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Dentistry and botulinum toxin

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ABSTRACT
There are many conditions in dentistry that do not see a complete solution by applying conventional methodologies. Botulinum toxin in this regard can often be used as an alternative therapeutic treatment modality. The use of botulinum toxin has been widely accepted for over twenty years, by the international scientific community, in medicine in various aesthetic and non-aesthetic conditions. Of particular interest are the applications of the toxin in the maxillofacial region, related to dentistry. The neurotoxin offers a transient, reversible and relatively safe treatment option for many dental conditions in the head and neck region.
The uses of the toxin in the maxillofacial field can be divided into cosmetic applications including vertical lip wrinkles, gummy smile, dental aesthetics, marionette wrinkles, mandibular contouring and square appearance of the face due to hypertrophy of the masseter muscle. And non-cosmetic mainly represented by hypertrophy of the masseter and temporal muscles, disorders of the temporomandibular joint, bruxism, Frey's syndrome, drooling, implantology and diagnostics.
Continuous research has paved the way for innovative uses of the neurotoxin in dentistry. Botulinum toxin offers substantial benefits as an adjunct to cosmetic dental procedures, as well as a minimally invasive alternative to conditions that are refractory to routine medical management or require surgery.

I. INTRODUCTION

The horizons of treatment options in dentistry are expanding rapidly. In this scenario, unconventional solutions such as the use of botulinum toxin are gaining momentum[7]. The use of botulinum toxin has been widely accepted for over twenty years, by the international scientific community, in medicine in various aesthetic and non-aesthetic conditions[1-2-26-41]. Of particular interest are the applications of the toxin in the maxillofacial region, related to dentistry[39]. The neurotoxin offers a transient, reversible and relatively safe treatment option for many dental conditions[6].

Dental specialists, by virtue of their extensive knowledge of the anatomy of the maxillofacial region, can fully exploit the potential of the neurotoxin: an alternative, minimally invasive response to refractory conditions or invasive protocols[37].

The main pharmacodynamic effect of Clostridium botulinum type A botulinum toxin is due to a chemical denervation of the treated muscle which determines a quantifiable decrease in the muscle action potential, causing a localized reduction or paralysis of muscle activity.

Botulinum toxin type A is a muscle relaxant that temporarily weakens muscle activity. After injection, botulinum toxin type A works by blocking the transport of the neurotransmitter acetylcholine across the neuromuscular junction, located between the nerve end and the muscle fiber. Botulinum toxin type A mode of action has four main stages, each of which must function properly for the activity to occur. The action of the toxin causes the blockage of muscle contraction of the target muscles. The effect lasts for prolonged periods until the neuromuscular junction recovers its functionality and muscle activity is restored.

Indications

Botulinum toxin type A works by blocking nerve impulses to the muscles into which it has been injected and prevents the muscles from contracting, leading to a loss of contraction force with temporary paralysis.

Given the mechanism of action, botulinum toxin is recommended for the treatment of dynamic wrinkles.

There are eight known serotypes of botulinum neurotoxin (A, B, C1, C2, D, E, F, and G), of which types A and B are used clinically. The first three commercially available botulinum neurotoxin type A formulations approved by the U.S. Food and Drug Administration are: onabotulinumtoxinA (Vistabex - Botox; Allergan USA, Madison, NJ), abobotulinumtoxinA (Azzalure - Alluzience - Dysport; Galderma Laboratories, LP, Fort Worth, Texas) and incobotulinumtoxinA (Bocouture - Xeomin; Merz Pharmaceuticals, LLC Greensboro, NC).

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New formulations include letybotulinum A (Croma-Pharma GmbH), approved by AIFA in May 2022 for glabella, prabotulinumtoxinA (Jeuveau; Daewoong Pharmaceuticals, Seoul, Republic of Korea), approved by the US Food and Drug Administration in February 2019 for glabella, and daxibotulinumtoxinA (Revance Therapeutics, Inc., Nashville, Tenn.), which has anticipated U.S. Food and Drug Administration approval in 2020 and claims to deliver treatment outcomes lasting 28 weeks.

Alluzience, a recently authorized drug, also contains the active ingredient botulinum toxin A. This new formulation joins the well-known other molecules. The concentration of the drug is 200 Speywood units for each ml of product. But a single vial contains 125 Speywood units, in 0.625ml of pre-made solution. Alluzience was created with the intention of simplifying the methods of reconstitution and dilution of botulinum toxin-based preparations. By offering the doctor an already reconstituted, diluted and therefore ready-to-use formulation.

