MAXILLOFACIAL SURGERY

EFFECTIVE APPLICATIONS OF BOTULINUM TOXIN IN DENTISTRY AND IN HEAD AND NECK SURGERY

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ABSTRACT

Background: Botulinum toxin A and B is approved for the treatment of many diseases, and we can read many papers experimenting with other possibilities. The use of botulinum toxin is a relatively new option with little or no pre-gradual training in dentistry.

Objective: This article aims to summarise current knowledge in this emerging field.

Data Sources: A search of MEDLINE, EMBASE, bibliographies of published systematic reviews was performed, as well as of the Cochrane trial registries between 1966 and June 10, 2016.

Study Selection: Randomized controlled trials comparing botulinum toxin A with placebo or other interventions were preferred, but for many emerging indication we used non-randomized studies as well to inspire further studies.

Data Extraction: Data were abstracted and quality assessed by 1 reviewer.

Data Synthesis: We have little-randomised data to quantify the effect of botulinum toxin in a majority of indications in dentistry precisely.

Conclusion: The rapid development of the botulinum toxin application brings new possibilities for treatment by dentists alone or in cooperation with other specialists. Besides the above-verified evidence-based indications, there are new and new case studies quickly appearing that need to be monitored and possibly applied. But we have very few randomised studies to make final guidelines in many indications, so further scientific works are really needed. Botulinum toxin should be part of undergraduate and postgraduate teaching.

Keywords: botulinum toxin, dentistry, dermatology, neurology, psychiatry.

1. Introduction

Botulinum toxin, a neurotoxic protein, the exogenous product of anaerobic microorganism Clostridium botulinum, has been known for long as the redoubtable "sausage poison" (but very rare). Due to the mechanism of the botulinum toxin action, e.i. blocking the release from nerve ending of the neurotransmitter acetylcholine, it was first used as the solution for spastic, cerebral and other rare syndromes in neurology. Subsequently expanded to ophthalmology, it has completely changed aesthetic dermatology and eventually helped to cause the emergence of a new medical discipline, non-surgical aesthetic medicine. It has become one of the fastest growing therapeutic modalities in history. The global markets for Botulinum products are estimated to be close to three billion dollars.1

The botulinum toxin application as an aesthetic procedure has become so popular that unskilled people often provide it, be it unqualified nurse practitioners, briefly trained cosmetic or spa physicians or only superficially trained physicians assistants.

The high elegance of this method is that there is virtually a zero risk of permanent consequences (provided that it is carried out by qualified professionals and we accept a legal definition of risk equal to 1:200).2 However, due to the rising number of unqualified applications, there is an increase in the frequency of complications not only in the absolute number but also in the relative incidence.2

A relatively new field covers applications in Oral
Surgery and Dentistry. We have few publications in this area but many clinical possibilities which are tested by some authors. Some clinical applications target rare diseases, some address very frequent and challenging problems like bruxism. The aim of this paper is to present current possibilities with little evidence-based literature which we have now and to inspire systematic research.

2. The principle of the method and its history

Botulinum toxin causes presynaptic blockade at the neuromuscular junction, which has the anatomically permanent character but due to the growth of new connections the effect is clinically reversible. The blockade prevents the transmission of the signal and the muscle cannot be activated until after three to four months by which time the sufficient amount of new synapses has been created to restore the function of the affected muscle. This formation mechanism of new synapses connections has not been exhausted even after a few decades of repeated treatment on long-term treated patients. (Fig. 1)

Originally it was thought that the mechanism influences the motor function selectively, but now it is considered proven that the botulinum toxin reduces the sensitive nerve function as well. Botulinum toxin is supplied to the market by several manufacturers, however the product molecule differs fundamentally so that the units of each product do not interconvert. Therefore different brands can not be interchanged arbitrarily as appropriate dosage to potency ratios varies.

