movement is essential for all practitioners inclined to use BoNT injections in clinical practice.

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