Reconstitution and storage

The information leaflets of Vistabex, Azzalure, Bocouture, Botox, Letybo and Dysport indicate: reconstitution with 0.9% sterile saline solution without preservatives, injection within 24 hours of reconstitution and use in individual patients. However, strictly following these suggestions in daily practice, generates high costs and significant waste. These prescriptions have led many Authors to carry out various experimental studies which demonstrate safety and efficacy even in the use of the drug after its reconstitution (up to 7 weeks) and in several patients, paying attention to sterility during the sampling phase. Bocouture, we recall, is the only botulinum toxin free of complexing proteins and can be stored at room temperature.

Reconstitution

Always check the type of botulinum toxin and above all the activation units contained in the vial.
For a vial of 50 IU botulinum toxin (onabotulinum Vistabex - incobotulinum Bocouture - letybotulinum Letybo) or 125 IU Speywood (abobotulinum Azzalure) using a needle and syringe of appropriate size, such as a 2.5 ml Luer Lock syringe and a 23 needle Gauge, withdraw 1 ml of sterile saline (0.9%).

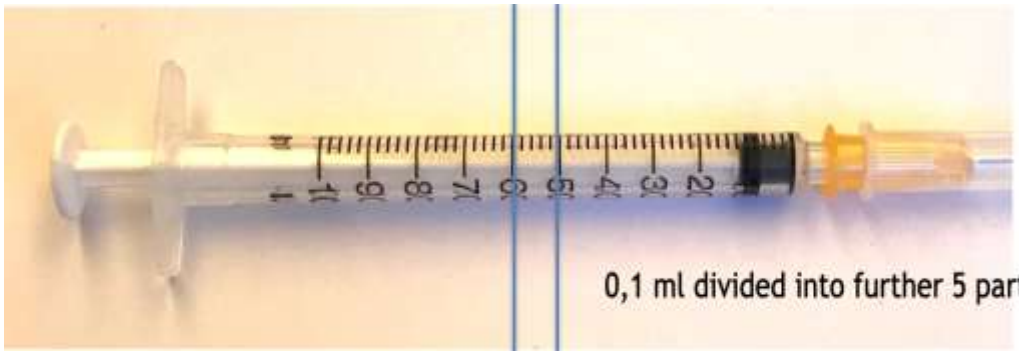
For a 100 IU botulinum toxin vial (onabotulinum Botox) it is therefore necessary to use a double quantity of diluent or 2 ml of sterile physiological solution (0.9%).

While for a 500 IU Speywood botulinum toxin vial (abobotulinum Dysport) it is therefore necessary to use a four times higher quantity of diluent or 4 ml of sterile physiological solution (0.9%).

Having added 1 ml of physiological water to a 50 IU vial (or 125 Speywood Units) each 0.1 ml of reconstituted solution will correspond to 5 Botulinum toxin Units if onabotulinum Vistabex (or incobotulinum Bocouture - Letybo) while 12.5 Speywood Units in case of abobotulinum Azzalure.

The same result, i.e. each 0.1 ml of reconstituted solution will correspond to 5 Units of botulinum toxin if onabotulinum, while 12.5 Speywood Units in the case of abobotulinum, will also be obtained using vials of 100 IU or 500 Speywood Units by adjusting the diluent (saline solution sterile) as discussed above.

Using a 1ml insulin syringe, graduated with 0.1ml intervals divided into 5 further parts (see Figure 1), each part will correspond to 1 International Unit (or 2.5 Speywood Units) making treatment easy and precise.



We recall the possibility (as present in the leaflet) of adding 1.25 ml of physiological water to a 50 IU vial (or 125 Speywood Unit) to obtain a more diluted solution. In this precise case each 0.1 ml of reconstituted solution will correspond to 4 Units of botulinum toxin if onabotulinum Vistabex (or incobotulinum Bocouture) while 10 Speywood Units in case of abobotulinum Azzalure.

Using a 1ml insulin syringe, graduated in 0.1ml intervals, each 0.1ml will correspond to 4 International Units (or 10 Speywood Units).

Once reconstituted, the botulinum toxin must be kept in the refrigerator (2-8° C; 36-46° F), protected from light and used, according to the manufacturers, within four hours. Discard the vial and needle in accordance with local regulations in the package insert. Do not freeze after reconstitution.

Dilution

The dilution of the product is a much debated topic which has created considerable confusion over the years and some difficulties in the operational phase. It is necessary to identify an agile and effective method at the same time.