The history of the botulinum toxin application in medicine is quite short. In ophthalmology, the first patient with strabismus was injected in 1997 by Alan B Scott (San Francisco, CA, USA), who subsequently also reported the clinical utility. In plastic surgery, it was used to treat facial asymmetry by Richard Clark (Sacramento, CA, USA) in 1989. Three years later it was further successfully elaborated in a study published by the Canadian couple, ophthalmologist Jean Carruthers and dermatologist Alistar Carruthers, who observed that blepharospasm patients after injections around their eyes and upper face enjoyed diminished facial glabellar lines. Today the interdisciplinary knowledge is essential for most applications, and the subject is thus an example of the necessity of broader medical education in dentistry to be able to deploy its full potential. (Table 1)

The precautionary principle, however, is a must due to the short history of indications alongside the lack of studies and binding recommendations. Doctors shall adhere to the principle of prudence to enhance the safety and satisfaction of patients and reduce the risk of complications.

3. Contraindications and systemic complications

The application of botulinum toxin has contraindications, which are often overlooked. They include neuromuscular diseases (eg. Myasthenia gravis), pregnancy, infection at the site

![Figure 1](image1.png)

**Table 1. Therapeutic uses of botulinum toxin.**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Effectiveness</th>
<th>First line treatment</th>
<th>Risk of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches in region m. Occipitofrontalis</td>
<td>medium</td>
<td>No</td>
<td>low</td>
</tr>
<tr>
<td>BTX for facial asymmetry</td>
<td>high</td>
<td>Possibly</td>
<td>high</td>
</tr>
<tr>
<td>Applications to the m. Masseter (mostly bruxism)</td>
<td>medium</td>
<td>Possibly</td>
<td>low</td>
</tr>
<tr>
<td>Syndrome of temporomandibular joint</td>
<td>low-medium</td>
<td>No</td>
<td>low</td>
</tr>
<tr>
<td>Trigeminal neuralgy</td>
<td>low</td>
<td>No</td>
<td>low</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>medium-high</td>
<td>Possibly</td>
<td>low-medium</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>low</td>
<td>No</td>
<td>low</td>
</tr>
<tr>
<td>Decreased or increased position of the upper lip</td>
<td>high</td>
<td>very likely</td>
<td>medium-high</td>
</tr>
<tr>
<td>Application into Orbicularis oris muscle</td>
<td>high</td>
<td>very likely</td>
<td>medium-high</td>
</tr>
<tr>
<td>Elevation of the mouth corners</td>
<td>medium-high</td>
<td>very likely</td>
<td>medium</td>
</tr>
<tr>
<td>Applications to the mimic m. of the lower facial third</td>
<td>medium-high</td>
<td>Very likely</td>
<td>medium-high</td>
</tr>
</tbody>
</table>
4. Botulotoxin and dentistry

The global market for the botulinum toxin is currently driven by its applications in aesthetic medicine. However, dentistry also has the potential to become one of the specialisations with top usage for some indications. In particular, the curative potential of this drug (outside the aesthetic medicine) is currently not fully deployed in Europe. With some minor exceptions, the use of the botulinum toxin is not yet part of an undergraduate programme, and we cannot find it even in the curriculum of medically oriented Maxillofacial Surgery.

The fact that dentists may apply the botulinum toxin outside the oral cavity i.e in aesthetic medicine might sound controversial. On the contrary, dentists might sound controversial. On the contrary, dentists have the largest undergraduate training in the topographic anatomy of the head and neck. Even if the botulinum toxin and they need to be investigated out for several years in collaboration with the anatomical institutes around the world. Therefore, it is possible to obtain the necessary information of an appropriate quality level globally.

4.1. Curative indication

4.1.1. Headaches in region m. Occipitofrontalis

The differential diagnosis of those pains has to be provided by a neurologist. But treatment is frequently done by an oral surgeon or maxillofacial surgeon due to their deep knowledge of the anatomy of the head and neck.

The botulinum toxin is approved for the treatment of a chronic migraine, where it helps to reduce the excessive muscular tonus (in this manner it is also used in psychiatry), it also has a direct systemic reduction effect on migraine which provides an alternative non-cholinergic mechanism of action. A successful therapy is subject to a complex differential diagnosis, where it is necessary to rule out other causes. A variety of pain in the head and neck should, therefore, be assessed by all specialists involved - a neurologist, an orthopedist, a spinal specialist, a-ENT specialist, a psychiatrist and last but not least, an oral surgeon.