The manufacturers' recommendations are as follows:

- dilution of Vistabex 50 U with 1 ml of saline solution (5 Units per 0.1 ml) or with 1.25 ml of saline solution (4 Units per 0.1 ml)
- dilution of 50 U Bocouture with 1 ml of saline (5 Units per 0.1 ml) or with 1.25 ml of saline (4 Units per 0.1 ml)
- dilution of Letybo 50 U with 1 ml of saline solution (5 Units per 0.1 ml) or with 1.25 ml of saline solution (4 Units per 0.1 ml)
- dilution of 100 U Botox with 2 ml of physiological solution (5 Units for 0.1 ml) or with 2.50 ml of physiological solution (4 Units for 0.1 ml)
- Dilution of 125 U Azzalure with 0.63 ml of physiological solution (10 Units for 0.05 ml) or with 1.25 ml of physiological solution (10 Units for 0.1 ml). Alternatively 1 ml of physiological solution (12 Units per 0.1 ml).
- Dilution of 500 U of Dysport with 2.50 ml of physiological solution (10 Units for 0.05 ml) or with 5 ml of physiological solution (10 Units for 0.1 ml). Alternatively 4 ml of physiological solution (12 Units per 0.1 ml).

Larger volumes at lower concentrations have greater product uptake as would be expected, but many studies report equivalent results in efficacy regardless of concentrations.

Several published experimental studies agree that higher doses of toxin, injected per single injection point, produce more lasting results. However, this undeniable benefit must be weighed carefully against the potential risk of possible adverse events. An injection technique that is spreading on the international scene, to limit the side effects, involves injections of microfocused botulinum toxin at high concentrations, i.e. higher doses of toxin in smaller volumes. Although this technique could theoretically help prolong the duration of action by limiting adverse events, thanks to the lower diffusion of the drug, further research is needed in this direction.

Dose equivalence of Vistabex (Botox) units, Azzalure (Alluzience - Dysport) units, Bocouture units.

Dose equivalence between the main products in the official pharmacopoeia Vistabex (Botox), Azzalure (Alluzience - Dysport) and Bocouture still remains a matter of controversy, even after almost 30 years of clinical use.

In general, the Vistabex-Azzalure conversion ratio is most commonly reported in terms of 1:2.5 although there are some scientific works reporting larger conversion ratios. The Vistabex-Bocouture ratio is reported in a ratio of 1:1. However, it has long been emphasized in many scientific works that, based on the treatment area, technique, dilutions and injection patterns, the formulations are not interchangeable for any single conversion ratio. Thus, although Vistabex-to-Azzalure ratios of 1:2.5 (1:3) and Vistabex-to-Bocouture ratios of 1:1 may be recommended as a good starting point especially in first-time patients, every practitioner modifies their dosage as he gains more experience with each product and the individual areas covered. There are currently no experimental trials in international scientific literature that have analyzed the equivalence of the dose of Letybo compared to other products.

Applications of botulinum toxin in the maxillofacial region

Botulinum toxin has various applications in the head and neck region[12]. The uses of the toxin in the maxillofacial field can be broadly divided into cosmetic and non-cosmetic applications. Continuous research has paved the way for innovative uses of the neurotoxin in dentistry. Botulinum toxin offers substantial benefits as an

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adjunct to cosmetic dental procedures, as well as a minimally invasive alternative to conditions that are refractory to routine medical management or require surgery[6].

Cosmetic applications in dentistry

Botulinum toxin has been widely accepted in medicine to temporarily treat hyperfunctional wrinkles on the face[13-14].

See Table 1.

Table 1 - Cosmetic applications in dentistry

• Vertical wrinkles of the lips
• Gummy smile and Dental Aesthetics
• Marrionette lines, with drooping corners of the mouth
• Bunny lines
• Irregular appearance of the skin of the chin, its lack of roundness or the presence of an accentuated labiomental sulcus
• Ptosis of the tip of the nose
• Platysmatic bands, horizontal wrinkles of the neck and ptosis of the tissues of the lower third of the face
• Mandibular contouring and facial square appearance

Of particular relevance for the dentist[40] is the treatment of:

- Vertical lines of the lips (barcode) determined by the orbicularis muscle of the mouth: Dosage 3 - 6 IU
- Gummy smile and dental aesthetics, whose responsible can be identified with the levator labii muscle complex (levator labii superior alaeque nasi, the levator labii superioris, the zygomaticus minor and major muscle): Dosage 4 - 10 IU
- Marrionette lines or sad smile, with drooping corners of the mouth, due to marked action of the depressor anguli oris (DAO)[19]: Dosage 6 - 18 IU
- Bunny lines, caused by overexertion of the levator labii superioris alequae nasi muscles: Dosage 4 - 6 IU
- Irregular appearance of the skin of the chin, its lack of roundness or the presence of an accentuated labiomental sulcus determined by the chin muscle: Dosage 4 - 10 IU
- Ptosis of the tip of the nose due to the action of the depressor septi nasi muscle: Dosage 2 - 6 IU
- Platysmatic bands, horizontal wrinkles of the neck (necklaces) and ptosis of the tissues of the lower third of the face, due to the marked action of the platysma muscle: Dosage 15 - 30 IU
- Mandibular contouring and facial square appearance due to masseter muscle hypertrophy: Dosage 30 - 50 IU

Figure 2 shows a schematic representation of the injection points of Botulinum Toxin in the region of the Face for cosmetic purposes in dentistry.

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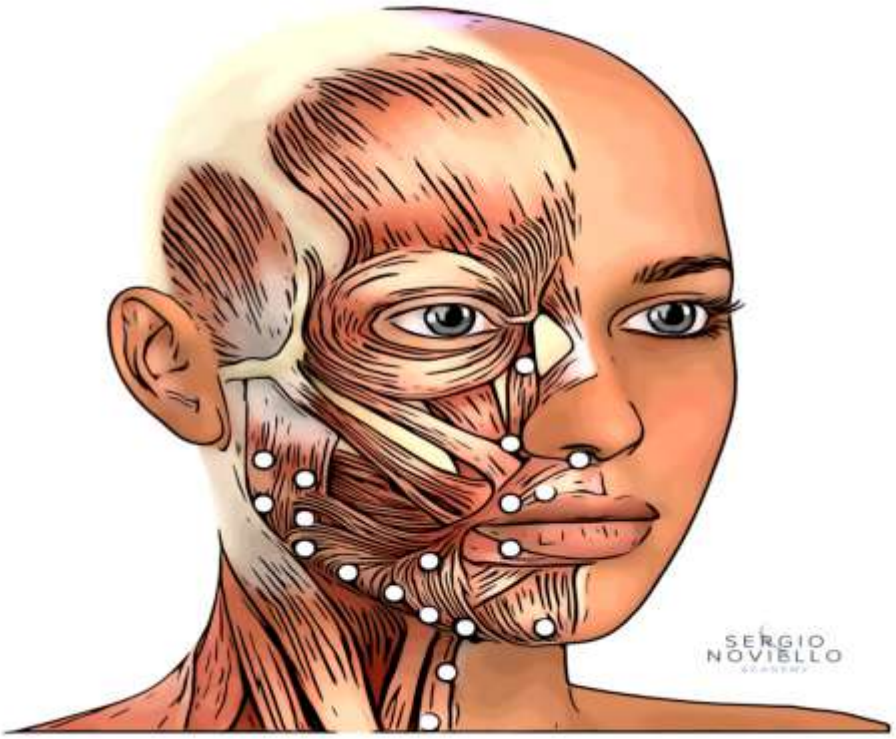

Therapeutic applications in dentistry

There are many conditions in dentistry that do not see a complete solution by applying conventional methodologies. Botulinum toxin in this regard can often be used as an alternative therapeutic treatment modality. Of particular interest are the applications of the toxin in the maxillofacial region, related to dentistry. The neurotoxin offers a transient, reversible and relatively safe treatment option for many dental conditions in the head and neck region.

Of particular relevance for the dentist are the following fields of intervention reported in table 2.

Table 2 - Therapeutic applications in dentistry

- Hypertrophy of the masseter and temporalis muscles
- Temporomandibular joint disorders
- Bruxism
- Oromandibular dystonia
- Mandibular spasm
- Pathological teeth clenching
- Dental implantology and surgery
- Gummy smile and cosmetic dentistry
- Frey's syndrome
- Sialorrhea and salivary secretion disorders
- Facial nerve paralysis
- Facial pain and trigeminal neuralgia
- Implantology
- Maxillofacial trauma
- Neoplasms
- Orthodontic prostheses
- Diagnostics

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Hypertrophy of the masseter and temporalis muscles

Hypertrophy of the masseter and temporalis muscles is generally associated with phenomena of involuntary contraction of the muscles of mastication or with other parafunctional uses of the jaws.

The results of the use of botulinum toxin in cases of hypertrophy of the masseter and temporal muscles are very encouraging and also prove to be safe and effective in the treatment of chronic pain associated with masticatory hyperactivity. Over time, reduction of masseter overactivity has been found to produce a concomitant reduction in muscle size[10] in the majority of patients.

There are different methods of injection treatment, while the dosage is between 15 and 25 IU per area.