Pain in the frontal region is often projected from the temporomandibular joint. The author of this article has experienced cases where the primary cause of a patient treated with botulinum toxin was a dental problem in the upper jaw, complicated/accelerated by inflammation of the maxillary sinus, so the oral surgeon has to participate in this treatment.

Sometimes the botulinum toxin is indicated for a migraine elimination as a therapy experiment, where in case of initial failure “a long and uncomfortable diagnostic process” begins. Besides the frequent failure of the botulinum toxin effect on migraine reduction and related unnecessary financial costs, it is a risky procedure, especially for patients who are primarily psychiatrically ill.

Due to the high incidence of pain projections in m. Occipitofrontalis (other than a migraine related), the implementation of such a therapy experiment is not very recommended and the decision on its indication shall be delegated to a neurologist (sometimes to a psychiatrist) subject to a thorough examination.

The involvement of a psychiatrist is interesting also in the light of recent publications demonstrating the antidepressant effect of botulinum toxin comparable with the most efficient antidepressants. It could be an interesting therapeutic option while providing an explanation for the addiction effect on the substance sometimes reported by some patients.

4.1.2. BTX as the solution for the facial asymmetry (hemifacial spasm, facial nerve palsy)

It is one of the most interesting and also one of the most demanding applications. The face is always a little bit asymmetrical, but there are certain boundaries, often subjectively observed as unacceptable disharmony and these asymmetries are perceived as an aesthetically undesirable situation, at a larger scale considered as...
pathological.
There is no doubt that we can address a variety of situations with botulinum toxin and thus avoid a complicated surgical intervention, but it is necessary to know the whole context and especially to make an exact precise application.
The botulinum toxin application could be effectively used to fix temporary faults (Bell’s palsy) or otherwise unmanageable situations (hemifacial spasm).

It is advisable to proceed with minimum doses for individual muscles and eventually after two weeks, when the full effect becomes visible, to increase the dosage if necessary.
The use of botulinum toxin for the treatment of temporary Bell’s palsy in the facial nerve is especially well documented. The application to the healthy half of the face will prevent “dragging” of the affected part, which reduces the aesthetic traumatization of the patient and helps prevent along with the rehabilitation the permanent consequences. If the restoration of full symmetry is not reached, the botulinum toxin can be used to compensate for the different permanent muscle tone. This application is covered by health insurance in many European countries, so we have restricted limits to try this opportunity in the situation when the pandemic herpes virus probably causes this disease. This indication belongs to the competence of oral or facial surgeon.

4.1.3. Applications to the Masseter muscle (especially therapy of bruxism)
Until recently, the only acknowledged indications of the botulinum toxin in the jaw muscle were for the purpose of hernia treatment caused by impairment fascia when the surgical intervention was not easy or nearly impossible.
However, recently the botulinum toxin has been applied to jaw muscle in higher doses repeatedly over longer time in order to cause a permanent volume muscle reduction and perhaps even the medial mandibular reconstruction in order to change the shape of the face from a square or box to oval. This treatment is popular in Asia and has recently become more popular in Europe too.

The more relevant application is into the Masseter muscle and the medial pterygoid muscle to fix bruxism, where we do not have many other successful alternatives (Fig. 2). Furthermore, apart from the expected temporary effect, a permanent result has been observed even after only single application, since in some cases the brain stops to project different psychological problems into the hyperfunction of discarded muscles. The therapy of the psychological problems by a competent professional should go hand in hand with the application of botulinum toxin.
The application of the Botulinum toxin serves to (a) inhibit hypertonicity, (b) enhance the action of the antagonistic muscles, and (c) avoid an impingement to reestablish “the balance of forces”.
It is, however, necessary to emphasise that it involves a relatively high dose of botulinum toxin to each side of the face at least 3-4 times a year. For a short-term treatment, it is an elegant method, for a long-term treatment the cost becomes expensive.
We have no evidence of the long-term effect on the volume reduction and reshaping of the Masseter muscle on the long-term health of the orofacial system.
It is, therefore, necessary to inform patients about a lack of publications that are now available and related to uncertain risks. The applications must be carried out very precisely to avoid damaging the facial nerve and parotid duct.
Exact training can minimize these risks to zero. The application of the botulinum toxin to the Masseter muscle can also address some other rare syndromes and symptoms such as myalgia bite, “the symptom of first bite pain” and oromandibular dystonia. The possible failure of this method was experienced in our department only due to under-dose. Due to the size of the Masseter muscle, the application of the botulinum toxin is usually up to five times higher than into facial muscles in aesthetic indications.