Gummy smile and cosmetic dentistry

The use of botulinum toxin is particularly effective in managing cases of excessive gingival exposure due to excessive contraction of the upper lip muscles; mainly levator labii superioris alaeque nasi muscles[16-17-18]. Hwang et al., at Yonsei University College of dentistry, Seoul, Korea, proposed an injection point for botulinum toxin and called it the Yonsei point. It is basically a point located in the center of the triangle formed by the levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor. A dose of 3 IU at a single injection site is therefore recommended.

Recently, neurotoxins and derma fillers[15] have been used to provide immediate volume to the so-called black triangles formed due to interpapillary tissue loss. This solution represents a minimally invasive treatment option compared to conventional therapies including aggressive gingivectomy or orthognathic therapeutic approaches.

Temporomandibular disorders

The term temporomandibular joint disorders indicates not only the disorders of the joint itself, but also a variety of disorders associated with chewing, often little known and included in pathological frameworks characterized by chronic pain.

Temporomandibular joint disorders can be myofascial (those related to the muscles themselves) or arthrogenic (those related to the joint), but most disorders include a myogenic component and muscle spasticity related to bruxism, external stresses, oromandibular dystonia and psychomotor behaviors[8].

Recall that oromandibular dystonia (OMD) is a disorder characterized by involuntary spasms of the masticatory muscles which manifests itself with difficulty speaking, swallowing and eating. Although it is a neurological disorder, it is included as a subgroup of temporomandibular disorders due to the involvement of the masticatory apparatus.

Conventional treatment approaches for temporomandibular joint disorders include physical therapy and exercise, anti-inflammatory and analgesic drugs, muscle relaxants, orthodontic appliances, or a combination of these modalities. Surgery is also sometimes indicated, but it is an expensive and invasive treatment option.

Botulinum toxin has proven to be effective in resolving symptoms such as pain and soreness in temporomandibular joint disorders, and has been proposed as an adjuvant in the management of such disorders, particularly in cases characterized by muscular hyperactivity[11-20-38].

Temporomandibular joint disorders that may benefit from neurotoxin injection include:

- Bruxism
- Pathological teeth clenching
- Oromandibular dystonia
- Myofascial pain
- Trismus
- Hypermobility
- Hypercontraction of the masseter and temporalis muscles

In numerous experimental trials, a significant reduction in pain and an improvement in masticatory joint function[43-44] was recorded at doses between 25 and 50 IU injected directly into the muscle belly of the temporalis and masseter muscles.

Injection of neurotoxin directly into the lateral pterygoid muscle has been shown to be effective in the treatment
of recurrent mandibular dislocation. Potential sites for botulinum toxin injection in therapeutic applications in dentistry are schematically shown in Figure 3.

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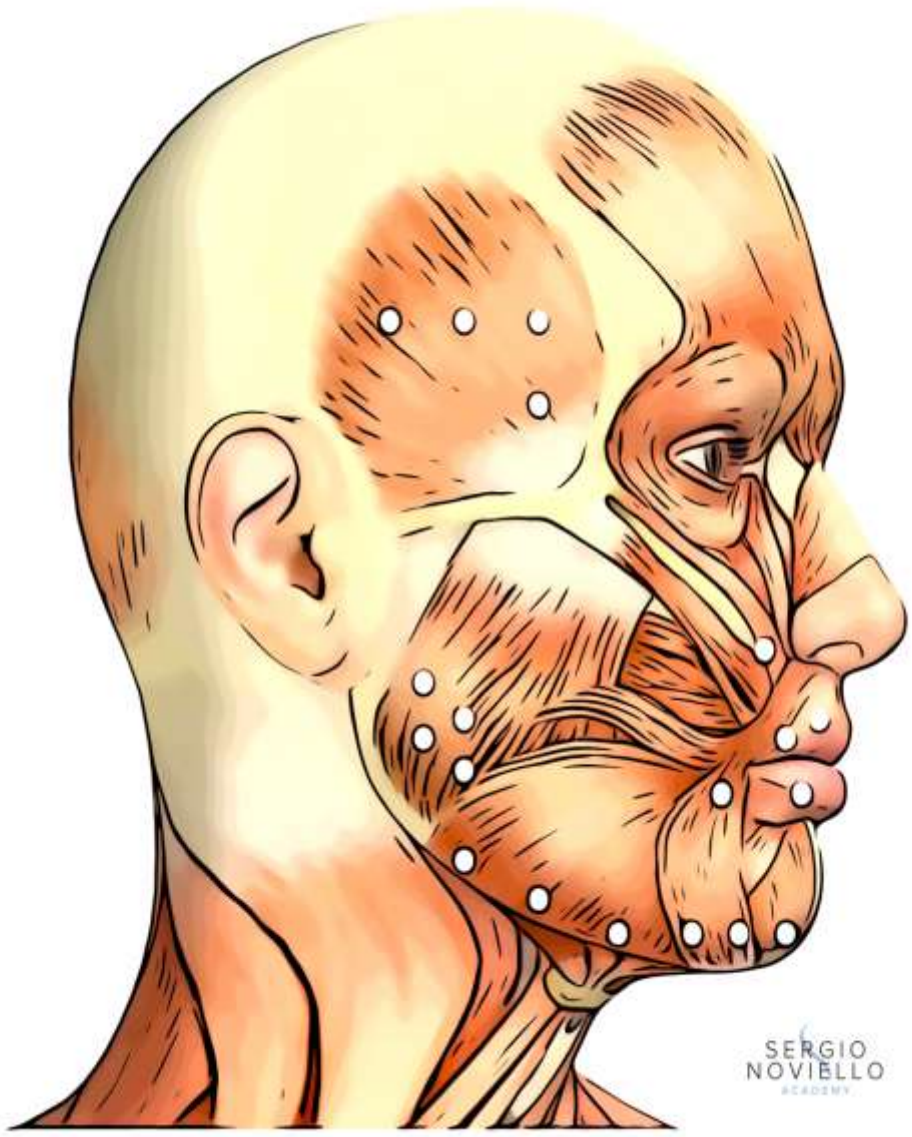

Since a very small percentage of the available muscle force is required for mastication, a partial reduction in the contraction force of the masticatory muscles does not affect masticatory activity, including swallowing.

Bruxism

The parafunctional clenching of the jaws due to involuntary contraction of the chewing muscles, i.e. grinding, is called bruxism and is often associated with generalized attrition, classic symptoms of temporomandibular joint disorders, headache and muscle pain. Botulinum toxin has been successfully used in cases of bruxism.

The international scientific literature amply confirms that the bilateral injection of neurotoxin into the masseter and temporalis muscles (in a dose range of 25-50 IU per side and per muscle district) significantly reduces the severity of symptoms for 12-16 weeks.

Sialorrhea and salivary secretion disorders

Sialorrhea (involuntary excessive salivation) is a common disorder that occurs when the salivary glands produce excessive amounts of

saliva or when there is poor control by the perioral muscles. Traditional treatment options consist of conservative medical solutions or surgical therapies.

In this regard, the effects of botulinum toxin on the salivary glands have been extensively studied. Injection of neurotoxin into the parotid and submandibular glands has been shown to be extremely effective in controlling salivation[21-22-23-27]. The dosage includes intervals of 30 - 40 IU bilaterally, divided into several points, injected directly into the parotid gland, or better subcutaneously, with a significant reduction in salivary flow observed in 2 - 4 weeks and maintained for 12 - 16[24-25].

Frey's syndrome

Frey's syndrome, known above all as Auriculotemporal Syndrome, can occur after operations on the temporomandibular joint, following parotidectomy surgery for benign or malignant tumors, or following trauma to the parotid.

The symptoms are represented by sweating and redness in the region dependent on the auriculotemporal nerve, in front of the ear and on the cheek, often appearing unilaterally, and almost always in relation to food ingestion or the mere thought of it. The intensity of the disturbances is variable but, sometimes, it can be disabling and create discomfort for the patients who suffer from it. Objectivity is usually negative.

Salivation is controlled, like many other functions of our body, by the cholinergic autonomic nervous system, which acts independently of our will.

During a parotidectomy operation some nerve fibers are inevitably cut which, regenerating, can innervate sweat glands and small blood vessels of the cheek. Ingestion of food stimulates the secretion of saliva by the parotid gland and at the same time the activity of the sweat glands and local vascular muscles.

From a therapeutic point of view, some invasive interventions have been proposed, with non-constant and non-reproducible results.

Botulinum toxin represents a practically painless and very effective therapeutic solution; it acts by blocking the release of the chemical mediator, i.e. acetylcholine, with inhibition of the phenomena[28].

In essence, the treatment is very similar to what is done in case of axillary hyperhidrosis of the palms of the hands; it is a matter of injecting the botulinum toxin into the dermis of the affected region; after about a couple of days sweating will be blocked, or greatly reduced, often eliminating the discomfort of patients.

The duration of the benefit varies, but it is still several months, sometimes even a year.

Facial nerve paralysis

In facial nerve paralysis, treatment with botulinum toxin is effective in reducing facial synkinesia, thus improving the symmetry of facial expression both at rest and in voluntary movements[29-30].

One of the complications of facial nerve palsy is salivation-associated hyperlacrimation due to the aberrant connection between the secretomotor fibers of the salivary gland and the lacrimal gland. Injecting botulinum toxin into the lacrimal gland has been successful in managing this condition.