4.1.4. The syndrome of the temporomandibular joint
This treatment modality combines applications into the Pterygoideus lateral and the Masseter muscle. The appropriate indications are for patients with
prolonged muscular hypertension. The application into the Pterygoideus lateral does not cause the symptom of the “frozen smile” that can emerge after the diffusion of botulinum toxin into the superficial facial muscles (Fig. 3). To avoid the symptom of the “frozen smile” authors personally have successfully proven the ultrasound navigation of the needle application which significantly minimizes the risk of side effects.

4.1.5. Trigeminal neuralgia
The botulinum toxin is used as a supportive therapy to medication before neurosurgical treatment starts or eventually as the main therapy if surgery is contra-indicated. The mechanism is not clear - blockage of proprioceptive sensation probably plays a role. The effect of the botulinum toxin is analgesic, but it never acts as a monotherapy without neurological medications.\textsuperscript{20}

4.1.6. Sialorrhoea
The botulinum toxin is frequently used in the treatment of akinetic diseases typically in parkinsonism and the compensation of stroke side effects. It is applied (sometimes under control of sonography) in parotid and submandibular salivary glands. This procedure ensures reduced salivation for 6-9 months. The same protocol can be successfully used for sialoadenitis and salivary fistula.\textsuperscript{21} It is important to give sufficient, i.e. very high doses of botulinum toxin, even higher when compared to the application to the Masseter muscle.

4.1.7. Tinnitus
This multifactorial and not fully understood disease can be decreased in intensity with the botulinum toxin if the myoclonus of the soft palate is present, which causes the pathology status in the smallest muscle in the body the stapedius. The application of the botulinum toxin into the soft palate is ideal for the control of EMG. The indications must be given by a neurologist; the application is frequently made by an ENT specialist or maxillofacial surgeon.\textsuperscript{22}

4.2. Esthetic indications
4.2.1. Decreased or increased position of the upper lip
One of the most popular procedures in aesthetic medicine and aesthetic dentistry is the reshaping of the upper lip to achieve the desired size, shape and position. As we get older, the dorsal maxilla retreats. Consequently, natural abrasion (shortening) of the front teeth and (lip) thinning lead to a syndrome of “long lip”. We often see, as a “popular solution”, a completely unnatural “inflated” lip red boosted by a variety of injectable filler materials based on hyaluronic acid, whereas the upper lip often exceeds the size of the bottom lip, which is unacceptable. Furthermore, this approach fails to camouflage the so-called “invisible teeth”. On the contrary, it further deepens the problem. The solution has to be interdisciplinary. In rare cases, the mesial orthognathic replacement of the upper jaw is fixed by surgery together with orthodontic pretreatment, or we can shorten a lip by plastic surgery. However, those treatment protocols are very complicated, with significant risk of complications, and we have to reserve them for most demanding cases.

Another common solution is to extend the clinical crowns of the anterior teeth with veneers or crowns with the overall increase of the patient’s intermaxillary distance. Even this complex procedure has its limits and possible side effects. The new alternative is the weakening of the lower lip depressants and the Orbicularis oris muscle with the botulinum toxin. This treatment improves the display of labial teeth surfaces without interfering to the dental tissues.

Unfortunately, even if it is easy and safe, currently it is not a common solution how to hide the unpopular high exposed gums so-called “gummy smile” due to relaxation of the lip levators (Figs. 4, 5). Some dentists still address this problem by difficult and potentially devastating procedures involving the shortening of alveolar bone with subsequent reduction of the gingiva with a final “extension” of the teeth.

It is much easier to apply the botulinum toxin to an area where there is an intersection of three upper lip levators, in the latero-caudal way from the nasal wing insertions (Fig. 6). We can also add additional applications, centrally in the subnasal way. This
application requires a small amount of botulinum toxin. Based on the author’s experience, it is a very effective and efficient procedure. However, it is one of the most interesting indications in the whole of dentistry.