Facial pain and trigeminal neuralgia

Botulinum toxin has been shown to be safe and effective in the management of pain in the maxillofacial region, particularly in cervical dystonia and chronic facial pain associated with masticatory muscle overactivity[36].

Botulinum toxin has also shown to be effective in case of trigeminal neuralgia, without demonstrating important adverse effects[31-32-33]. This minimally invasive solution is increasingly establishing itself as the therapy of choice.

Implantology

Botulinum toxin has been shown to be effective in facilitating the osseointegration of implants by reducing the contraction force of muscles such as the masseter and temporalis[34-35]. To this end, we mention among the obstacles precisely the excessive stress caused by hyperactivity of the chewing muscles and the so-called parafunctions or that set of voluntary muscle activities, which have no functional objectives and are potentially harmful.

Although extremely interesting, the international scientific literature in this regard needs further experimental clinical trials.

Maxillofacial trauma

Botulinum toxin has proved to be extremely useful in improving the healing of traumas affecting the bones of the maxillofacial region. In particular in lesions of the maxilla, mandible, zygomatic bone, nasal bones and orbital bone complex. In an experimental study, in fractures of the zygomatic bones, the temporary

reduction of the contraction force of the masseter muscles made it possible to use fewer plates for osteosynthesis.
The use of botulinum toxin in the management of mandibular condyle fractures is strongly recommended in many scientific papers.

Neoplasms

Injection of botulinum toxin following reconstructive surgery in patients with tumors of the parotid gland can improve some movement disorders such as synkinesis. Also useful as a decontracting agent in palliative care for severe pain.

The neurotoxin represents a minimally invasive treatment option with minimal side effects in various functional disorders, thereby improving the quality of life of head and neck cancer patients.

Orthodontic prostheses

Botulinum toxin can be used with considerable advantage in all patients who find it difficult to get used to the usage of an orthodontic prosthesis due to irregular and uncoordinated muscle activity.
In particular, it is effective in providing muscle relaxation in edentulous patients for long periods of time.
The muscles of the maxilla and mandible are able to adapt to changing functional demands by altering their size, cross-sectional area and physiological properties.
Orthodontic Prostheses are represented by individual medical devices used to prevent, intercept and correct various types of malocclusion, malposition and dysfunction of the teeth and related structures.

Removable dentures

Removable orthodontic prostheses cause dental displacement by means of the forces generated by the elastic deformation of the appliance (sequential dental aligners), by the action of stimulation and rebalancing of the patient's biological (functional) forces, or by the forces produced by activation of built-in mechanical parts (mechanics): screws, springs, vestibular arches.

Mechanical mobile dentures

These are orthodontic prostheses made up of an acrylic resin body which holds in its structure both the elements that allow it to be hooked to the teeth and the more properly mechanical ones, screws, springs, arches, which, once activated, are able to move the teeth. The correction of malocclusion with this type of appliance is determined by a prevailing action on the dental positions.

Functional mobile dentures

These are characterized by the fact that the forces capable of determining the correction of the malocclusion are extrinsic to the denture. Produced by the modifications of the functional matrix which determines the skeletal growth of the jaws and the development of the dentition. This type ofprostheses acts on both dental positions and skeletal growth, correcting malocclusion with a real combined effect, orthodontic and orthopedic.

Aesthetic mobile dentures

These are thin transparent plastic aligners (sequential dental aligners) that the patient applies to the dental arches. Teeth alignment is also called invisible orthodontics, due to the fact that the denture does not alter the aesthetics of the smile. The displacement of the teeth is caused by the force generated by the elastic deformation of the appliance.

Fixed orthodontic prostheses

Fixed dentures are able, in less time, thanks to greater forces, to determine a displacement of the teeth and their roots in any direction, with any type of movement on the teeth and jaw bones.

In patients characterized by hyperactivity of the jaw muscles, such as that of the masseter muscle or the chin muscle, recurrences are possible following orthodontic correction.
In such circumstances, the use of botulinum toxin during the use of prostheses can reduce the intensity of muscle contractile activity. The chewing muscles can thus be trained gradually and more slowly to a more physiological movement.

Diagnostic application

In patients with chronic intermittent tooth pain, neurotoxin injection can be used to identify the origin of the pain (muscular or pulpal) for diagnostic or prophylactic purposes. The relaxation of the masticatory muscles (masseter and temporal) markedly reduces the painful muscular component, if present.

General precautions

As with any injection, the procedure may lead to infection, pain, swelling, abnormal skin sensations (for example, tingling or numbness), decreased skin sensation, soreness, redness, bleeding/bruising at the injection site, and decreased blood pressure or fainting; this may be a

consequence of the pain and/or anxiety associated with the injection[5-42].

Adverse reactions possibly related to toxin spread distant from the site of administration have been reported with botulinum toxin (e.g. muscle weakness, difficulty swallowing, or unwanted food or liquid in the airways). These adverse reactions range from mild to severe, may require treatment, and in some cases can be fatal. This is a particular risk for patients with an underlying disease that makes them susceptible to these symptoms[3].

Serious and/or immediate allergic reactions have been reported, the symptoms of which may include hives, swelling of the face or throat, shortness of breath, wheezing and fainting. Delayed allergic reactions (serum sickness) have also been reported which may include symptoms such as fever, joint pain and skin reaction.

Adverse reactions related to the cardiovascular system, including irregular heartbeat and heart attacks, have also been observed in treated patients, sometimes with a fatal outcome. However, there was a prior history of cardiac risk factors in some of these patients.

Seizures have been reported in adults and children treated with the neurotoxin, especially in patients more prone to seizures. It is not known whether the toxin is the cause of these seizures. The seizures that have been reported in children have occurred mostly in patients with cerebral palsy treated for persistent muscle spasms in the legs.

If the patient is treated with neurotoxin too often or the dose is too high, muscle weakness and adverse reactions related to the spread of the toxin may occur, or his body may start producing antibodies[9] which may reduce the effect[4].

Other medicines and botulinum toxin

Precautions if the patient is taking antibiotics (used to treat infections), anticholinesterase drugs or muscle relaxant drugs. Some of these medicines can increase the effect of the toxin.

Be careful if a patient has recently received treatment with a medicine containing botulinum toxin as this can greatly increase the effect of the neurotoxin.
Precautions when using any antiplatelet agent (aspirin-like products) and/or anticoagulants.

Pregnancy and breastfeeding

Botulinum toxin should not be used during pregnancy and in women of childbearing potential not using contraception, unless clearly necessary. The neurotoxin is not recommended for breastfeeding women.
If you are pregnant, suspect or plan to be pregnant, or are breastfeeding, the use of the toxin is not recommended.

Driving and using machines

Botulinum toxin can cause dizziness, drowsiness, fatigue, or vision problems. If the patient has previously experienced any of these effects, do not drive or use machines.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.In general, side effects occur within the first few days of treatment. These usually only last for a short time but can last for several months and, in rare cases, even longer.

Treatment with botulinum toxin is based on a palliative rather than a therapeutic approach as the blockage is temporary. The block lasts from 3 to 4 months, after which there is the germination of new axon terminals with a consequent return of neuromuscular activity.

Latency in general for the neurotoxin is 1 week and it is recommended that the injection is given no more than once every 12 weeks to avoid the development of antibodies against the toxin.

After application, the clinical effect occurs within approximately 3-7 days, followed by 1-2 weeks of maximum effect, which then stabilizes at a moderate plateau until complete nerve recovery within 3-6 months.

Side effects

In general, adverse reactions are localized and uncommon.

As previously reported side effects include allergic reactions, rash, itching, headache, neck or back pain, muscle stiffness, difficulty swallowing and shortness of breath. This picture may also be accompanied by nausea, diarrhea, stomach pain, loss of appetite, injection site reactions, sore throat, runny nose, tinnitus, and increased sweating in areas other than the armpits.

The two most common side effects related to the use of botulinum toxin in the maxillofacial area are weakness of swallowing, speech and facial muscles and changes in salivary consistency. These complications are injection site specific and dose dependent.

In some cases, the effects of the neurotoxin can be observed at sites distant from the site of local application, known as the "diffusion effect of the toxin". Symptoms of such a

presentation are consistent with the actions of the neurotoxin and include generalized muscle weakness manifesting as diplopia, dysphagia, hoarseness, ptosis, and urinary incontinence or even difficulty breathing. The likelihood of this toxin effect spread is even greater in the face and head and neck region due to the facial planes and spaces.

The lethal dose of neurotoxin in humans is not known. Although it has been estimated to be around 3000 IU. The maximum dose recommended for dental applications in one injection session is around 80-100 U. It means that at least 30 injected vials of neurotoxin would result in a potentially lethal outcome.

II. CONCLUSION

The journey of botulinum toxin has broadened the horizons of dentistry. Certainly the neurotoxin has been shown to have significant value in the management of cases where the patient does not respond to less invasive treatment modalities or in combination with them.

It offers a minimally invasive approach to manage and treat selected suitable cases with minimal complications. However, the dentist must ensure that the treatment is within their scope of action and are adequately trained not only to administer it but also to deal with its potential adverse effects.

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