4.2.2. Application into the Orbicularis oris muscle
Although an application to the lower face is demanding and still not approved by regulators, it is frequently used in many cases even by beginners or physicians, not specifically trained in the botulinum toxin. The application of a small amount of botulinum toxin into the orbicularis oris muscle smooths very unpopular transverse wrinkles. Nevertheless, it is extremely demanding to catch a fine muscle without control by an imaging technique.

It is always necessary to count with the weakening of the Orbicularis oris muscle function, which leads to the limited capability of the mouth to retain drinks and food. Surprisingly, this complication is well tolerated by patients, in particular by women, but they should be informed about this frequent side effect in advance. Other consequences of weakening the Orbicularis oris muscle are asymmetries of the face which are not so well tolerated. They could be corrected only by the further deepening of the muscle paresis, or by fading which could take a few weeks or months.

Typically we use four points for the application regularly distributed over the circumference of the muscle with half the amount of the drug compared to the amount applied in another area of the face.

4.2.3. Elevation of the mouth corners
Application of botulinum toxin into the Depressor anguli oris muscle, or to the Platysma muscle is the most popular solution for “slack” corners of the mouth that can escalate from simple visual problem to the inflammatory disease. It is, however, important to note that the most common cause of this problem is the reduction of the intermaxillary position or teeth abrasion. The primary treatment for slack corners should be made by a dentist because it prevents some serious complications, such as the damage of the temporomandibular joint. The solution with botulinum toxin\(^{25}\) should be effective only for patients where dental treatment cannot resolve the problem completely or if the patient refuses the dental solution due to associated risks. We can use the botulinum toxin as an adjuvant treatment to escalate the effect of the dental treatment. From many possible schemes, we use in our clinical praxis the application in two points at the edge of the mandible affecting not only the Depressor anguli oris but also the Platysma muscle. The muscle insertion is easy to find and palpate in this location.

4.2.4. Applications to the mimic facial muscles of the lower facial third
Bone borders allow us to intervene relatively safely into the group of lip depressors and elevators, which can correct the smile line of the patient, a key parameter of aesthetic dentistry. It is relatively easy to determine the position of the jaw muscles. However, it is always vague to hit the orbicularis oris muscle, and it is nearly impossible to target the precise orientation of the Risorius.

The future approval of the applications in this area (lower facial third) is probably possible only with the ultrasound navigation which is safer, and it is also approved for some other applications of the botulinum toxin (e.g. sialorrhea).\(^{26}\) Our clinical experience shows a decreased rate of complications with ultrasound guiding.

4.3. Guidelines
We have no specific guidelines for dentistry and oral surgery yet but it is possible to find the latest recommendations in the field of Aesthetic Medicine in the guidelines of specialised societies, one of the most accepted being the American Society for Aesthetic Plastic Surgery (ASAPS), with frequent updates in their journal or online. The application of the botulinum toxin as a treatment possibility for pathologies in the head and neck area is, except for a few indications (a migraine), a new domain with few scientific papers, and we are waiting for treatment guidelines.

5. Conclusion
The rapid development of the botulinum toxin application brings new possibilities for treatment by dentists alone or in cooperation with other specialists. Besides the above-verified evidence-based indications, there are new and new case studies quickly appearing that need to be monitored and possibly applied. But we have very few randomised studies to make final guidelines in many indications, so further scientific works are really needed. The botulinum toxin should be part of undergraduate and postgraduate teaching.

Author Contributions
Equal contribution to the paper.

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Questions

Botulinum toxin is:
- a. Hepatotoxin;
- b. Neurotoxin;
- c. Karcinogen;
- d. Teratogen.

Botulinum toxin is used in the Dentistry for treatment of:
- a. Anodontia;
- b. Dysgnatia;
- c. Bruxism;
- d. Myasthenia gravis.

We have most aesthetic and medical indication to apply botulinum toxin in the:
- a. Lateral pterygoideal muscle;
- b. M. Masseter;
- c. Internal pterygoideal muscle;
- d. M. Risorius.

We can balance complicated muscular situation with the botulinum toxin in the case of:
- a. Myasthenia gravis;
- b. Bell’s palsy;
- c. Trigeminal neuropathy;
- d. Damage of n. Alveolaris inferior.